REVIEW

Adult-onset asthma: is it really different?

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ABSTRACT: Asthma that starts in adulthood differs from childhood-onset asthma in that it is often non-atopic, more severe and associated with a faster decline in lung function.

Understanding of the underlying mechanism of adult-onset asthma and identification of specific phenotypes may further our understanding of pathophysiology and treatment response, leading to better targeting of both existing and new approaches for personalised management. Pivotal studies in past years have led to sustained progress in many areas, ranging from risk factors for development, identification of different phenotypes, and introduction of new therapies.

This review highlights and discusses literature on adult-onset asthma, with special focus on the differences from childhood-onset asthma, risk factors for development, phenotypes of adult-onset asthma and new approaches for personalised management.

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Asthma is a heterogeneous disorder, in which age of onset seems to play an important role. Although the vast majority of asthma publications in the literature are about allergic asthma starting in childhood, the incidence among adults is as high as 12 cases per 1,000 person-years [1, 2]. Recently, clustering methods to group together patients with similar clinical characteristics led to the identification of different asthma phenotypes [3, 4]. In the Severe Asthma Research Program, for example, five clusters were identified using 34 clinical variables [4]. 80% of the subjects could be assigned to a cluster using only three variables: baseline forced expiratory volume in 1 s (FEV_1) (before bronchodilation); maximum FEV_1 after bronchodilation; and age of onset of asthma [4]. One of these phenotypes (cluster 3), consisting exclusively of patients with adult-onset asthma, was characterised by a preponderance of obese females, but also, the most severe asthma phenotype (cluster 5), consisted mainly of patients with adult onset disease. This was the cluster with the most severe airflow limitation at baseline and residual airflow limitation after bronchodilation. This finding fits with earlier observations that adult-onset asthma is associated with a more rapid decline in lung function [5, 6]. However, despite ample evidence that asthma can develop in patients who never had any relevant respiratory symptoms as a child, there still exists some controversy about the existence of adult onset asthma as a separate entity [7].

This narrative review focuses on asthma that starts in adulthood and provides an overview of recent studies regarding differences between childhood-onset asthma, risk factors for development, different phenotypes and new approaches for personalised management.

HISTORICAL PERSPECTIVE

More than half a century ago, adult-onset asthma was already recognised as a separate subtype of asthma by several renowned physicians. It started in 1940 when RACKEMANN [8] distinguished ''extrinsic'' or allergic asthma from ''intrinsic'' or nonallergic asthma. He noticed that patients with intrinsic asthma typically had a late onset and a more severe clinical course of the disease than patients with extrinsic asthma. In addition, females were more often affected and symptoms often started following a respiratory infection. The terminology ''extrinsic'' and ''intrinsic'' asthma was replaced by ''allergic'' and ''nonallergic'' asthma in an official European Academy of Allergy and Clinical Immunology position statement in 2001 [9]. Although several studies could not find convincing differences between allergic and nonallergic asthma regarding inflammation [10], the clinical phenotypes of allergic and nonallergic asthma were found to be highly distinct [11]. In 2004, instead of reintroducing the term ''intrinsic'' asthma, MIRANDA et al. [12] suggested differentiating asthma on the basis of age at onset (early versus late onset) and presence of airway eosinophilia. Interestingly, adult-onset eosinophilic asthma was also identified as a separate asthma phenotype in a large asthma cohort in the UK in 2008 [3]. Thus, the differentiation between

childhood-onset asthma and adult-onset asthma is not new, and now that the importance of phenotyping of asthma is increasingly recognised, adult-onset asthma seems to have been ''rediscovered''.

CHILDHOOD-ONSET ASTHMA

Before discussing adult-onset asthma in more detail, we will briefly discuss childhood-onset asthma. The vast majority of asthma starts in early childhood. About 95% of asthma patients have their first episode before the age of 6 years [2]. Young males are consistently reported to have more prevalent wheeze and asthma than young females [13]. However, at the age of 11 years, the prevalence of asthma in young males (7.7%) and young females (7.4%) is similar and after 16 years of age the disease is more common in females (6.2%) than in males (4.3%) [14].

The main risk factors associated with childhood-onset asthma are genetic predisposition, and a family history of allergy and asthma, viral respiratory infections, bacterial colonisation, allergic sensitisation and tobacco exposure [15].

