Risk factors associated with irreversible airflow limitation in asthma
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Purpose of review
Irreversible airflow limitation develops in some patients with asthma and is related to poorer prognosis. This paper reviews recent literature on natural course, risk factors, and potential mechanisms of persistent airflow limitation in asthma.

Recent findings
The natural course of persistent airflow limitation in asthma is poorly known, but reduced lung function at disease onset and an increased rate of decline during adult life contribute to its development. Risk factors for progressive irreversible airway obstruction in asthma include adult onset, frequent exacerbations, smoking, occupational exposure, ongoing eosinophilic airway inflammation and airway hyperresponsiveness. Polymorphisms of the ADAM33 gene predict excess decline in lung function, in asthma as well as at population level. It is still not clear how different components of airway remodeling affect lung function in asthma. Airway epithelium and airway smooth muscle seem to be highly important, but the interrelationship between persistent airflow limitation, airway inflammation, remodeling and airway hyperresponsiveness has not been clearly defined.

Summary
Whereas several factors have been implicated as being important in the development of fixed airway obstruction in asthma, we are just beginning to explore the different components of airway remodeling and their relevance, deleterious or beneficial, to clinical outcome.

Keywords
airway remodeling, asthma, persistent airflow limitation, risk factor

Introduction
Most patients with asthma have mild to moderate disease that can be easily controlled, with preservation of lung function. However, in a small subset of asthmatic patients even aggressive treatment fails to control the disease. The exact prevalence of these patients with so-called refractory asthma is not known, but may fluctuate around 5–8% of the total asthma population. Severe or refractory asthma is a heterogeneous disorder, involving different phenotypes, one of them being represented by patients with irreversible airflow limitation [1]. In the current review, recent data on the prevalence, risk factors, and potential mechanisms of persistent airflow limitation in asthma will be discussed.

Definition and prevalence
It has been shown that a proportion of adult patients with asthma develop persistent airflow limitation, despite apparently appropriate therapy [2,3]. The airway obstruction in these patients may become indistinguishable from the smoking-related chronic airflow limitation seen in patients with chronic obstructive pulmonary disease (COPD), and is presumed to be due to structural changes in the airways, widely referred to as airway remodeling.

Although persistent airflow limitation in asthma has attained growing attention, a universal definition of this feature has not yet been decided upon. Such a definition should include agreement on repeated postbronchodilator lung function measurements performed in a stable phase of the disease after a period of appropriate treatment. Differences in definition hamper an accurate evaluation of the dimension of this problem. Prevalences are reported varying from 16% in mild asthma [4] up to as high as 49% in a Dutch population of patients with severe asthma [5].

Asthmatic patients with persistent airflow limitation are likely to have a poorer prognosis, since the level of postbronchodilator forced expiratory volume in 1 s (FEV₁) has been shown to predict both asthma-related [6] and overall [7] mortality. Most clinicians will therefore...
try to keep lung function at normal levels in all their patients with asthma, but unfortunately their attempt is not always successful.

**Natural course**
The natural course of persistent airflow limitation in asthma is poorly known. Longitudinal surveys have shown that individuals with asthma experience an accelerated decline in lung function [2], which appears to be related to duration [8] and severity of the disease [9]. However, several studies also showed lower levels of lung function at young age [10–12] (Fig. 1), suggesting that structural changes occur early in the disease already. So, it remains unclear whether lung-function decline in asthma proceeds gradually or is characterized by sudden episodes of deterioration, induced by several different events, for instance exacerbations. In a recent 11-year follow-up study, asthma exacerbation rate significantly predicted an excess decline in FEV\(_1\) of 30 ml/exacerbation [13]. In another study, however, the delayed lung-function recovery following virus-induced asthma exacerbations was not related to increased airway inflammation during the exacerbation [14], leaving the question unanswered as to whether severity of airway inflammation during exacerbations is driving the loss in lung function.

**Risk factors of persistent airflow limitation**
Data about risk factors of persistent airflow limitation in patients with asthma are limited and sometimes contradictory.

**Sex**
In adults, severe asthma is more commonly seen in women, but there are no data showing a greater decline in lung function in women compared with men. Nevertheless, women with asthma seem to have less advantage from inhaled corticosteroid (ICS) treatment than men, both in the short-term [15] as well as the long-term, with less beneficial effect on the decline in lung function [16]. Explanations for differences in response on ICSs between the sexes might be related to female sex hormones, airway geometry, differences in deposition of ICSs, or genetic factors [17].

**Adult onset**
Asthma that starts in adult life might represent a separate clinical entity. In cross-sectional studies, adult-onset asthma appeared to be associated with an increased decline in lung function [5,18,19], in particular in nonatopic patients, possibly related to persistent infection [20]. In addition, the rate of decline of FEV\(_1\) appeared to be increased in subjects with new asthma as compared to subjects with chronic asthma [3].

