

Cigarette Smoking, But Not Sensitization to *Alternaria*, Is Associated with Severe Asthma in Urban Patients

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ABSTRACT

*Hereditary susceptibility and allergen exposure have been identified as general risk factors for asthma. However, risk factors for severe asthma still remain to be identified. To further assess and quantify risk factors associated with severe asthma in adult patients apart from clinical exacerbations, 306 randomly selected subjects (mean age 40 ± 17 years, 46% males) presenting to an inner city pulmonary practice between 1995 and 1996 were retrospectively investigated. Of these, 117 patients were atopic, 112 had current asthma, and 22 asthmatics had severe asthma. Risk factors associated with atopy were family history of atopy and any domestic pet ownership (OR: 3.1, 95% CI: 1.6–6.1). Asthma was generally associated with atopy (OR: 4.2, CI: 2.4–7.4) and pet ownership (OR: 2.4, CI: 1.2–4.6). Severe asthma was strongly associated with current smoking (OR: 4.8, CI: 1.3–18.3), and lung function was negatively correlated with the amount of consumed cigarettes per day ($r = -0.61$, $p = 0.04$). However, no association with sensitization to *Alternaria* was found in severe asthma. Cigarette smoking is an independent risk factor associated with severe asthma in urban patients, whereas sensitization to *Alternaria* is of less importance in these patients.*

KEY WORDS: Asthma; Atopy; Adults; Risk factors; Smoking; *Alternaria*.

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INTRODUCTION

Bronchial asthma is characterized by lower respiratory tract inflammation; bronchial hyperresponsiveness (BHR); and variable, reversible airflow obstruction. Unraveling the causal factors associated with the pathogenesis of asthma requires a better understanding of the interactions between the host at risk for the disease and the environment, such as disease-causing agents. Most subjects with asthma have an allergic background with sensitizations to common aeroallergens such as pollen, animal dander, molds, or house dust mites (1,2). Therefore, atopy is considered to be one of the major risk factors for the onset of allergic diseases (3).

The worldwide prevalence of both atopy and asthma is on the rise (4–6), but mechanisms underlying this increase are not completely understood (3). Besides genetic susceptibility (7,8), a growing body of evidence indicates that the development of atopy and clinical allergy is significantly influenced by environmental factors, with seasonal and perennial allergen exposure independently contributing to the development of asthma (9,10) in susceptible individuals.

Indoor allergens have been reported to be associated primarily with asthma, while seasonal outdoor allergens such as pollen mainly contribute to allergic rhinitis, probably owing to the particle size of the allergens (11,12). However, regional differences in the spectrum of individual sensitizations naturally occur (10,13), and there is still ongoing debate as to whether distinct patterns of sensitization cause differences in asthma severity. Climate (14,15), outdoor pollution (16), and mold allergy (17), especially to *Alternaria alternata* (18,19), have repeatedly been linked to an increased risk of severe asthma, while the influence of smoking habits on asthma severity in adults is still controversial (19–22).

Comparative epidemiological studies in former East and West Germany (6,23) clearly demonstrated that different living circumstances play a pivotal role in the development of asthma and related allergic diseases. It is less clear, however, whether these differences result in not only different prevalences, but also different severities of the disease. This may be because epidemiological approaches are often limited to a “semiquantitative” asthma diagnosis, such as by self-reported-asthma questionnaires (24). Furthermore, many of these studies focused on childhood asthma (25,26), whereas data about severe asthma in adults are scant. Therefore, this study was performed to identify risk factors for atopy and asthma in urban patients from a large German city. In particular, the analysis was focused on risk factors associated with severe asthma in adults.

METHODOLOGY

Patients

Files from 1224 consecutive patients newly admitted to a pulmonary specialist practice in Frankfurt, Germany, with respiratory symptoms or for a health check-up between January 1995 and January 1996 were retrospectively investigated. For detailed analysis, 306 patients were randomly picked from the total patient population by computed ID numbers on a 1:4 ratio.

