

ORIGINAL ARTICLE Asthma and Rhinitis

Non-atopic males with adult onset asthma are at risk of persistent airflow limitation

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Summary

Background Patients with asthma have on average a more rapid decline in FEV₁ as compared with the general population. Recent cluster analysis has revealed different asthma phenotypes that can be distinguished by age of onset and reversibility of airflow limitation.

Objective This study aimed at detecting risk factors associated with persistent airflow limitation in patients with the adult onset asthma phenotype.

Methods We recruited 88 patients with adult onset (≥ 18 years) asthma from an academic pulmonary outpatient clinic in the Netherlands. The associations of age, age of asthma onset, asthma duration, gender, race, atopy, smoking packyears, BMI, use of oral corticosteroids with post-bronchodilator FEV₁/FVC were investigated.

Results Multiple linear regression analysis showed an association of absence of atopy ($r = -0.27$, $B = -0.26$, $P = 0.01$) and male gender ($r = 0.31$, $B = 0.30$, $P = 0.004$) with post-bronchodilator FEV₁/FVC. Multiple logistic regression analysis showed that male patients were 10.8 (CI: 2.6–45.2) times the odds than women to have an FEV₁/FVC < 0.7 , and non-atopic patients were 5.2 (CI: 1.3–20.3) times the odds to have an FEV₁/FVC < 0.7 than atopic patients.

Conclusions and Clinical Relevance We conclude that in patients with adult onset asthma, male gender and absence of atopy are associated with persistent airflow limitation. This might suggest that amongst patients with adult onset asthma, non-atopic male patients are at increased risk of accelerated decline in lung function.

Keywords allergy, asthma, persistent airflow limitation, risk factors

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Introduction

Asthma is a heterogeneous condition with many clinical subtypes differing in severity, natural history, and response to therapy [1]. The classical, most prevalent type of asthma is associated with atopy, starts in early childhood, and typically runs in families [2, 3]. This type of asthma has been extensively studied in *in vivo* and *in vitro* asthma models, and can be reasonably well controlled by current anti-asthma medications [4].

There are, however, many other phenotypes of asthma, in particular in adults, that have received less attention. These phenotypes often have no evidence of atopic disease or allergic sensitization [5], present with a negative family history, and typically report the onset

of their asthma in adult life [3, 6]. Adult onset asthma is still poorly understood, and mechanisms have never been investigated systematically. Some studies have shown that it is often severe at onset [7], less responsive to therapy [8] and more likely to persist [7]. Cross-sectional and population based studies in patients with severe and non-atopic asthma have shown that those with adult onset disease are also more prone to develop persistent airflow limitation [9–11]. Hence, adult onset asthma represents a population of major interest with regard to the risk factors of accelerated loss of lung function as observed in asthmatics as compared with controls [12].

Recently, two subtypes of adult onset asthma have emerged after applying cluster analysis to a large database

of patients with asthma [13]. One consisting mainly of obese women with high symptoms scores and little airway inflammation, and one consisting of more males with intense airway inflammation, low symptom scores and persistent airflow limitation. An adult asthma phenotype of obese women was confirmed by cluster analysis in another large database of patients with asthma, and these patients were characterized by less atopy and reduced FEV₁ [14].

We questioned whether obesity, male or female gender, and absence of atopy might be risk factors of persistent airflow limitation in patients with adult onset asthma.

Therefore, the aim of the present study was to investigate whether these and six other potential risk factors (age, age of asthma onset, asthma duration, smoking history, race, and use of oral corticosteroids) were associated with persistent airflow limitation in patients with the adult onset asthma phenotype.