A parental history of atopic diseases has been long recognised to be a strong risk factor for asthma in children [16]. Although genetic studies have showed that asthma is genetically heterogeneous, genome-wide association studies have identified a novel region containing *ORMDL3* at chromosome 17q21 that is strongly associated with childhood-onset asthma and significantly linked to *ORMDL3* transcript abundance [17]. These results have been successfully replicated in other childhood-onset asthma cohorts [18]. Thus, genetic predisposition seems to play a major role in the onset of asthma in early childhood.

Large, prospective follow-up studies have shown that early and persistent sensitisations to perennial allergens are a strong risk factor for asthma in childhood [19]. Furthermore, childhood-onset asthma is typically associated with other atopic diseases, including allergic rhinitis and atopic dermatitis [20]. Even at adult age the amounts of total and specific immunoglobulin (Ig)E are higher in childhood-onset asthma than in adult-onset asthma [12]. Thus, atopy and allergy seem to be closely linked to asthma starting in childhood.

Viral infections are another risk factor for developing early childhood asthma [21]. Long-term follow-up studies have shown that wheezy episodes associated with rhinovirus infection are a strong predictor of asthma by the age of 6 years [22, 23]. However, studies have also reported that children with early wheezy symptoms and a predisposition to asthma and atopy are at increased risk of lower respiratory infection [24–26]. Therefore, the direction of causality of viral infection and the development of asthma is still unclear.

Bacterial colonisation may play a role in the development of childhood-onset asthma. A study showed that neonates colonised in the hypopharyngeal region with *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*, or with a combination of these organisms, are at increased risk for recurrent wheeze and asthma early in life [27]. Of interest, some aspects in early life appear to protect against the development of asthma. In children, contact with livestock and being born and raised on a farm reduces the risk of asthma in adulthood [28–30]. Similar to viruses, it is unknown whether the bacterial colonisation acts as the environmental trigger in genetically predisposed persons or whether this colonisation is merely a marker of the underlying genetic asthmatic constitution.

Pre-natal and post-natal smoke exposure has been linked to asthma and other wheezy disorders, particularly in the first years of life [31]. Also, exposure to traffic-related air pollution may cause asthma in children [32].

With respect to response to treatment, daily inhaled corticosteroids are highly effective in improving asthma control in childhood-onset allergic asthma as demonstrated by one systematic review [33] and another meta-analysis [34]. However, the effect of inhaled corticosteroids is less evident among children with recurrent wheezy episodes not diagnosed as asthma [34].

Taken together, childhood-onset asthma typically runs in families, is associated with allergy in most patients, and has a good prognosis with a satisfactory response to medical treatment. The role of bacteria and viruses in childhood-onset asthma is still unclear.

ADULT-ONSET ASTHMA

Adult-onset, or late-onset, asthma is considered when asthma symptoms represent for the first time during adulthood. Several definitions of adult-onset asthma can be found in the literature. The age at diagnosis determining the term late-onset asthma varies from 12 years of age [12] to ⩾65 years of age [35]. Most studies about asthmatic symptoms earlier in life are based on questionnaires. The possibility of recall bias is a frequently made comment [7]. For example, in the Tucson study, a relationship was found between asthma manifesting at age 40 years and persistent wheezing at age 6 years (presumably long forgotten about by the family) [36]. However, a study performed by TOREN et al. [37] showed that the reported age of asthma onset in adults is quite accurate.

In contrast to childhood-onset asthma, less is known about the prevalence and factors associated with adult-onset asthma. Studies have shown that it mainly effects females [8], has a low remission rate [38] and is less often associated with allergy and atopic diseases [39]. In addition, many patients with adult-onset asthma have a poor prognosis [38], with a faster decline in lung function [6, 40] and more severe persistent airflow limitation [41]. New-onset adult severe asthmatics have compromised lung function even if they have asthma of short duration [42], suggesting that significant loss of lung function occurs at or soon after the initial diagnosis. Still, adult-onset asthma is largely under investigated and far from completely understood.

