Asthma transition from childhood into adulthood

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For more on **asthma prevalence** see http://www.ginasthma.org

Asthma is the most prevalent chronic respiratory disease both in children and adults and resembles a complex syndrome rather than a single disease. Different methods have been developed to better characterise distinct asthma phenotypes in childhood and adulthood. In studies of adults, most phenotyping relies on biomaterials from the lower airways; however, this information is missing in paediatric studies because of restricted accessibility. Few patients show symptoms throughout childhood, adolescence, and adulthood. Risk factors for this might be genetics, family history of asthma and atopy, infections early in life, allergic diseases, and lung function deficits. In turn, a large proportion of children with asthma lose their symptoms during school age and adolescence. This improved prognosis, which might also reflect a better treatment response, is associated with being male and with milder and less allergic disease. Importantly, whether clinical remission of symptoms equals the disappearance of underlying pathology is unknown. In fact, airway hyper-responsiveness and airway inflammation might remain despite the absence of overt symptoms. Additionally, a new-onset of asthma symptoms is apparent in adulthood, especially in women and in the case of impaired lung function. However, many patients do not remember childhood symptoms, which might reflect relapse rather than true initiation. Both relapse and adult-onset of asthma symptoms have been associated with allergic disease and sensitisation in addition to airway hyper-responsiveness. Thus, asthma symptoms beginning in adults might have originated in childhood. Equivocally, persistence into, relapse, and new-onset of symptoms in adulthood have all been related to active smoking. However, underlying mechanisms for the associations remain unclear, and future asthma research should therefore integrate standardised molecular approaches in identical ways in both paediatric and adult populations and in longitudinal studies.

Introduction

Wheezing disorders and asthma are the most prevalent chronic respiratory diseases both in childhood and adulthood, with about 300 million people of all ethnicities affected worldwide across all ages. Despite common pathophysiological factors that lead to characteristic clinical symptoms, individuals affected by asthma vary substantially in their complaints, in their clinical manifestations, including comorbidities, and across age groups.[1]

Childhood and adult asthma resemble a complex syndrome rather than a single disease and present with different phenotypes[1,2] that lead to the recognised state of variable airway obstruction, which at times is not fully reversible or even fixed during the disease course.[3]

Key messages

- For persistent asthma symptoms, epidemiological studies have identified genetic background, family history of asthma and atopy, infections early in life, allergic disease, and lung function deficits as risk factors
- Data for remission and relapse of asthma symptoms are sparse, but point towards male sex and a milder and less allergic disease being associated with remission of symptoms, and a role of allergic disease and persisting airway hyper-responsiveness for their relapse
- For new-onset of asthma symptoms in adults, risk is increased for women and in the case of allergic disease, pre-existing airway hyper-responsiveness and lung function impairment
- Equivocally, persistence into adulthood and relapse and new-onset of asthma symptoms in adulthood have all been related to uptake of active smoking

Presumably, however, variable airway obstruction is affected through diverse underlying pathophysiological processes adding further to the complexity of our pathophysiological understanding.[1,4] These diverse underlying mechanisms could be used to further define asthma, which is known as an asthma endotype. This approach also includes complex but refined molecular information in a network approach with the aim to better link biology to clinical presentation.[5,6] However, symptoms, especially during early life, are rather poor predictors of asthma later in life, and the disease displays a variable course across all ages. These variabilities are possibly the reason why asthma phenotypes have not helped to improve prognosis in the clinical setting for children or for adults, although such predictors and targeted treatment strategies are urgently needed.

Independent of age, several methods for the definition of asthma phenotypes have been developed. These methods are either based on a combination of clinical and empirical approaches and data obtained from epidemiological studies, including molecular information,[5–7] or they use objective and unsupervised data-driven techniques to determine endophenotypes and phenotypes from collated data,[7–14] which remain subjective because of the a-priori choice of data used in the analyses.

However, most endophenotyping and phenotyping have been investigated in children and adults separately, with an inherent bias towards data on underlying pathophysiology in adults and epidemiological data for children. Accordingly, data on the important link between childhood and adult asthma are sparse, despite some prospective studies spanning the age ranges. A substantial knowledge gap exists regarding the

transition of asthma from childhood to adulthood. We termed this unknown phase a black box. In this Review, we address the concepts of persistent disease symptoms beyond childhood, their remission and relapse, and their onset during adulthood (figure 1), and collate the knowledge from both paediatric and adult pulmonologists' perspectives with the aim to bridge and translate ideas for a common research agenda.