The data were anonymized by one investigator (M.K.) and consecutively analyzed by another (K.-M.B.). All patients had undergone thorough clinical evaluation (age, race, gender, occupation, patient and family history, smoking status, concomitant medication and diseases, physical examination), skin prick test (SPT) with 14 allergen extracts, and lung function (spirometry and diffusion capacity). Nonspecific bronchial provocation with histamine was performed to verify bronchial hyperresponsiveness if baseline lung function revealed no abnormalities ($FEV_1 \geq 85\%$ predicted). Additionally, a blood sample had been drawn to determine peripheral blood eosinophils and total and specific serum IgE levels.

A diagnosis of asthma was based on the following criteria: (1) airflow obstruction ($FEV_1 < 85\%$ predicted) with reversibility $>12\%$ and at least 200 mL from baseline after bronchodilation or (2) positive histamine challenge combined with typical clinical signs such as dry cough and wheezing in absence of acute respiratory tract infection (27–29). Severe asthma was defined as $FEV_1 < 60\%$ of the predicted value in the absence of an acute exacerbation on initial presentation (28). Criteria for clinical signs of asthma exacerbation were increases in rescue β_2 -agonist use, daily symptoms, and nighttime awakenings due to asthma.

Atopy was defined as at least one positive SPT result against common aeroallergens, positive specific IgE (EAST/RAST class ≥ 1), or patient history of atopic dermatitis or allergic rhinoconjunctivitis.

Subjects without asthma, nonsevere asthmatics (i.e., mild and moderate asthmatics), and nonatopic individuals served as controls for group comparison.

Skin Prick Test

Skin prick tests (BENCARD, Neuss, Germany) were performed, including the following allergens: grass pollen mix, ryegrass, weed pollen mix, tree pollen mix, dog, cat, feather mix, horse, guinea pig, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria*



alternata, *Aspergillus fumigatus*, and *Penicillium notatum*. Results were read as skin reaction graded from 0 to +4 according to wheal and erythema diameters in millimeters, as previously described (30). To quantify the individual degree of allergic sensitization, an atopy score was defined as sum score of single skin wheal diameters (mm).

Pulmonary Function Tests

Pulmonary function tests were performed in a whole-body plethysmograph (Masterlab II, Jaeger, Wuerzburg, Germany). The best of three consecutive spirometry recordings were used (31,32). Measurements included forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), forced expiratory flow rates in relation to FVC (FEV₁/FVC, Tiffeneau-Index), and pulmonary diffusion capacity (DL_{CO}). DL_{CO} was quantified by the carbon monoxide single-breath method (Masterlab I, Jaeger, Wuerzburg, Germany). Histamine challenge was performed using a modified reservoir method (PARI Provocation Test II, Dr. Beckmann Co., Germany) (33). Briefly, histamine chloride was administered by an inhalation reservoir in doubling concentrations of 1, 2, 4, and 8 mg/mL, respectively. The test was regarded as positive if a 20% fall of baseline FEV₁ occurred (PC₂₀). A histamine concentration of >8 mg/mL defined a negative response. Airflow reversibility tests, if necessary, were performed after application of 200 µg of aerosolized albuterol (two puffs), followed by a second lung function test after 15 minutes. Reference values were obtained from the European Community for Steel and Coal (34).

Total and Specific IgE Measurements

Total and specific IgE were quantified by using an IgE Micro-Turbo-ELISA (Fooke Laboratories, Neuss, Germany). Seven WHO standards were used for total IgE measurements (0, 2, 5, 20, 100, 500, 1500 U/mL), and four standards were used for specific IgE levels (EAST/RAST classes 1–4). All patient sera were tested for total IgE levels and specific IgE against six allergens (*der far*, *der pt*, *asp fum*, *alt alt*, *clad herb*, *cat*). A result of EAST class ≥1 was considered positive. Normal values for total IgE ranged between 20 and 120 U/mL in this assay.