EPIDEMIOLOGY OF ADULT-ONSET ASTHMA

During the past 20 years, overall asthma prevalence has increased by 38%, in parallel with a similar increase in asthma-like symptoms and allergic rhinitis [43]. Although prevalence rates have been studied more extensively in children, most studies confirm a real increase in asthma prevalence among adults as well. The estimated adult incidence of asthma from pooled general population studies appears to be 4.6 cases per 1,000 person-years in females and 3.6 in males, and there is a trend towards a higher incidence with age [1]. The 5-year age- and sex-specific incidence of newly diagnosed asthma in adults ⩾65 years of age is estimated to be 103 per 100,000 people,

where two thirds of asthma deaths occur in people aged ⩾65 years [44]. Only one study investigated the long-term outcome of adult-onset asthma and changes in asthma severity over time [45]. In this study, 95% of subjects still had an active asthma 5 years after diagnosis, and half of them had moderate-to-severe disease. Due to a relatively low remission rate [45], the prevalence of asthma in older adults (⩾65 years of age) has been reported to be as high as 10%, where females predominate the age group of 64–75 years [35]. Still, these studies probably underestimate the true prevalence and incidence of asthma [46].

RISK FACTORS, TRIGGERS AND CO-MORBID CONDITIONS ASSOCIATED WITH INCIDENT ASTHMA IN ADULTS

The role of genetic predisposition in adult-onset asthma is less clear than in atopic childhood-onset asthma. In adult-onset asthma, a family history of asthma is often lacking and atopy is not more common than in the general population. One study in a Chinese Han population found an association between genetic variants in chromosome 17q21 and adult-onset asthma, similar to that observed in childhood asthma [17]. Although this study was flawed by the possibility of recall bias in self-reported age of asthma onset, it may point towards similar mechanisms in childhood- and adult-onset asthma, including exposure to environmental triggers such as environmental pollution or infection.

It is difficult to know exactly whether a condition is causally related or just a comorbid condition or a trigger factor. For example, obesity is a comorbid condition but is also a trigger factor for new asthma onset [47]. In the literature, several exogenous and endogenous trigger factors have been associated with the development of asthma in adulthood which will be discussed in the following sections.

Asthma related to sensitising or irritant exposure in the workplace

Occupational asthma has become the most common type of adult-onset asthma in many industrialised countries, having been implicated in 9–15% of adult-onset asthma [48]. Two types of occupational asthma have been defined: sensitiser induced (which can be IgE or non-IgE mediated) and irritant induced (*i.e.* reactive airway syndrome).

Sensitiser-induced asthma is a subtype of occupational asthma typically presenting with a latent period of exposure, followed by the onset of clinical disease. After sensitisation, airway reactions develop from levels of exposure to the sensitising agents that were tolerated before sensitisation. Although the mechanism causing occupational asthma from some sensitisers has been demonstrated to have an immunological basis (IgE-mediated or otherwise), the mechanisms for some suspected sensitisers are yet to be defined. There are more than 250 agents that have been adequately documented to cause sensitiser-induced asthma [48]. Some sensitising agents have differential effects on asthma onset depending on the dose. For example, in farmers, exposure to low-dose endotoxins and fungal spores appears to have a protective effect on the development of atopic asthma but may induce non-atopic adult-onset asthma at higher doses [49].

Irritant-induced asthma is a subtype of occupational asthma without immunological sensitisation and includes the typical reactive airways dysfunction syndrome and a more gradual form called not-so-sudden irritant-induced asthma, when asthma follows repeated low-dose exposure to irritants [48]. The World Trade Center tragedy brought new insight in the understanding of irritant-induced asthma, suggesting that it can exhibit a prolonged interval between exposure and recognition of clinical symptoms and disease. A comprehensive review of irritant-induced asthma has been published recently [50].

Environmental pollutants

Active and passive cigarette smoking is a risk factor for adult-onset asthma that is not to be underestimated [51]. A prospective study in patients with allergic rhinitis showed that smoking was significantly related to the risk of incident asthma, with the odds ratio (OR) being 2.67 (95% CI 1.70–4.19) for univariate and 2.98 (95% CI 1.81–4.92) for multivariate analyses. A clear dose–response association for exposure to tobacco and risk of new-onset asthma was observed in the multivariate analyses: those with 1–10 pack-years had an OR of 2.05 (95% CI 0.99–4.27), those with 11–20 pack-years had an OR of 3.71 (95% CI 1.77–7.78), and those with ⩾21 pack-years had an OR of 5.05 (95% CI 1.93–13.20) compared with never-smokers [52]. It is likely that persistent exposure to airborne allergens and cigarette smoking in combination have an additive or synergistic effect.