Definition of the knowledge gap

Importantly, to discuss childhood and adult asthma phenotypes or endotypes, paediatric and adult pulmonologists have to agree on a common language. Among adult-asthma specialists, the term early-onset asthma largely refers to childhood-onset asthma. However, this single label probably comprises different childhood asthma phenotypes that track from childhood to adulthood.[1,2,7,15] Late-onset asthma, as used by adult pulmonologists, refers to asthma with onset in adulthood and this might include some patients who had episodes of transient wheeze in childhood. For the purpose of this Review, we use the terms childhood-onset and adult-onset when referring to a generalisation of the age of onset in addition to the concept of different phenotypes.

With regards to asthma transition, one of the arising and most imminent questions is about the true difference between childhood and adult asthma besides age of onset and disease duration. There are similarities and differences between the two diseases, and their relative proportion seems to be associated with age of symptom onset and developmental aspects, since identical underlying mechanisms might manifest differently in children and adults. As outlined in a review by de Nijs and colleagues,[16] adult asthma generally seems to exhibit a poorer treatment response and worse prognosis compared with childhood asthma. However, given the different disease patterns (figure 1), further unresolved questions remain. For example, which individuals are at risk of developing persistent symptoms, and in whom will they resolve? Is there (ever) a full resolution of the underlying pathology in addition to symptoms in cases of remission? Could there be a group that is at risk of developing relapse in adulthood after some years without any overt symptoms? In other words, do adult asthma phenotypes exist that have their origin in childhood, although they are not recognised as such because of a long phase of so-called remission before relapse, in contrast to truly new-onset adult disease? Does the existence of childhood asthma predispose an adult patient to other forms of chronic airway disease, without recognition of its link to the pre-existing condition?

Asthma phenotypes

Why is it necessary to phenotype asthma? Asthma is increasingly recognised as a complex syndrome that consists of several different entities or phenotypes, which might be determined by different mechanisms rather than a single disease attributable to one single mechanistic pathway. Simply collating all asthma phenotypes under one umbrella term—asthma—could mean that important pathways to the disease might not be identifiable, and therefore such an approach might create one of the main limitations in asthma research.[17]

Phenotypes can be defined in various ways on the basis of: (1) the presence or absence of intermediate traits such as atopy,[18,19] (2) temporal patterns of symptom manifestation,[20] (3) triggers of symptoms,[15,21] (4) disease severity,[17] (5) patterns of airway inflammation,[5] and (6) response to medication.[22] These categorisations have been set empirically by investigators or, in hypothesis-free approaches, with unsupervised and data-driven techniques such as principal component analyses,[23] cluster analyses,[13,24] and latent class analyses (LCA).[11,12,25,26] However, these statistical methods appear to be investigator-driven and based on a-priori choices such as time intervals or factors to be included, and therefore these methods are not as objective as they are often suggested to be. Models that allow patients to change disease classes, thereby gaining information from these shifts such as latent transition analysis, could be a more promising development.[14]

The view of the paediatric pulmonologist

What is the strength of paediatric approaches to phenotyping asthma? In our view, the strength is primarily the abundance of data derived from prospective epidemiological studies, although little is known about underlying endotypes, which are restricted to severe asthma.[27–32] Strong evidence exists in the epidemiological literature for a sequence of events. Wheezing is very common in the first years of life, but most infants and young children will grow out of it as their lungs develop. These transient wheezers do not usually progress to asthma in childhood and adolescence, but can be at increased risk of chronic obstructive pulmonary disease in adulthood.[33] Wheezing will persist until childhood, adolescence, and even adulthood in a small proportion of infants.[11,12,25,34] Beyond

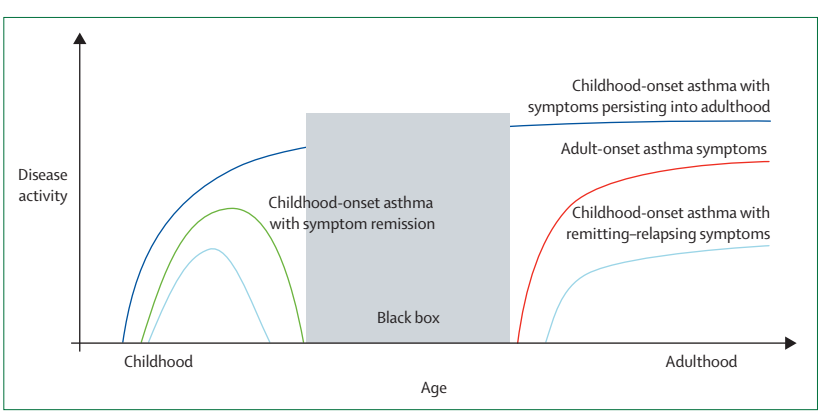

Figure 1: **Disease course across childhood and adulthood**
The figure suggests a disease course of different asthma phenotypes by course and time of onset of symptoms.