Statistical Analysis

Statistical analysis was performed by using the intercooled STATA 5.0 software package (Stata Corp.,

Texas, USA). Unless specified otherwise, data are reported as means with standard deviations (±S.D.). The Shapiro-Wilk Test was used to test values for normal distribution. Group comparison tests were done by using the two-sided *t*-test for normally distributed values and the Mann-Whitney *U*-test for nonnormally distributed values. Categorical variables between groups were compared by using the Fisher exact test. Correlational coefficients were calculated by simple linear regression, and odds ratios (OR) correlated by multivariate logistic regression model were adjusted for confounding parameters. IgE values, atopy score, and number of consumed cigarettes per day were log normally distributed in our population and therefore log transformed for correlational analysis. For all statistical analyses a value of *p* < 0.05 was considered statistically significant.

RESULTS

Patients

Three hundred and six randomly selected patients (46% male, mean age ± S.D.: 40.3 ± 17.1 years) were analyzed. Among these 112 subjects had current asthma (37%). Leading diagnoses besides asthma were acute upper respiratory tract infection (25%), chronic obstructive pulmonary disease (COPD, 10%), lone allergic rhinitis (6%), and pneumonia (2%). Twelve percent of all patients had no clinical diagnosis (e.g., health check-up); 117 of 306 (38%) subjects were atopic.

Atopics were younger than nonatopics (*p* < 0.0001), and domestic pet ownership was significantly more prevalent in atopics patients than in nonatopics. No further differences in gender, smoking habits, or occupational exposure to inhalants were observed. The median total IgE was 188 U/mL in atopics (range: 2–1308) and 53 U/mL in nonatopics (range: 1–1109) (Table 1).

Asthma was more prevalent in allergic patients than in nonallergics (*p* < 0.0001), and domestic pet ownership was more prevalent in asthmatics than in controls (*p* = 0.0001). Gender, smoking habits, and occupational exposure were similar in the two groups (Table 2).

Twenty-two asthmatics had severe asthma. Severe asthmatics were not different from mild or moderate asthmatics (*n* = 90) in terms of serum IgE (median IgE: 309 U/mL, range: 5–872), gender, and occupational exposure but had a higher percentage of current smokers (*p* = 0.005) and a higher age (*p* = 0.04) (Table 3).



Table 1

Characteristics of Atopic and Nonatopic Subjects

	Nonatopics <i>n</i> = 189	Atopics <i>n</i> = 117
Age (years), mean $\pm$ S.D.	45 $\pm$ 17	33 $\pm$ 14*
Sex, M/F (%)	45/55	48/52
Family history of atopy (%)	4	21*
Current smokers (%)	28.5	23.1
Occupational exposure to inhalants (%)	11	8
Domestic pet ownership (%)	15	35**
Asthma (%)	22	61*
Median serum IgE (U/mL)	53	188*

* $p < 0.0001$.

** $p < 0.0001$.

Allergic Sensitization

Among all atopics ($n = 117$), pollen allergy was most frequently observed (75%), followed by allergy to house dust mites (48%), cat (39%), dog (12%), and *Alternaria* (12%). Patients with lone allergic rhinitis were sensitized primarily to pollen (100%), followed by cat (41%), house dust mites (18%), and *Alternaria* (12%).

In patients with allergic asthma, pollen allergy was found in 67%, followed by allergy to house dust mites (57%), cat (43%), dog (17%), and *Alternaria* (14%).

Table 2

Characteristics of Subjects with Asthma and Controls

	Asthmatics <i>n</i> = 112	Controls <i>n</i> = 194
Age (years), mean $\pm$ S.D.	36 $\pm$ 15*	43 $\pm$ 18
Sex, M/F (%)	44/56	47/53
Current smokers (%)	25	27
Occupational exposure to inhalants (%)	10	10
Domestic pet ownership (%)	36*	15
Atopy (%)	63*	24
Median serum IgE (U/mL)	238*	50
FEV ₁ (% predicted), mean $\pm$ SD	78 $\pm$ 21*	92 $\pm$ 21

* $p < 0.001$.