Methods

Patients

Consecutive secondary referral centre patients with adult onset asthma visiting the outpatient clinic of the Academic Medical Centre between October 2008 and 2009 entered this study. Patients were eligible if they had a physician's diagnosis of asthma onset after the age of 18 years. A diagnosis of asthma was defined by a history of episodic dyspnea and wheezing, and documented reversibility in FEV₁ of greater than 12% of the predicted value, or hyperresponsiveness to inhaled methacholine chloride (PC20 < 8.0 mg/mL) in the past 5 years. Patients with a history of childhood dyspnea attacks (spontaneous or during exercise), a childhood doctors' diagnosis of asthma or chronic bronchitis, or childhood use of pulmonary medication were excluded, as were patients with other pulmonary diseases or non-related major co morbidities.

Current and ex-smoking was allowed only if the patient had normal diffusion capacity and a > 12% improvement in FEV₁ after inhalation of 400 mcg of salbutamol at the time of inclusion [15]. The study was approved by the hospital Medical Ethics Board and all patients provided written informed consent (MEC 08/358).

Design

In this cross-sectional study all patients underwent several measurements to identify factors that could be associated with lung function decline, including a standard questionnaire, physical examination, allergy testing and pre- and post-bronchodilator spirometry.

Measurements

Questionnaire and physical examination. The questionnaire included demographic data, age at asthma onset, duration of asthma, severity of asthma symptoms, smoking history and medication use. Physical examination included weight, height, assessment of co-morbidities and signs of any other disease.

Allergy tests. Atopic status was assessed by specific IgE to a panel of common aeroallergens (house dust mite, grass and birch pollen, herbs and cat and dog dander) by RAST or by a positive skin prick test to one of these allergens. Atopy was defined as a score of > 0.35 kU/L for at least one of the specific IgE's or by > 3 mm wheal response.

Lung function testing. Spirometry was performed according to standard lung function technique [16] using spirometry (Masterscreenpneumo; Jaeger; Wurzburg, Germany) by an experienced technician. Reversibility in FEV₁ was measured 10 min after administration of 400 µg inhaled Salbutamol and was expressed as change in percentage predicted.

Analysis

Group differences were analysed using unpaired student's *t*-test and Chi-square analysis. Factors considered to be potentially associated with a lower FEV₁/FVC were age, gender, age of asthma onset, asthma duration, race, body mass index, number of smoking packyears, atopy and chronic use of oral corticosteroids. Age of asthma onset was defined as age at which the physician's diagnosis of asthma was established for the first time. Asthma duration was defined as the number of years since asthma onset. Number of smoking packyears was calculated by defining 1 packyear as smoking 20 cigarettes a day for a whole year. Chronic use of oral corticosteroids was defined as the daily use of oral corticosteroids in the previous 6 months before the study.

Potential risk factors were analysed both as continuous and dichotomous independent variables, using the following contrasts: asthma duration ≥ 10 year vs. < 10 year (median for whole group); age ≥ 47 year vs. < 47 year (median for whole group); atopic vs. non-atopic; Caucasian vs. non-Caucasian Race; chronic use of oral corticosteroids vs. no use of oral corticosteroids, never smoker vs. (ex)-smoker and packyears ≥ 1 year vs. 0 year (median for whole group).

Linear regression was used to analyse the association between potential risk factors and FEV₁/FVC. Results were expressed as slope of the regression line (B) with 95% confidence interval (CI), which indicates the increase in the dependent variable per one unit increase

in the independent variable. For further statistical analyses, subjects were divided into two groups for $FEV_1/FVC \geq 0.7$ and < 0.7 (median of the whole group). Logistic regression was used to estimate odds ratios with 95% CI for persistent airflow limitation. In addition, a full multiple logistic regression analysis was applied with all significant factors forced into the model. Analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL). P -values < 0.05 were considered statistical significant.

Sample size estimation

For multivariate prognostic analysis there is no formal way to calculate statistical power. However, the sample size was based on the requirement for the ratio of the number of patients vs. the number of predictors to be ten or higher [17]. Therefore, including eight predictors required at least 80 participants.

Results

Comparison between patients with an $FEV_1/FVC \leq 0.7$ vs. ≥ 0.7

Eighty-eight patients with adult onset asthma were included in this study. The median (range) age of the cohort was 47.6 (26–75) years, 51.7% was atopic and 58% of the cohort was female as shown in Table 1.