these consistently and easily identifiable temporal phenotypes, other intermediate phenotypes of variably associated characteristics have been described.[11,12,25]

Many studies have followed up patients who have matured from the care of their paediatrician and the transition into adulthood either in a clinical[35–37] or population-based setting. These population-based studies that cross the gap between childhood and adulthood address: persistence,[3,20,24,34,38–63] remission,[20,34,38–50,54–57] relapse,[20,34,38,39,51–57,64] and new-onset of symptoms in adulthood (table).[20,54–57,65–70]

The view of the pulmonologist managing adult patients

In contrast to paediatrics, adult asthma care has a definitive absence of longitudinal studies that start tracking the course of the disease at early adulthood and follow patients up for an adequate length of time. Our literature search identified only five studies following adult patients with asthma for at least 10 years.[71–75] However, physicians taking care of adult patients with asthma can reference numerous cross-sectional studies and clinical trials. Most cross-sectional studies and some clinical trials report lung

	Participants	Study country	Age at enrolment, years	Age at follow-up, years	Additional notes
Prospective study, no birth cohort study					
British 1958 National Cohort (National Child Development Study)[34,38,39]	18 559	UK	7 years	11, 16, 23, 33, 35, and 42 years	..
Tasmanian Asthma Survey (Tasmanian Longitudinal Health Study [TAHS])[40–45]	8683	Australia	7 years	13, 29, 32, 43, and 44 years	..
Melbourne Asthma Study[46–50]	374 cases 105 controls	Australia	7 years	10, 14, 21, 28, 35, and 50 years	Phenotypes were defined as follows: mild wheezy bronchitis was fewer than five episodes of wheeze associated with bronchitis or respiratory tract infection; wheezy bronchitis was at least five episodes of wheeze associated with bronchitis or respiratory tract infection; asthma was wheeze not associated with respiratory tract infection; and severe asthma was onset of asthma symptoms before age 3 years, persistent symptoms at age 10 years, barrel-chest, FEV1/FVC ≤50%, or combination of above factors
Dunedin Multidisciplinary Health and Development Study (DMHDS)[51–53]	1139	New Zealand	3 years	5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years	Wheezing patterns were defined as follows: persistent wheezing was wheeze reported at every successive assessment after onset; remission was absence of wheeze after it had been reported at two or more successive previous assessments; relapse was wheeze reported at two or more successive previous assessments, then absent at one or more successive assessments, then reported at all successive assessments; intermittent wheezing was presence of wheeze at some assessments but not others, not at two consecutive assessments, and not fitting the other patterns; and transient wheezing was when wheeze was reported at one assessment only
Obstructive Lung Disease in Northern Sweden Studies (OLIN)[58]	3431	Sweden	7–8 years	Yearly until age 19 years in 248 children with asthma at baseline	..
Childhood Asthma Management Program (CAMP)[3,62,63]	1041	USA	5–12 years	10–14 years, 15–18 years, and mid-twenties	Prospective, randomised, double-masked, multicentre clinical trial of children with mild to moderate asthma
Prospective study on random population sample[65,66]	983	Denmark	7–17 years	After 6 years (ages 13–23 years), 12 years (ages 19–29 years), and after 20 years (ages 30–42 years)	..
Cross-sectional prospective study based on the Nijmegen Continuous Morbidity Registration (CMR)[67]	551	Netherlands	10–22 years	24–37 years	..
Cross-sectional prospective study based on the National Population Health Survey (NPHS)[68]	17 276	Canada	12–18 years	After 2 years (age 14–20 years) and 12 years (age 24–30 years) in individuals with no asthma at baseline	..
Nijmegen Cohort[69]	1439	Netherlands	2 years	Every 3 months between ages 2–4 years, then again at age 21 years	..