Female sex hormones

Female sex hormones are associated with adult-onset asthma [53]. Recently, sex differences in asthma prevalence were investigated in 9,091 males and females randomly selected from the general population and followed for 8–10 years [54]. At baseline, asthma was 20% more frequent in females than in males over the age of 35 years. The follow-up of subjects without asthma at baseline showed a higher incidence of asthma in females than in males (hazard ratio (HR) 1.94, 95% CI 1.40–2.68), which was not explained by differences in smoking, obesity or lung function. More than 60% of females and 30% of males with new-onset asthma were non-atopic. The incidence of non-allergic asthma was higher in females than in males throughout all the reproductive years (HR 3.51, 95% CI 2.21–5.58), whereas no sex difference was observed for the incidence of allergic asthma. In addition, parity has been shown to be associated with prevalence of asthma from 8% for one birth to 29% for four or more births. Alternatively, asthma prevalence decreases with the number of years of oral contraceptive pill use [55]. Likewise, there is evidence that the incidence of asthma is decreased after menopause [56], whereas hormone replacement therapy in post-menopausal females is associated with an increased risk of asthma onset, particularly in never-smokers [57]. Finally, clear associations between puberty and increased incidence of asthma in young females, and a higher remission rate in young males have been described in several reports [14, 58, 59]. These findings suggest that endogenous and exogenous hormonal influences play a role in the genesis of adult-onset asthma in females. Still, associations between asthma and sex hormones remain complex [60, 61].

Upper airway diseases

Rhinitis is a well-recognised risk factor for the onset of asthma in adulthood [39, 62, 63]. A role of chronic rhinosinusitis and nasal polyposis in the development of asthma in adulthood has also been suggested, but is less clear. Recently, a large population-based study found a strong association between chronic rhinosinusitis and asthma, where chronic rhinosinusitis in the absence of nasal allergies was positively associated with adult-onset asthma [64]. In turn, adult-onset asthma has been associated with the development of nasal polyps and aspirin intolerance [65]. The mechanisms underlying the relationship between nasal polyposis and adult-onset asthma are poorly understood. Recently, BACHERT et al. [66] found that the presence of IgE against Staphylococcus aureus enterotoxin was associated with more severe upper airways inflammation, as well as comorbid asthma suggesting a causal role for these bacteria in chronic upper and lower airways disease.

Aspirin and paracetamol intake

Among individuals with existing asthma, aspirin can acutely precipitate bronchospasm in the subset of patients with aspirin-intolerant asthma. In contrast, long-term intake of 100 mg aspirin has been shown to reduce the relative risk of a newly reported diagnosis of asthma in healthy females [67, 68]. Thus, in individuals without asthma, aspirin might reduce the risk of developing asthma via cyclo-oxygenase (COX)-dependent and COX-independent pathways.

On the contrary, the use of paracetamol represents a putative risk factor for the development of asthma [69–71]. Glutathione depletion in the airways and increased oxidative stress may be the mechanism underlying the link between paracetamol use and asthma development.

Respiratory infections

The occurrence of acute lower respiratory infections is strongly associated with the risk of new adult-onset asthma [72]. The link between respiratory infections and the development of asthma in adulthood has been proposed for many decades [73], although it is still unclear how respiratory infections might induce asthma. Age-related altered antigen presentation and decreased specific antibody responses may lead to subtle immune deficiencies that may allow respiratory infections to provoke injury to the airways. This, in turn, may set up a vicious cycle of an ongoing inflammatory process leading to asthma [74]. Another explanation is that respiratory pathogens may act as triggers of asthma onset to other factors, such as environmental exposures.

Of interest, certain early exposures seem to decrease the risk of asthma in adulthood. A recent study showed that an increased load of common infections in childhood protected against incident asthma risk in adult life, whereas pertussis and measles were associated with an increased risk of incident asthma later in life [75].