Table 1. Baseline characteristics of patients with adult onset asthma ($N = 88$)

Age*	47.6 (11.7)
Gender (Female)%	58
Age of onset (years)*	36.8 (11.9)
Asthma duration (years) [†]	10 (1–31)
Atopy%	51.7
Asthma severity (35)%	
Severe	58
Non-severe	42
Race (Caucasian)%	63.3
BMI [†]	27 (18–45)
ex-smoker%	27.3
Current smoker%	6.8
Packyears [†]	0 (0–26)
ICS dose ($\mu\text{g}/\text{day}$) [†]	1000 (250–2000)
Chronic OCS use%	27.3
Total IgE ($n = 73$) [†]	161 (5–5295)
pbFVC% pred*	107.3 (18.2)
pbFEV ₁ % pred*	89.9 (17.5)
pbFEV ₁ /FVC% pred*	109.0 (14.3)

*mean (SD)

[†]median (range)

BMI, body mass index; ICS, Inhaled corticosteroids fluticasone equivalent; OCS, oral corticosteroids; pb, post-bronchodilator; FVC, Forced Vital Capacity; FEV₁, forced expiratory volume in 1s.

Comparison between characteristics of patients with and without persistent airflow limitation is shown in Table 2. Patients with persistent airflow limitation were significant older, more often male, had a longer asthma duration, were less often atopic, were more often Caucasian, and were more often on chronic oral corticosteroids.

Association between FEV_1/FVC and associated characteristics.

Linear regression analysis showed a negative association for age ($r = -0.43$, $B = -0.19$, $P = < 0.01$), asthma duration ($r = -0.34$, $B = -0.02$, $P = 0.002$), atopy ($r = -0.31$, $B = -0.31$, $P = 0.004$), use of oral corticosteroids ($r = -0.24$, $B = -0.26$, $P = 0.03$), number of packyears ($r = -0.24$, $B = -0.02$, $P = 0.03$), Caucasian race ($r = -0.23$, $B = -0.24$, $P = 0.03$) and a positive association for male gender ($r = 0.37$, $B = 0.37$, $P = < 0.01$) and BMI ($r = 0.21$, $B = 0.02$, $P = 0.05$) with FEV_1/FVC . There was no association with age of onset ($P = 0.2$). Multivariate regression analysis including all significant co-variables showed a negative association between post-bronchodilator FEV_1/FVC and absence of atopy ($r = -0.27$, $B = -0.26$, $P = 0.01$) and a positive for male gender ($r = 0.31$, $B = 0.30$, $P = 0.004$) (Table 3).

Table 2. Comparison of adult onset asthma patients with or without persistent airflow limitation

	pbFEV ₁ / FVC ≥ 0.7 ($n = 45$)	pbFEV ₁ / FVC < 0.7 ($n = 43$)	P-value
Age (years)*	43.2 (11.0)	53.5 (10)	< 0.001
Gender (Female)%	74.0	37.8	< 0.001
Age of onset (years)*	35.4 (11.2)	38.8 (12.7)	0.2
Asthma duration (years) [†]	7.9 (1–30)	13.7 (1–31)	0.03
Atopy%	65.3	35.8	0.004
Asthma severity [35]%			
Severe	40	67.7	0.03
Non-severe	60	32.3	
Race (caucasian)%	54.0	74.4	0.03
BMI [†]	27.5 (19–45)	26.0 (18–42)	0.52
ICS dose ($\mu\text{g}/\text{day}$) [†]	500 (250–2000)	1000 (500–2000)	0.07
OCS use%	18.0	39.5	0.04
(ex)smoker%	26.0	44.7	0.052
Packyears [†]	0.0 (0–25)	0.0 (0–26)	0.08
pbFVC% pred*	102.8 (15.9)	112.7 (19.5)	0.001
pbFEV ₁ % pred*	95.9 (14.9)	80.0 (14.8)	0.003

*mean (SD)

[†]median (range)

BMI, Body mass index; ICS, Inhaled corticosteroids fluticasone equivalent; OCS, oral corticosteroids; pb, post-bronchodilator; FVC, forced vital capacity; FEV₁, Forced expiratory volume in 1s.