(Table continues on next page)

	Participants	Study country	Age at enrolment, years	Age at follow-up, years	Additional notes
(Continued from previous page)					
Prospective study, birth cohort study					
Tucson Children's Respiratory Study[20,54–57,61]	1246	USA	Birth	2, 3, 6, 8, 11, 13, 16, 22, 24, 26, and 29 years	Phenotypes were defined as follows: transient-early wheezing was start of symptoms before age 3 years and remission before age 6 years; persistent wheezing was start of symptoms before age 3 years and persistence beyond age 6 years; and late-onset wheezing was start of symptoms after age 3 years and persistence beyond age 6 years
Isle of Wight Birth Cohort[24,59,60]	1465	UK	Birth	1, 2, 4, 10, and 18 years	..
Retrospective cohort study					
Retrospective study on residents with asthma diagnosis in the Ontario Asthma Surveillance Information System database[64]	613 934	Canada	Not applicable retrospective data (youngest were 5 years old, oldest were 65 years or more)	Not applicable, retrospective data, follow-up during 15 years	..
Clinical study					
Cohort of allergic asthmatic children admitted to the outpatient clinic of the University Hospital of Groningen[35]	119	Netherlands	5–14 years	21–33 years and 32–42 years	..
Children admitted to hospital for bronchiolitis and healthy controls[36,70]	78 patients with bronchiolitis and 72 healthy controls	Finland	1–23 months	26–29 years	..
Adolescents selected from the Sophia Children's Hospital patients' files and healthy volunteers[37]	19 patients with persistent symptoms, 18 with remission, and 17 healthy controls	Netherlands	Unknown, childhood	18–25 years	..

FEV_1=forced expiratory volume in 1s. FVC=forced vital capacity.

Table: **Studies that address the concepts of persistence, remittance, and relapse of symptoms beyond childhood and the factors that impact newly-diagnosed asthma in adulthood**

function data and investigate biomaterials. Samples can be extracted from local (eg, sputum, bronchoalveolar lavage [BAL], BAL fluid) or systemic (blood) sources, which are relatively easily accessible especially when compared with children. Particularly, the pattern of airway inflammation is a valuable phenotypical marker that also carries information on underlying pathobiology. Inflammatory patterns along with clinical characteristics could lead to improved disease concepts that can also be tested in experimental models. Close communication between bench and bedside facilitates a biology-driven phenotyping approach in adult asthma research, enabling extensive phenotyping approaches that are more difficult to achieve in infants or young children with asthma.

Endophenotyping by airway inflammation

In contrast with children, in whom the majority of analyses were performed in the field of severe childhood asthma,[27–31] the cellular pattern of airway inflammation has been studied extensively in adults with asthma[76–78] and might be related to an underlying endotype.[6] Changes in the degree and pattern of airway inflammation could indicate treatment response and guide therapy,[79] for example, in adults with asthma, eosinophil concentrations in blood, sputum, and airway mucosa, are responsive to therapeutic intervention with steroids.[77] By contrast, sputum eosinophilia-guided therapeutic algorithms have been less successful in children with severe asthma.[28] Therefore, at least in adults, endophenotyping by airway inflammation pattern might also cover two aspects of previously mentioned longitudinal concepts: persistence, as indicated by the pattern of airway inflammation, and remission, as indicated by changing levels of airway inflammation. In children, no differences in sputum cellularity were found between severe and milder asthma forms. Moreover, sputum cellularity was less stable than in adults but highly variable across time.[27]

Complicating matters, even persistent type 2 (T2)-associated airway inflammation, does not reflect

one single disease trait and might have different consequences in childhood-onset versus adult-onset disease. In the case of adult-onset symptoms with T2-mediated airway inflammation, allergy is less frequent[80] and patients are less responsive to corticosteroid treatment.[13,81,82] In these cases, innate lymphoid cells might be more important in maintaining eosinophilic response than T-helper type 2 cells,[80,83,84] with an emerging role in the paediatric literature.[31] These observations suggest that a similar and persistent pattern of airway inflammation might reflect different underlying disease mechanisms when taking age at onset of symptoms into account.

Changing levels in sputum differential cell count within the natural course of the disease might indicate an aspect of inflammation remission. However, this indication is mere speculation, since the longitudinal use of sputum induction is restricted to therapy guidance in severe disease, which reflects treatment and symptom response rather than true disease remission. Moreover, long-term follow-up data spanning from true onset of disease into adulthood or even senescence are not available.