Table 3

Characteristics of Subjects with Severe and Mild or Moderate Asthma

	Severe Asthma <i>n</i> = 22	Mild to Moderate Asthma <i>n</i> = 90
Age (years), mean $\pm$ S.D.	42 $\pm$ 16*	35 $\pm$ 15
Sex, M/F (%)	41/59	44/56
Current smoking (%)	50**	19
Atopy score (mm), mean $\pm$ S.D.	34 $\pm$ 27	26 $\pm$ 16
Median serum IgE (U/mL)	309	204
Eosinophil count (%) mean $\pm$ S.D.	4.7 $\pm$ 1.5	5.1 $\pm$ 4.5
Dog allergy (%)	45***	12
<i>A. alternata</i> allergy (%)	9	7

* $p = 0.04$.

** $p = 0.005$.

*** $p = 0.01$.

Asthma prevalence was lower in patients with lone pollen allergy than in those with sensitization to indoor allergens (48% vs. 67%, $p = 0.05$).

However, in severe asthmatics the percentage of patients with dog allergy was significantly higher than that in mild asthmatics ($p = 0.01$), whereas no differences in the frequency of sensitization to other allergens were observed.

The mean atopy score was 25 ± 18 mm in all atopics. Atopy scores showed no differences in patients with lone rhinitis and asthmatics (25 ± 11 vs. 27 ± 18 , $p = 0.6$) and severe or mild asthmatics ($p = 0.2$). Log atopy scores were significantly correlated with log IgE levels ($r = 0.37$, $p < 0.0001$) in atopic subjects.

Lung Function Parameters

Lung function parameters indicating obstructive airway disease were lower in asthmatics than in controls with regard to FEV₁ (2.62 ± 0.99 l vs. 2.95 ± 0.92 l, $p = 0.003$) and FEV₁%FVC (75.5 ± 11.3 vs. 81.5 ± 12.5 , $p < 0.001$). Patients with nonallergic asthma had lower absolute FEV₁ values than did allergic asthmatics (2.35 ± 0.9 vs. 2.78 ± 1.0 l, $p = 0.02$), but predicted values of FEV₁ ($74.2 \pm 22.1\%$ vs. $80.2 \pm 19.4\%$, $p = 0.13$) and FEV₁%FVC (76.5 ± 11.9 vs. 74.9 ± 11.1 , $p = 0.44$) revealed no differences in the severity of airflow obstruction between these groups.



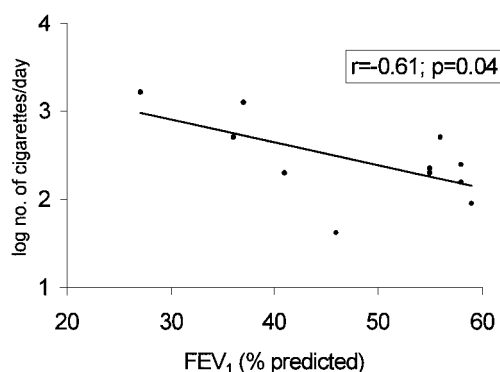


Figure 1. Inverse correlation of consumed cigarettes per day and lung function (FEV_1 % predicted) in severe asthmatics: $r = -0.61$, $p = 0.04$.

In atopic subjects there was a negative correlation between FEV_1 % FVC values and log atopy score ($r = -0.23$, $p = 0.02$), indicating an impact of the individual degree of allergic sensitization on asthma severity. The amount of consumed cigarettes per day was negatively associated with the predicted FEV_1 value in all subjects ($r = -0.24$, $p = 0.03$). This association was even stronger when only asthmatics ($r = -0.45$, $p = 0.02$) and severe asthmatics ($r = -0.61$, $p = 0.04$, Fig. 1) were analyzed.

Diffusion capacity (DL_{CO} % predicted) was similar in severe and mild asthmatics ($83 \pm 10\%$ vs. $83 \pm 14\%$).