Obesity

Obesity is a risk factor for the development of asthma in adulthood [76]. The incidence of asthma is increased by 50% in overweight and obese patients [76]. Recently, two observational studies [77, 78] showed that abdominal obesity, assessed by waist circumference, was independently associated with increased prevalence and incidence of asthma. How obesity contributes to asthma development is complicated and there is no single mechanism that supports this association. However, in the literature, several mechanisms have been implicated [79]. First, asthma in obesity is associated with increased adipokines, such as leptin, in visceral adipose tissue. Leptin and other adipokines may have direct effects on the airway rather than enhancing airway inflammation to induce asthma in obesity [80]. Secondly, mechanical factors might be responsible. Obese patients breathe at a lower than normal functional residual capacity which is associated with the risk of both expiratory flow limitation and airway closure and airway hyperresponsiveness. Thus obesity has effects on lung function that can reduce respiratory well-being, even in the absence of specific respiratory disease, and may also exaggerate the effects of existing airway disease [81]. Finally, obesity may increase the risk for asthma onset through its effects on other disease aggravators; for example, sleep-disordered breathing and gastro-oesophageal reflux disease [79]. Since the prevalence of obesity is rapidly increasing, asthma associated with this condition will become a real epidemic in future decades.

Stressful life events

Stress is increasingly recognised as a risk factor for incident asthma. High versus low stress was found to be associated with a two- to three-fold higher risk of self-reported asthma incidence in several longitudinal population studies [82–85]. Of the 10 most stressful life events, the illness of a family member, marital problems, divorce or separation, and conflicts with a supervisor were most strongly associated with the onset of asthma [82]. Moreover, a study performed by ENG et al. [86] investigated the association between work-related stress and asthma. Participants with very or extremely stressful jobs were 50% more likely to have adult-onset asthma (OR 1.50, 95% CI 1.05–2.15). This association was evident for both sexes and was not explained by either occupation, age, body mass index or smoking; although the results did differ by smoking status. Stress has been shown to modulate and activate a number of biological pathways that may be involved in asthma pathophysiology [87, 88]. It can modulate inflammatory processes via the release of hormones and neuropetides, which have the potential to interact with immune cells. Not only does stress activate the hypothalamic–pituitart–adrenal axis, with subsequent production of cortisol and adrenalin, it may also shift the immune response from an antibacterial T-helper (Th)1 response toward a humoral Th2 response. In this way, stress may alter the psychological, immunological and endocrine systems, and contribute to the onset of asthma.

PHENOTYPES OF ADULT-ONSET ASTHMA

There are numerous classifications of asthma based on proposed cause (allergic, nonallergic and occupational), pathology (eosinophilic and non-eosinophilic), severity and physiological parameters [89]. To provide a more integrated classification of asthma, taking into account multidimensional parameters, statistical methods such as unsupervised cluster analysis have been used [90]. These clustering techniques have identified several asthma phenotypes distinguished by symptoms and eosinophilic inflammation [3] and by lung function and age of onset [4].

Adult-onset obese female preponderant asthma

This adult-onset asthma phenotype was identified by two independent cluster analysis studies. It was characterised by a predominance of female patients with a higher body mass index (BMI), less atopy and a high symptom expression, in the absence of eosinophilic airway inflammation [3, 4]. Despite a shorter duration of asthma, patients in this group had decreased lung function, often reported complicated medical regimens and many of them received regular systemic corticosteroids [4]. These patients' symptoms and healthcare utilisation appeared out of proportion to their degree of airflow obstruction. This suggests an important relationship between obesity, level of symptoms and healthcare utilisation in this adult-onset asthma phenotype.

As described previously, obesity is associated with changes in immune cell function and airway pathology, which are likely to lead to new onset disease in individuals without pre-existing asthma [91]. Patients with childhood-onset asthma are less affected by obesity, indicating that obesity is primarily associated with the adult-onset asthma phenotype [92]. A recent study confirmed that obese patients have more severe clinical expression of their asthma [93]. In this study, greater asthma medication requirements, steroid-burst therapy and short-acting β_2-agonist use per day were found in these obese patients with severe asthma. In addition, increased gastro-oesophageal reflux disease and increased proton-pump inhibitor use were seen in the obese group. Given the fact that obese patients with severe asthma do not exhibit more severe eosinophilic airway inflammation [94] than those without obesity, the primary treatment should consist of weight reduction, rather than stepping up anti-inflammatory treatment [95].