Table 3. Odds ratio's for factors potentially associated with FEV₁/FVC < 0.7

	OR	95% Confidence Interval		P-value
		Lower	Upper	
Male gender	10.8	2.61	45.24	0.01
Absence of atopy	5.18	1.32	20.29	0.02
Asthma duration > 10 years	4.16	1.02	16.90	0.05
Age > 47 years	3.21	0.85	12.05	0.08
OCS use	1.58	0.33	7.48	0.57
Caucasian race	1.16	0.30	4.49	0.83
Packyears > 10 years	0.00	0.00	0.00	0.90
BMI > 27	0.04	0.9	1.2	0.52

Odds ratios from multivariate logistic analysis including all significant factors from the univariate analyses.

OR, Odds ratio; OCS, oral corticosteroids.

Logistic regression analysis showed that patients with a lower FEV₁/FVC were 10.8 (CI: 2.6–45.2) times the odds to be male and 5.2 (CI: 1.3–20.3) times the odds to be non-atopic (Table 3). To illustrate the magnitude of the changes in lung function in non-atopic males and the other patients with adult onset asthma we calculated the 'surrogate decline' in FEV₁/FVC for the 2 groups by analysing the relationship between asthma duration and post-bronchodilator FEV₁/FVC ratio, shown as regression lines in Fig. 1.

Discussion

This study shows that in patients with adult onset asthma, male gender and absence of atopy are independently associated with persistent airflow limitation irrespective of age, smoking habits or body mass index. The present study confirms and extends previously published data by showing that non-atopic patients with adult onset asthma are particularly at risk of developing persistent airflow obstruction [9–11]

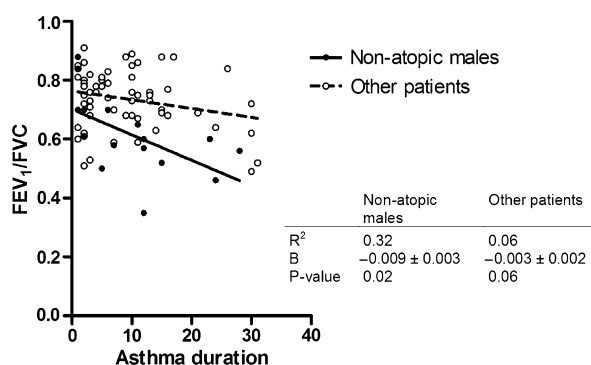


Fig. 1. Relationship between asthma duration (years) and post-bronchodilator FEV₁/FVC in male non-atopic patients vs. the other patients with adult onset asthma.

Although more women presented with adult onset asthma, which confirms previous findings [10], male gender was found to be an independent risk factor for persistent airflow limitation in the adult onset asthma phenotype. Studies investigating the association between gender and decline in lung function have shown inconsistent results. Several studies have shown that young, mostly atopic females are at higher risk for developing more severe asthma [18] and for lung function decline [18, 19], whereas other studies have shown no increased risk for decline in lung function in females [20]. In the TENOR study [21] males with asthma appeared to have an increased risk for persistent airflow limitation, independent of smoking habits and asthma duration. Absence of atopy as a risk factor for persistent airflow limitation has been found by one study showing an accelerated decline in lung function in patients with 'intrinsic' asthma as compared with 'extrinsic' asthma [20]. Our study shows that amongst patients with asthma that starts in adulthood, women are most prevalent, but males are at highest risk of developing persistent airflow limitation.