Eosinophil Count

Peripheral blood eosinophil counts were similar in atopics and nonatopics ($5.1 \pm 5.2\%$ vs. $5.9 \pm 5.7\%$), asth-

Table 4

Odds Ratios (OR) for Atopy (Adjusted for Age and Sex)

Variable	RR	95% CI
Family history of atopy	4.2*	1.7–10.5
Any pet ownership	3.1*	1.6–6.1
- Rodents	10.1*	1.8–55
- Dogs	3.6**	1.1–12.7
- Cats	2.9***	1.1–7.7
- Cage birds	1.4	0.4–4.7
Current smoking	0.8	0.4–1.5
Occupational exposure to inhalants	0.7	0.3–1.8

* $p < 0.01$.

** $p = 0.04$.

*** $p = 0.02$.

Table 5

Odds Ratios (OR) for Severe Asthma (Adjusted for age and sex)

Variable	RR	95% CI
Current smoking	4.8*	1.3–18.3
Ever smoking	5.6**	1.5–21.6
Dog allergy	7	0.74–68
House dust mite allergy	0.6	0.12–2.8
<i>Alternaria</i> allergy	0.7	0.1–8.9
Nasal sinus disease	0.9	0.1–15.7

* $p = 0.02$.

** $p = 0.01$.

maties and controls ($5 \pm 3.9\%$ vs. $6 \pm 6.2\%$), and severe and mild asthmatics (Table 3).

Multivariate Analysis

After matching for age and sex, a multivariate logistic regression analysis was performed to further assess and quantify risk factors for atopy, asthma, and severe asthma in our patient population. Risk factors for atopy were family history of atopy and any domestic pet ownership, while smoking status and occupational exposure were not associated with an increased risk of atopy. For pets the strongest risk was seen with rodents, followed by dogs and cats, while cage birds were not associated with atopy (Table 4).

Asthma in general was primarily associated with atopy (OR: 4.2, 95% CI: 2.4–7.4; $p < 0.001$), allergy to indoor allergens (OR: 4.1, 95% CI: 2.2–7.7; $p < 0.001$), and domestic pet ownership (OR: 2.4, 95% CI: 1.2–4.6, $p = 0.009$). No association with smoking status was found.

However, a history of current or ever smoking was the only significant risk factor associated with severe asthma in the multivariate model. Allergic sensitizations to *Alternaria* or house dust mites were not associated with severe asthma in the study population (Table 5).

DISCUSSION

The worldwide prevalence of atopy and related diseases like asthma is rising (3,4). Despite therapeutic improvements, asthma mortality rates still tend to increase in Western countries (35), and explanations of possible underlying



mechanisms are scant. Numerous exogenous and endogenous risk factors for atopic diseases and asthma have been identified. It is still controversial, however, which factors may contribute to severe forms of asthma, which are held responsible for rises in mortality.

Hence, the present study was performed to further assess risk factors for asthma in an urban patient population. Although our study may be limited by (1) the fact that the patients included in this study are not a representative sample of the general population but patients referred to a pulmonary specialist and (2) the retrospective character of the analysis, we were able to use a clear-cut definition of asthma and allergy in our population, based on extensive history, clinical features, a broad range of allergy tests, lung function parameters, beta₂-agonist reversibility of airway obstruction, and bronchial challenge with histamine. Furthermore, an exact quantification of airway obstruction was possible, with a cutoff value of FEV₁ < 60% of the predicted value apart from an episode of exacerbation defining severe asthmatics.

In this study, atopy was strongly associated with a family history of atopy and domestic pet ownership. This was true only for households with rodents, dogs, and cats; cage birds were not associated with atopy. These observations are in accordance with other studies, which have implicated exposure to indoor allergens as a possible cause for atopic disorders (36,37).

Consistent with other studies (11,12), sensitization to indoor allergens but not pollen allergy was primarily associated with asthma. The individual degree of sensitization, measured by atopy score, was significantly correlated with serum IgE levels and degree of airflow obstruction in atopic individuals.