Treatment response might not only be assessed by the degree of airway inflammation but could also be predicted by the type of inflammation—eg, T2 high versus T2 low.[85] T2-high asthma is characterised by airway and systemic eosinophilia, and greater disease severity, but also therapeutic responsiveness to glucocorticoids and inhibitors of T2 inflammation.[85] In adult patients with a T2-high phenotype, novel inhibitory treatment strategies that target interleukin-5 (mepolizumab,[86–89] reslizumab[90]), the interleukin-5 receptor (benralizumab[91,92]), or interleukin-13 (lebrikizumab,[93] tralokinumab,[94,95] dupilumab[96]) have shown promising results in clinical trials. These treatments might help to evolve the field since they require careful phenotyping in advance to ensure efficacy and to justify the use of expensive medication.[97]

However, whether these substances also modify underlying disease mechanisms and whether such therapies have to be applied permanently or can be stopped after some time are unclear. Therefore, questions dealing with a relapse of certain features of the disease after discontinuation of drug treatment cannot be answered with data from published efficacy studies in adults.

Biology-driven studies have changed and advanced phenotyping in adult patients with asthma substantially when compared with the longitudinal observational concepts that still dominate paediatric phenotyping despite emerging data. The longitudinal concepts of paediatricians—persistence, remission, and relapse—are difficult to transfer to the biomarker-driven concepts of adult asthma. This difficulty, however, hampers comprehensive disease concepts and highlights the principal need to better link both research approaches.

Closing the gap

Persistent wheeze and asthma

About 3–5% of individuals will develop wheeze symptoms that persist from childhood into adulthood.[34] Since in many cases wheeze manifests within the first year of life, prenatal determinants probably play a substantial role, but specific data are not available. In turn, genetics, epigenetics, lung development, and postnatal environmental exposures have been studied in more detail.

A family history of asthma or atopy, or both, has been shown to be associated with a persistent wheeze phenotype in childhood,[11,12,57] which might reflect shared environmental exposures or genetic determinants. For asthma, several genetic variants have been found.[98,99] The first asthma genome-wide association study described the gasdermin B/orosomucoid like 3 (*GSDMB-ORMDL3*) locus on chromosome 17q21, which had the most pronounced effect on childhood-onset compared with adult-onset asthma symptoms and has been replicated in several populations.[100,101] In surveys that distinguished temporal wheezing phenotypes, children with persistent wheeze had the strongest association with this genetic locus with a relative risk ratio of 1·60 (95% CI 1·40–1·84, $p=1·4\times10^{-11}$) in the Avon Longitudinal Study of Parents and Children.[102] Since persistent wheeze in childhood is likely to continue until at least early adulthood, as exemplified in the seminal Tucson Children's Respiratory Study (TCRS)[57] with a multinomial odds ratio (MOR) of 14·0 (95% CI 6·8–28·0), the *GSDMB-ORMDL3* locus could be an important risk factor for asthma symptoms persisting beyond childhood, but this notion needs support from future studies. The role of other asthma genes has not been specifically investigated for the persistent wheezing phenotype.

Alterations in gene expression due to inactivation or activation of genes through epigenetic effects—eg, by methylation or demethylation—and also through alterations in post-translational modifications through microRNAs (miRNAs) could also play a role.[103,104] Data from two independent Spanish pregnancy cohorts showed that hypomethylation at cytosine-guanine dinucleotide sites of the *ALOX12* gene was associated with persistent wheezing during childhood.[105] Moreover, in an analysis of 37 monozygotic asthma-discordant twins, persistent disease at ages 10 years and 18 years was associated with a differentially methylated position near the *HLX1* gene,[106] a locus that has been related to childhood onset of asthma symptoms[107,108] and immune development[109] in other studies.

Persistent wheeze has repeatedly been associated with impaired lung function in childhood.[20,110] Therefore, impaired lung growth, especially during rapid development early in life, might adversely affect airway anatomy or airway wall mechanics;[111] however, the findings are ambiguous. The Hammersmith Hospital cohort (UK)[112] showed that lung function measured at age 1 month with the rapid thoracic compression (RTC) technique in infants who were not sedated did not predict subsequent wheezing except for a small trend to smaller lung volumes in boys.