Obesity was not a risk factor for persistent airflow limitation in our study population. This seems to be in contrast with the results of the SARP study, showing an asthma phenotype characterized by obese women with late onset asthma and low post-bronchodilator FEV₁ [14]. However, in this latter study FEV₁ was analysed as an absolute value whereas in our study we used the ratio of FEV₁ and FVC, which may explain the difference in interpretation. Several studies have shown that obesity is inversely related to the severity of airway inflammation [22–24]. It is therefore plausible that obesity per se does not lead to loss of lung function, which is in agreement with our findings.

The mechanism underlying the association between male gender and persistent airflow limitation is not straightforward. It could be related to a genetic predisposition to develop persistent airflow limitation, or to environmental factors other than smoking. A genetic predisposition is a possibility, but until now there are no data to support in gene polymorphisms that are associated with persistent airflow limitation in males [19]. Environmental factors cannot be entirely excluded either, because we did not take a detailed occupational history from our patients, and thereby cannot judge the influence of potential harmful exposures in the past. However, exposure to occupational agents, including traffic related air pollution has been shown to be associated with increased risk for the development of adult-onset asthma [25–27], and therefore, a common cause of onset of asthma in adulthood and progressive decline in lung function could be a plausible explanation for our findings. Prospective studies taking ongoing occupational and environmental exposures in atopic and

non-atopic males into account are needed to further explore this possibility.

In our study, patients with allergic asthma were found to be less prone to develop persistent airflow limitation. This confirms earlier observations in patients with severe asthma, showing that only those with adult onset non-atopic asthma had lower FEV₁ for a given duration of asthma [9]. It suggests that non-atopic asthma is a different disease with different predisposing factors and causal mechanisms, possibly related to infections with viruses [28], atypical bacteria [9] or fungi. Sensitization to fungi, in particular *Aspergillus fumigatus*, has recently been described to be associated with persistent airflow limitation [29]. Unfortunately, our allergen panel did not include *Aspergillus* spp. Therefore, a proportion of our 'non-atopic' patients might have been monosensitized to *Aspergillus* after all.

Taken together, the findings of our study raise novel hypotheses on mechanisms of airway remodelling that need further investigation.

The present study might have some limitations. First, the cross-sectional design implies that the associations that were found in our study may not represent true predictors of accelerated lung function decline. However, by relating duration of asthma to actual lung function, we calculated a 'surrogate' decline in FEV₁/FVC for the groups as a whole (Fig. 1). The regression lines clearly show a difference between non-atopic males and other subjects with adult onset asthma, suggesting that gender and non-atopic status affect decline in lung function irrespective of asthma duration. Of course, prospective studies have to confirm our findings. Second, assessment of asthma duration was based on self report, and could therefore be influenced by recall bias. Despite careful attempts to avoid this, we cannot exclude this entirely. However, if airway disease was present during childhood, it was apparently not severe enough to be remembered, and therefore probably not severe enough to cause persistent airflow limitation during childhood. In addition, reported year of asthma onset appears to be rather accurate [30], and it is unlikely that any recall bias applies to non-atopic male patients only.

The results of the present study have clinical and research implications. There is an increasing awareness of the heterogeneous character of asthma and its response to treatment. Our results show that amongst patients with asthma, the subgroup of male patients with non-atopic adult onset asthma is more at risk of developing persistent airflow limitation than patients without these characteristics. These patients in particular require close monitoring of lung function and conscientious adjustment of asthma treatment, to prevent the development of persistent airflow limitation [31]. The

challenging question remains whether clinical parameters and lung function measurements are adequate enough to monitor asthma and to prevent persistent airflow limitation, or that cellular [32] or molecular markers [33] of lower airway inflammation are necessary.

In conclusion, male gender and absence of atopy are independently associated with persistent airflow limitation in adult onset asthma irrespective of age, smoking history or body mass index. This implies that patients with newly diagnosed asthma, in particular males without known allergies should be monitored closely and treated carefully [31, 34]. Future research should be directed towards a better understanding of the functional, cellular and molecular processes in the airways of these patients to detect potential causative factors and, eventually, to prevent excessive loss of lung function.

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