A possible association of allergy against molds such as *Alternaria* with severe asthma has recently been reported (19). However, actual prevalence data of sensitization to *Alternaria* shows variations in different geographic areas (13) and may therefore be less relevant to the contribution of asthma in other regions. In this population, mold allergy was almost completely due to sensitization to *Alternaria*. Overall prevalence of allergy to *Alternaria* was low, and a postulated association of severe asthma and sensitization to *Alternaria* was not confirmed. Although, unfortunately, data on spore counts in the area under survey were not available, it is very unlikely that relevant selectional differences have biased the present results, since patients were selected homogeneously regarding season and month of initial presentation. Hence, allergy to *Alternaria* as a risk factor for severe asthma may be area dependent and of less importance in most urban populations.

This study provides clear evidence that current smoking is associated with severe asthma apart from life-threatening exacerbations. Additionally, the number of consumed cigarettes per day was significantly correlated with the severity of airflow obstruction in all asthmatics, and the contributory effect of cigarette smoking was even stronger in severe asthmatics, indicating a dose-dependent phenomenon. When the factors that are generally associated with asthma were analyzed in a multiple regression model for severe asthma, only current smoking was independently associated with severe asthma. These data are in line with previous reports, indicating that active smoking enhances the annual decline of lung function in asthmatic adults (38). It is therefore tempting to speculate as to whether smoking habits may contribute to the rising trend of asthma mortality in Western societies (39), in particular since active smoking is capable of modulating the extent of the allergic response (40,41). However, total serum IgE and individual sensitizations were similar in severe and mild asthmatics in this study, indicating that worsening of lung function was not related to the degree of allergy.

Several reports confirm that smoking habits in asthmatics do not differ from those of the general population (21). While the general prevalence of current smoking has decreased in United States (42,43), this is not the case in several European countries, especially Germany (44,45). Therefore, increases in certain subpopulations that are at risk for asthma, as seen in the United States (46), could have significant impact on asthma morbidity. Another relevant consideration may be that asthmatics who smoke could be generally more susceptible to accepting health risks and may therefore be less compliant regarding medication. Undertreatment with asthma controllers is a major risk factors for severe and especially life-threatening asthma (47).

These observations also contribute to the debate about clinicopathological definitions, since it appears worthwhile to consider whether the reported patients with severe asthma rather represented subjects with COPD. We are certain that these patients are truly asthmatic or at least suffer from a predominantly asthma-like disease, since the prevalence of atopy among severe asthmatics was as high as in mild asthmatics and bronchodilator response revealed clearly reversible airway obstruction (FEV₁ > 12% change from baseline) in all patients with severe asthma (Δ FEV₁ change from baseline: $35 \pm 24\%$). In this regard, recent evidence from pathology has raised the question of how far in certain individuals a clear distinction between severe asthma and COPD can be sufficiently made at all, in particular since severe asthma shares major features of



neutrophilic inflammation with COPD (48,49). Although in the present study we cannot report about sputum differential cell counts, at least peripheral blood eosinophils were not increased in severe asthmatics when compared with mild to moderate disease. This could suggest that greater asthma severity in these patients was rather due to neutrophilic than eosinophilic inflammation, as a consequence of smoking (50).

SUMMARY

In conclusion, this study supports the evidence that sensitizations to indoor allergens are major risk factors for asthma, whereas pollen allergy seems to be associated primarily with allergic rhinitis. Furthermore, domestic pet ownership (e.g., rodents, dogs, and cats) contributes significantly to the onset of atopic diseases in urban patients. Additionally, this study provides convincing evidence of an independent association of smoking and more severe asthma, whereas allergy to *Alternaria* was not associated with severe asthma.

These findings highlight contributory effects of cigarette smoking on airway remodeling in asthmatics (51). As a consequence, the importance of smoking prevention and cessation should be further stressed in asthma educational programs. It is clearly warranted to confirm the results of this analysis in larger population-based studies.

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