However, in prospective unselected birth cohorts from Norway[110] (quiet tidal breathing in awake children shortly after birth) and Perth, WA, Australia,[113–115] (RTC technique in sedated infants), decreased airway function after birth[110,114] and airway hyper-responsiveness in late infancy[113,115] might precede wheeze and asthma onset. By contrast, in the TCRS,[110,113–115] patients with persistent wheeze started with normal postnatal lung function (measured in sedated children with the RTC technique), which decreased until age 6 years, suggesting that this progressive lung function deficit might have been caused by persistent disease.[20] However, these seemingly contradictory findings could at least be partly attributable to differences in techniques used to assess neonatal lung function.

In adolescence[116] and early adulthood,[38] persistent asthma symptoms are also associated with reduced lung function, (FEV_1, forced vital capacity [FVC], and their ratio FEV_1/FVC [$p<0·001$ for each]), as shown in the British 1958 Birth Cohort[38] and in the Childhood Asthma Management Program (CAMP) trial.[3] In the latter trial, children with persistent asthma and reduced growth of lung function were at an increased risk for fixed airflow obstruction and possibly chronic obstructive pulmonary disease in early adulthood.[3] Additionally, airway hyper-responsiveness and reduced lung function are also important predictors for persistence of symptoms from childhood into adulthood. In the TCRS,[57] reduced lung function and airway hyper-responsiveness at age 6 years were associated with so-called chronic asthma at age 22 years (MOR 2·1 [95% CI 1·1–3·9] for lung function and MOR 4·5 [1·9–10·0] for airway hyper-responsiveness). Age of onset of wheeze showed a linear association with FEV_1 at age 22 years, suggesting that both early childhood onset and chronic, persistently impaired lung function might have the strongest effects on disease persistence.[57] This association was strongest in children with early-life infections, particularly pneumonia.[61]

The fact that reduced lung function predicts symptom persistence was further supported by a Dutch hospital-based study[35] and two population-based cohort studies—the Melbourne Asthma Study (MAS)[46,47] and the Dunedin Multidisciplinary Health and Development Study (DMHDS)[52] (table). In MAS,[46] patients with persistent asthma displayed the lowest values for FEV_1 across the whole course of disease. In DMHDS,[52] the same was shown for FEV_1/FVC, although the adjusted odds ratio (aOR) for the association of airway hyper-responsiveness with persistence was 3·00 (95% CI 1·71–5·26).

Further important determinants of persistent symptoms include cigarette smoking and the presence of atopy and comorbidities.[49,58] In the DMHDS,[52] active smoking at early adulthood increased the risk of asthma persistence by almost double with an aOR of 1·84 (95% CI 1·13–3·00), whereas atopic sensitisation by age 13 years had a stronger effect with an aOR of 2·41 (1·42–4·09).[52] In the Tasmanian Asthma Survey/Tasmanian Longitudinal Health Study (TAHS)[44] allergic comorbidities (ie, manifestation of both eczema and allergic rhinitis in childhood) substantially increased the risk for persistent asthma with an adjusted MOR (aMOR) of 11·7 (95% CI 3·5–37·9). Childhood rhinitis already significantly contributed to risk of symptom persistence with an aMOR of 2·7 (1·3–5·6).[44] Unfortunately, limiting its significance, atopy has been treated as an all-or-nothing process in the sense of binary logics in the DMHDS and in other longitudinal studies in this Review. Of note, late approaches to use of atopic sensitisation as continuous variables either in the sense of quantification of specific-immunoglobulin E (sIgE) subclasses[19,117] or by the application of unsupervised methods to different sIgE patterns such as LCA[109] might be more appropriate.

Given its relationship with eosinophilic inflammation, exhaled nitric oxide (eNO) might serve as a relevant proxy both for eosinophilic inflammation of the airway wall and for sputum eosinophilia.[118] eNO measurements beyond infancy could be a useful and simple tool for the identification of patients at risk of developing asthma.[119] Indeed, in the Dutch Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study,[120] a large population-based cohort with prenatal inclusion and follow-up until age 18 years, children with persistent wheeze had the highest eNO values. Importantly, the relation between eosinophilic inflammation and increased eNO concentrations in childhood and adult asthma was shown in bronchial biopsies (airway wall) and in sputum or BAL fluid, which even displayed increased eosinophil invasion after an allergen challenge.[118] Challenging its role as a predictor of future disease course—especially in the case of treatment with inhaled corticosteroids—it is important to note that this relation is also very variable, such that eNO concentrations do not always seem to reflect eosinophilia.[29,121]