Adult-onset nonatopic, inflammation-predominant phenotype with fixed airflow limitation

The most severe adult-onset asthma phenotype that was identified by one of the cluster analyses comprised mainly of males with few daily symptoms and active eosinophilic airway inflammation [3]. Persistent sputum eosinophilia, the key characteristics of this phenotype, has important clinical implications since it is associated with frequent asthma exacerbations [96], persistent airflow limitation [41] and oral corticosteroid dependence [97]. Moreover, this phenotype is associated with chronic rhinosinusitis, nasal polyps [98] and aspirin sensitivity [99]. The eosinophilic asthma phenotype with severe sinus disease has also been shown to have more air trapping and reduced diffusion capacity, suggestive of more peripheral airway inflammation [100].

Since eosinophilis seem to play a key role in the pathophysiology of this adult-onset asthma phenotype, drugs that inhibit recruitment and activation of eosinophilis might be particularly efficacious. Recent large-scale studies with anti-interleukin (IL)-5 therapy suggest that this is indeed the case [101].

Adult-onset mild asthma

In addition to the two phenotypes with severe adult-onset asthma, a recent cluster analysis in 724 Korean patients with asthma also identified a milder adult-onset asthma phenotype [102]. This cluster covered one-third of the total asthma population and had the best lung function. 74% of these patients were female, 54% were atopic, none of them had a significant smoking history, BMI in these patients was low, and there were no other characteristics that distinguished them from the other clusters. As in this study there were no data on asthma duration, this milder asthma phenotype might have represented recent or even transient cases of adult-onset asthma. Apparently, adult-onset asthma is not always severe and can have a milder clinical course and prognosis as well.

Smoking-related asthma

In the same Korean cluster analysis study, a separate phenotype of adult-onset smoking-related asthma was identified [102]. This cluster mainly consisted of male patients with a mean age of asthma onset of 46 years. About 66% of the patients were non-atopic and this group had a relatively well preserved FEV1. Although cigarette smoking is known to increase the risk of incident asthma [52], the smoking asthma phenotype has not been identified in other cluster analysis studies to date. This is probably due to the fact that smokers and ex-smokers with a smoking history of >5 pack-years were not included in these studies. It would be worthwhile to redo these cluster analyses after inclusion of smoking asthmatics and by taking markers of airway inflammation into account.

In summary, the identification of specific, clinically well-recognised adult-onset asthma phenotypes by cluster analysis is the first step to better understand the mechanisms of asthma development in adulthood. The next step will be to refine the characteristics of these phenotypes adding well-known aetiological factors such as occupational exposure, nasal polyposis and aspirin sensitivity into the models. Furthermore, the stability of the asthma phenotypes has to be further explored [103]. In children, the clinical expression of the disease varies over time and novel wheezing phenotypes have been identified on the basis of longitudinal follow-up data [104]. Whether specific longitudinal phenotypic patterns also exist in adult-onset asthma is currently unknown.

PHENOTYPES VERSUS "ENDOTYPES"

While phenotypes are usually clinically relevant in terms of presentation, triggers and treatment response, they do not necessarily relate to or give any insight into the underlying disease processes. An endotype is a subtype of a disease that is defined by a distinct functional or pathobiological mechanism [105]. Until now, such endotypes have not been identified, although some investigators have proposed a few asthma endotypes on the basis of their clinical phenotypes and putative pathophysiology [106]. However, at present, there is no evidence that these proposed endotypes are defined by specific molecular pathways. More advanced approaches, such as systems biology relying on multiple disciplines including genomic, proteomic and metabolomics, are therefore needed to understand mechanisms and identify the real asthma endotypes.

Phenotype-driven treatment of adult-onset asthma

In childhood-onset allergic asthma, daily therapy with inhaled corticosteroids combined with long-acting β_2-agonists is effective in improving asthma control in the vast majority of patients [33]. In adult-onset asthma, a large proportion of patients respond poorly to corticosteroid therapy [3, 4]. Given the heterogeneity of causative factors, this group of patients might benefit from a more targeted, phenotype-driven treatment [107].

For example, for some patients, prevention of exposure to the proposed cause (occupational sensitisers and smoking) is the best treatment option. In other patients, discontinuation of specific drugs such as hormonal preparations might be most beneficial. In addition, with regard to novel treatments, there are now exciting possibilities for a more targeted, phenotypic approach.