**Childhood**
Factors in childhood have also to be taken into account. For instance, exposure to perinatal smoking or environmental tobacco smoke [21], severity of childhood asthma, and a subnormal lung function in childhood have all been shown to be related to a low level of FEV\(_1\) in adult life.

**Genetics**
Asthma is a complex disorder in which multiple genetic and environmental factors interact. Several genes have been associated with airway hyperresponsiveness (AHR) and asthma, one of them being a disintegrin and metalloprotease 33 (ADAM33) [22]. Recently, a Dutch follow-up study showed an association of a variant of ADAM33 with excess decline in FEV\(_1\) suggesting its importance not only in the development of asthma but also in disease progression, possibly related to enhanced airway remodeling [23]. ADAM33 mRNA is preferentially expressed in smooth muscle, fibroblast, and myofibroblasts [22], again

![Figure 1 The effects of asthma and cigarette smoking on lung function](image)
Figure 1 The effects of asthma and cigarette smoking on lung function

Data are from the Busselton Health Study and show in (a) males and (b) females height-corrected forced expiratory volume in 1 s (FEV\(_1\)) against age for nonasthmatic nonsmokers (solid line), asthmatic nonsmokers (dotted line), nonasthmatic smokers (long-dashed line) and asthmatic smokers (short-dashed line). Asthma is associated with both a lower level of lung function at 19 years and an increased rate of decline in FEV\(_1\). Reproduced from [11] with permission.
suggesting its functional role in airway remodeling. First evidence for the relevance of this gene expression to physiologic changes has been provided by the observation of an inverse correlation between FEV\(_1\) (expressed as a percentage of the predicted value) and ADAM33 protein levels in bronchoalveolar lavage fluid in patients with mild to severe asthma [24]. The exciting observation of an increased expression of ADAM33 with increasing asthma severity [25] raises the possibility that ADAM33 could be used as a biomarker of asthma severity and chronicity and could play an important role in asthma pathogenesis [26]. In addition to asthma, polymorphic variation in ADAM33 also seem to influence the rate of decline of lung function at population level and in COPD [27]. Moreover, in a prospective birth cohort study, polymorphisms in ADAM33 predicted impaired lung function at the age of 5 years [28]. These latter findings point to a function of ADAM33 relating to lung growth and repair in general rather than being solely associated with asthma.

### Environmental factors

Several environmental factors have been implicated as playing a role in the decline of lung function in patients with asthma.

#### Smoking

Although up to 20% of patients with asthma are current smokers, only recently have the effects of smoking on asthma severity, asthmatic airway inflammation and its response to steroids been subject of research. Cigarette smoking may contribute to the development of severe asthma and has been associated with a more rapid decline in lung function in asthma [2,11]. In a 23-year follow-up study in patients with moderate to severe asthma, treatment with ICSs was associated with a reduction in the decline in FEV\(_1\), but only in men who had smoked fewer than 5 pack years [16]. Remarkably, as mentioned above, in women no effect of ICSs on the decline in lung function was found. So, smoking seems to interfere with the beneficial effect of corticosteroids. Although the mechanism of steroid-insensitivity in smokers is unclear, it might be related to smoking-induced changes in airway inflammation, with a predominance of neutrophils instead of eosinophils [29]. Alternatively, oxidative stress as a result of cigarette smoking – which reduces histone deacetylase-2 (HDAC2) activity – might be crucial [30]. These studies strongly encourage further exploration of the relationship between smoking, airway inflammation, and steroid-sensitivity in asthma, especially severe asthma.

#### Occupation

In occupational asthma, continued exposure to the causative agent is associated with a poor prognosis and more rapid decline in lung function [31]. However, studies on how removal from exposure affects impaired lung function are contradictory, with results varying from no recovery to complete recovery of FEV\(_1\) [31,32]. Yet, early diagnosis of occupational asthma and removal from specific sensitizers is highly important in the prevention of further deterioration of lung function.

#### Infections

Infections may also contribute to the development of irreversible airflow limitation. Many cross-sectional studies have found an association between *Chlamydoma pneumoniae* infection and asthma, sometimes associated with lower levels of FEV\(_1\) [20]. This was confirmed in a longitudinal study where chronic *C. pneumoniae* infection seemed to accelerate the loss of lung function in patients with newly diagnosed nonatopic asthma [33]. In addition, mucosal inflammation, airway fibrosis, and airway wall thickness have been shown to develop in response to *Mycoplasma pulmonis* infection and evidence for persistent adenoviral infection in chronic obstructed airways has been demonstrated in children. Together these data suggest that chronic or recurrent infections with specific respiratory pathogens might be involved in the development of persistent airflow limitation in asthma.