Many of these determinants were substantiated in the Isle of Wight Birth Cohort[24] by *k*-means clustering for study participants at age 18 years. Among patients with either symptoms or asthma medication use, six clusters were identified. Three clusters were characterised by early childhood onset of symptoms, which suggested a chronic course. Of these clusters, the one representing the most severely affected patients was characterised by female predominance, childhood atopy, impaired lung function, and a high smoking prevalence, suggesting that the factors mentioned in this Review not only contribute to symptom persistence but also to disease severity as defined by number of hospital admissions and level of asthma control.[24]

In summary, approximately 3–5% of children develop persistent asthma symptoms from childhood through to adulthood. A genetic background is likely to substantially contribute to persistence of symptoms across ages since a positive family history of asthma and atopy, genetic polymorphisms, and epigenetic markers have all been identified as relevant. Additionally, respiratory tract infections early in life, childhood allergic comorbidities, and active smoking in adolescence and beyond, all contribute to increased risk. Whether lung function deficits are a consequence of chronic persistence of symptoms or whether impairments already present at

birth are a primary cause of onset of the persistent phenotype remain to be elucidated.

Asthma remission until adolescence

Most children with asthma display symptom remission during adolescence and early adulthood.[34,40] In the population-based British 1958 Birth Cohort[34] about 67% of children with asthma at age 7 years were symptom-free as adults, and in the TAHS[40] about 75% of children with asthma at age 7 years were symptom-free as adults. In a Dutch clinical cohort,[35] which followed up patients with asthma from a tertiary care centre, symptom remission until adulthood was noted in 52% of enrolled patients. Only a minority of these patients (42%) had complete remission (ie, neither symptoms nor steroid use) in addition to remission of once impaired lung function and of airway hyper-responsiveness. The remaining patients no longer reported symptoms but had retained airway hyper-responsiveness or impaired lung function,[35] which suggests that symptom remission does not reflect remission of underlying airway pathology and that the clinical manifestation might need a certain threshold to elicit symptoms. This view has been substantiated in another study of a Dutch clinical cohort[37] that investigated whether young adults in clinical remission displayed persistent airway inflammation or airway remodelling, or both. In addition to markers of airway inflammation, substantial airway remodelling was found in people with symptom remission compared with healthy controls, who were all lifelong non-smokers. Importantly, the degree of remodelling was similar to that of people who were still symptomatic.[37] Thus, the term remission remains unequivocal as a superficial view and could suggest no symptoms with persisting underlying pathology.

Several studies have shown that symptom remission is associated with male sex. For example, in the TCRS,[57] remittance of asthma signs by age 22 years was higher in men than in women, with an MOR of 2·0 (95% CI 1·2–3·2). Furthermore, the rate of symptom remission depends on the asthma phenotype and severity. In the MAS,[49] 64% of children with wheezy bronchitis—ie, symptoms only triggered by viral infections—remitted with regards to overt symptoms by age 50 years compared with 47% of children with asthma and 15% of children with severe asthma. Thus, children with milder disease are more likely to become asymptomatic. In the DMHDS,[122] the decrease in airway hyper-responsiveness during adolescence was more likely in children with a lower atopy index summarising wheal sizes to skin prick tests of indoor aeroallergens.

Asthma relapse in adulthood

The findings from the British 1958 Birth Cohort[34] demonstrate the potential for symptom relapse in individuals with childhood asthma who no longer had symptoms in adolescence and early adulthood. About 28% of these individuals showed reoccurrence of wheezing up to age 33 years. The process appears highly heterogeneous since time to symptom relapse and age at symptom relapse differed substantially between individuals. Reoccurrence of symptoms was associated with active smoking, especially among non-atopics (p value for interaction, p_{int}<0·001).[34] Reoccurrence of asthma was further studied in the DMHDS[52] in which symptom relapse until age 26 years only occurred in 12·4% of study participants and was associated with sensitisation at age 13 years and asymptomatic airway hyper-responsiveness during adolescence (aOR 2·18 [95% CI 1·18–4·00]) and early adulthood (aOR 3·03 [1·65–5·55]).[52] In the TCRS,[57] participants reported new onset of symptoms by age 22 years. However, the continued follow-up included previous questionnaire assessments and about 63% of parents of the participants had already reported episodes of wheezing during their childhood. This follow-up highlights again that patients are likely to forget about their childhood symptoms, and underlines the role of recall bias.