Omalizumab
Omalizumab, a humanised antibody against IgE, was originally designed as a therapeutic option for severe allergic asthma. This drug has been shown to effectively reduce asthma exacerbations, emergency visits for asthma and hospitalisation admissions among children and adults with allergic asthma [108–112]. Recent studies, however, also showed a positive effect on non-allergic asthma [113, 114] and on nasal polyps [113], suggesting that this drug might be effective in specific subtypes of adult-onset asthma as well. However, before the indication of omalizumab can be broadened, further large prospective clinical trials need to be conducted.

Mepolizumab
A novel, promising strategy to treat patients with adult-onset asthma who have persistent eosinophilia is to target the eosinophil itself. Mepolizumab, a humanised monoclonal antibody against IL-5, selectively and effectively inhibits eosinophilic airway inflammation. Recently, PAVORD et al. [101] provided evidence for mepolizumab as an effective, well tolerated and safe treatment that reduces the risk of asthma exacerbations in patients with severe eosinophilic asthma. A previous smaller scale study showed that mepolizumab allows a reduction of the oral corticosteroid dose in patients with corticosteroid-dependent eosinophilic asthma. Interestingly, a recent study showed that mepolizumab is also effective in the treatment of severe nasal polyposis [115]. All these studies are very promising for patients with severe adult onset asthma characterised by eosinophilic inflammation for whom no effective drugs are available without significant adverse effects.

Lebrikizumab
Another drug that might be effective in severe adult-onset eosinophilic asthma is lebrikizumab. Lebrikizumab is a humanised monoclonal antibody that binds to IL-13. A recent study reported the effects of lebrikizumab in a cohort of patients with moderate asthma who were symptomatic despite taking inhaled glucosteroids and, in most cases, an additional long-acting β-agonist [116]. Although there was an effect on airflow limitation in all the patients who were treated with lebrikizumab, the effect was greater in patients who had circulating levels of periostin above the median and exhibited the high Th2 phenotype than those without this phenotype. These data confirm the proof of concept that asthma therapy can be targeted to specific asthma phenotypes.

Bronchial thermoplasty
Bronchial thermoplasty is a bronchoscopic procedure that is approved for the treatment of severe asthma. In non-obese patients with adult-onset non-eosinophilic severe asthma, this might be one of the only effective therapeutic options. During this procedure, controlled thermal energy is applied to the airway wall to decrease the amount of smooth muscle [117].

Studies suggest that this intervention could improve lung function, airways hyperresponsiveness, asthma-related quality of life and symptom scores, and reduce exacerbations and hospitalisations [118–120]. Thermoplasty has been proven safe in the long run, without long-term complications and maintenance of stable lung function [121]. Therefore, thermoplasty might be an option for some patients with adult-onset asthma, but this has to be confirmed in large-scale prospective studies.

Bariatric surgery
For the obese adult non-eosinophilic asthma phenotype, there is currently only one treatment option, which is drastic weight reduction. A study using bariatric surgery showed that this treatment can markedly improve asthma control [95]. Bariatric surgery was performed in 23 asthmatic and 21 nonasthmatic patients. After surgery, asthmatic patients experienced improvements in asthma control and asthma quality of life. Moreover, airway hyperresponsiveness to methacholine improved in obese asthmatic patients with normal serum IgE levels [95]. Several large trials are now underway to confirm the beneficial effect of bariatric surgery on asthma control and airway hyperresponsiveness.

CONCLUSION
Compared to childhood-onset asthma, adult-onset asthma has worse prognosis and poorer response to standard asthma treatment. Many risk factors responsible for the onset of asthma in adulthood have been recognised, varying from respiratory infections to environmental sensitisers, hormonal factors, obesity and stress. Recently, cluster analysis identified specific and clinically well-recognised adult-onset asthma phenotypes and, consequently, new exciting possibilities have been developed for a more targeted, phenotypic approached in patients with adult-onset asthma. Still, the underlying pathophysiological mechanisms of asthma severity and poor clinical outcome are largely uninvestigated. A better understanding of key biological pathways by using systems medicine approaches will not only help to prevent the development of asthma in adulthood but will certainly lead to better targeted treatments. Therefore, large scale prospective follow-up studies of patients with adult-onset asthma are urgently needed, especially in those who are in an early stage of their disease.

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