#### Others

Several other factors have been implicated as being important for the development of severe or difficult-to-control asthma, for example sinusitis, obesity, allergy, or compliance with the regime. However, data on their relationship with the rate of decline in lung function are lacking.

#### Disease parameters as predictors of persistent airflow limitation

Early identification of patients at risk for disease progression may lead to better treatment opportunities and better disease outcomes. Disease parameters that have been indicated as potential predictors of an accelerated decline in FEV\(_1\) in asthma include increased bronchodilator reversibility [12,34] and AHR [4,5,12,35]. These factors, however, have been both implicated and rejected as being important for the decline in lung function in diverse asthma populations. Noteworthy is a very recent 2-year follow-up study in children with moderate asthma showing that an AHR-driven asthma treatment, as compared with the conventional symptom-driven strategy, prevented long-term worsening of prebronchodilator FEV\(_1\), suggesting a preventive or even therapeutic effect of ICSs on airway remodeling [36].

Several studies have reported an association between ongoing eosinophilic airway inflammation and persistent airflow limitation [5,8,37], as well as parameters of airway remodeling [18]. In addition, preliminary data of a 5-year
follow-up study in severe refractory asthma also showed that persistently high levels of nitric oxide in exhaled air might predict a decline in lung function [38]. These findings suggest that refractory eosinophilic airway inflammation might be the reflection of a clinical asthma phenotype exhibiting more severe disease. However, treatment strategies based on parameters of eosinophilic airway inflammation [39,40] resulted in more controlled asthma, but no improvement in lung function. Although the eosinophil in airway inflammation in chronic asthma has been extensively studied, its definite role as recruiter, effector, or bystander remains obscure.

**Mechanisms of persistent airflow limitation**

The nature of persistent airflow limitation in asthma is still unknown, but is presumed to be due to structural changes in the airways and perhaps parenchyma [41**]. Distinct remodeling responses in asthmatic airways have been defined, including epithelial denudation, subepithelial fibrosis, increased airway smooth muscle (ASM) mass, hyperplasia of mucous glands and goblet cells, angiogenesis, and alterations in extracellular matrix components [42] (Fig. 2). Airway remodeling is assumed to result in AHR, persistent airflow limitation and progressive loss of lung function. However, the precise sequence of events that take place during the remodeling process and the mechanisms regulating these changes remain poorly understood. Although chronic inflammation is thought to initiate and perpetuate cycles of tissue injury and repair in asthma, remodeling may also occur in parallel with or actually precede airway inflammation [43**]. So far, the interrelationship between airway inflammation, remodeling, and AHR and their role in the development of persistent airflow limitation in asthma have not been clearly defined.

Unfortunately, data on asthma pathology in relation to disease severity or abnormal physiology are still limited, in particular with respect to the development of persistent airflow limitation [41**]. It has been shown that, despite similar fixed airflow obstruction, patients with asthma have distinct pathologic characteristics compared with COPD patients, with increases in airway eosinophilia and reticular basement-membrane thickness [44], the latter being proposed as a specific hallmark of severe asthma [45]. However, these aspects did not prove to be predictive of the decline in lung function in a longitudinal study in asthma [46]. A striking feature of asthmatic airways is the increased bulk of ASM cells, most marked in patients who died of asthma. The exact role of the ASM cell in the pathogenesis of asthma is not defined yet [47], but ASM mass has been proposed to be highly important in airway remodeling and subsequent airflow limitation [48,49]. Other factors, such as elastic recoil or airway distensibility may also contribute to airflow limitation. Airway distensibility was shown to be reduced in patients with asthma as compared with normal controls, unrelated to elastic recoil or bronchomotor tone [50]. In fatal asthma, abnormal alveolar attachments with decreased elastic fibre content were observed in the small airways and peribronchial alveoli, probably pathologically explaining the reduction in airway distensibility observed in patients with asthma [51].

Finally, it is unclear whether remodeling is always detrimental or also plays a protective role [41**]. From a clinical point of view it could be argued that different patterns of asthma may occur within one patient over time. Several asthma patients with persistent airflow limitation report a history of frequent, unpredictable, serious asthma attacks in the early years of their disease, probably related to...
excessive airway narrowing, whereas later on they experience a more stable disability with exertional dyspnea but without distressing attacks. It might be hypothesized that within these patients remodeling changes have occurred, leading to thickening of the airway wall, which protects them from symptoms or even fatalities due to excessive airway narrowing [52]. So, more studies are needed to investigate the relative importance of remodeling aspects as being beneficial or deleterious.

**Therapy**

Treatment of severe asthma and, in particular, persistent airflow limitation, is difficult. Although a beneficial effect of ICSs on lung-function decline has been observed in several studies [10,16,36*,53*], there is considerable variability in treatment response. In severe asthma, a reduced responsiveness to corticosteroids is common. Ongoing inflammation might occur in regions of the airways that are not or are hardly accessible to ICSs, such as the small airways [54] or upper airways including the paranasal sinuses. In individual patients, treatment of nasal polyps may lead to impressive increases in FEV\textsubscript{1} and residual inflammation can be overcome by systemic anti-inflammatory treatment resulting in improvement in lung function and airway mechanics [55,56].

In addition, the relative steroid insensitivity might be related to abnormalities in glucocorticoid receptor signaling pathways or impaired HDAC2 recruitment, as is observed in smokers and patients with severe asthma [57*], with subsequent inadequate suppression of inflammatory genes [58*]. Interestingly, theophylline, by activating HDAC, may reverse this corticosteroid resistance.

Finally, the absence of a beneficial effect of treatment might be explained by airway remodeling processes that are, at least partly, insensitive to corticosteroids. The limited knowledge about how corticosteroids and other currently available drugs affect individual components of airway remodeling was very recently reviewed by Mauad and colleagues [59**]. They conclude that collaborative efforts need to be done to explore the regulation and function of the different components of airway remodeling and their relevance for the clinical severity and progression of asthma.

If ASM mass plays an important role in the development of irreversible airflow limitation in asthma [48*], bronchial thermoplasty, a therapy designed to remove ASM bundles and decrease ASM contractility, might be very promising. In this procedure, controlled thermal energy is delivered to the central airway walls through a bronroscope. In the first, uncontrolled study, bronchial thermoplasty resulted in a reduction in AHR, associated with improvements in daily symptoms and modestly increased flow rates: effects that persisted for 2 years without serious complications [60]. However, a recent randomized, controlled study in 112 patients with moderate to severe asthma reported improvements in the rate of mild exacerbations, symptoms, and use of rescue medication, but no effect on AHR or FEV\textsubscript{1} after 1 year of follow-up [61**]. Definitely, more studies are needed to assess histological and clinical outcomes of this intriguing new treatment modality.

**Conclusion**

Several interesting studies have been published during the last year on the risk factors of and mechanisms underlying the development of irreversible airway obstruction in asthma. Both a reduction in lung function at young age as well as an increased rate of lung-function decline during adult life seem to contribute to the development of persistent airflow limitation. Still, longitudinal studies are needed to understand whether lung-function decline in asthma is a gradually ongoing process or is characterized by episodes of sudden deterioration.

Some individuals seem to be genetically predisposed to a more rapid decline in lung function, probably related to ADAM33 expression. Several risk factors for the development of irreversible airway obstruction in asthma have been indicated, including adult onset of disease, frequent exacerbations, occupational exposure, and AHR.

A relationship between persistent airflow limitation and structural changes in the airways seems to be likely, but it still remains to be established which components of airway remodeling are relevant, deleterious or beneficial to clinical severity and decline in lung function. The search for known and novel therapies that can directly target individual components of the remodeling process and hopefully lead to an improvement in the treatment of airflow limitation and the prognosis in severe asthma will be made.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:• of special interest** of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 94).

This study describes the comprehensive phenotypic characterization performed in a large cohort of patients with severe asthma in comparison with asthma that is not severe. Parameters associated with persistent airflow obstruction in chronic severe asthma. Eur Respir J 2004; 24:122–128.


Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict reduced lung function decline in subjects with asthma with elevated total IgE. J Allergy Clin Immunol 2007; 119:405–413.


This study identifies the children at highest risk to be undertreated when guided by a symptom-driven strategy and shows the benefits on lung function to be accessible when using a treatment strategy guided by airway hyperresponsiveness.


This is the first meta-analysis evaluating the efficacy of tailoring asthma interventions based on sputum analysis in comparison with clinical symptoms for asthma in children and adults. Cochrane Database Syst Rev 2007; 2:CD005603.

This very comprehensive review examines the relationship between airway remodeling in asthma and COPD with respect to symptoms, abnormal lung function, airway hyperresponsiveness and decline in lung function.


This study shows the relationship between levels of ADAM33 protein in bronchoalveolar lavage fluids and severity of airway obstruction.


This review links new pathophysiological concepts of asthma with different treatment modalities.


This study identifies the children at highest risk to be undertreated when guided by a symptom-driven strategy and shows the benefits on lung function to be accessible when using a treatment strategy guided by airway hyperresponsiveness.


This is the first controlled study of an intriguing new treatment modality in patients with moderate to severe asthma.