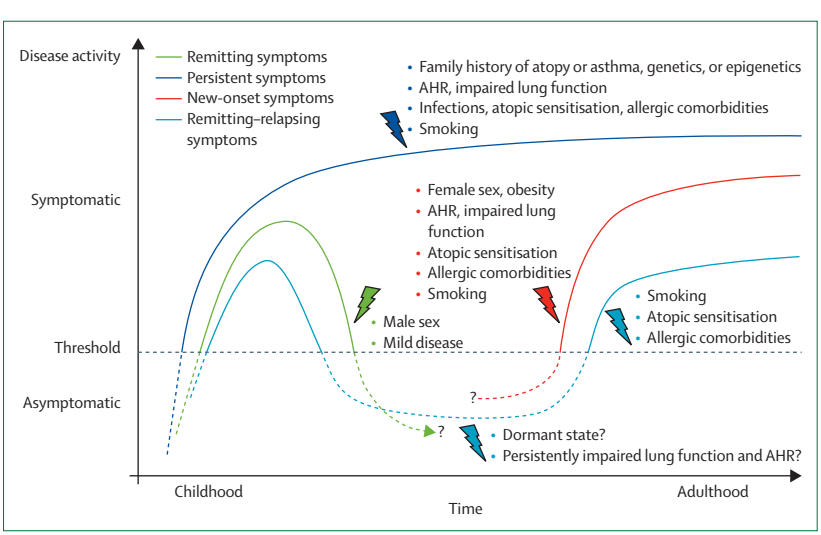

Figure 2: **Determinants of disease course across asthma transition and ages**
This figure displays putative determinants that affect the disease course of different asthma phenotypes by course and time of onset. AHR=airway hyper-responsiveness.

Search strategy and selection criteria

To review the existing evidence, we searched PubMed (MeSH) with the terms "asthma", "adult", "adolescent", and "longitudinal studies", or "asthma", "child", "adolescent", and "longitudinal studies" until Dec 31, 2015. We largely selected publications reported in English from the past 10 years and did not exclude commonly referenced older publications or manuscripts that were published after Dec 31, 2015. The last search we performed was on Jan 30, 2016. In total, more than 921 abstracts were screened and 79 publications selected. We also searched the reference lists of identified articles and selected manuscripts that we judged as relevant. Review articles are cited to provide readers with more details and more references.

Adult-onset asthma

We discuss the factors that might influence the risk of adult-onset disease. Some of these factors might go back to childhood. For example, in the TCRS,[57] reduced lung function (MOR 2·8 [95% CI 1·1–6·9]) and airway hyper-responsiveness (MOR 6·9 [2·3–21·0]) at age 6 years were predictors of adult-onset symptoms. Importantly, caution is needed to interpret these findings because recall bias means that adult-onset asthma could still, at least partly, mean relapse of asthma symptoms. The role of airway hyper-responsiveness preceding adult-onset symptoms has been confirmed in a Danish cohort.[65,66] However, by contrast, in a Dutch hospital-based study,[67] airway hyper-responsiveness during adolescence was not associated with risk of asthma onset in adults.

More conclusive data exist for the effect of smoking. A dose-dependent effect of active smoking was shown in a follow-up of the International Study of Asthma and Allergies in Childhood, Phase 2 (ISAAC II),[123] for adolescent-onset asthma symptoms in 2936 study participants at a mean age of 17 years (adjusted incidence risk ratio of 2·56 [95% CI 1·55–4·21). This risk was highest in patients with non-atopic asthma (p_{int}=0.0016).[123] The associations of adult-onset asthma symptoms with active smoking are further supported by results from the British 1958 Birth Cohort.[34] Smoking at ages 16, 23, or 33 years was related to adult onset of symptoms (OR 2·25 [95% CI 1·75–2·89]), even more so if participants were smokers at all three timepoints of follow-up (OR 4·42 [3·31–5·92]), thus displaying a dose response in relation to both duration and amount of active smoking.

Furthermore, data from the British 1958 Birth Cohort[34] support a role for allergic comorbidities, particularly for allergic rhinitis (OR 1·54 [95% CI 1·36–1·74]) and adult-onset asthma. This observation is supported by findings from the participants of the TAHS,[41] in which allergic rhinitis in childhood was associated with a two times increased risk for adult onset of asthma symptoms.

Across all ages, sex has been shown to influence symptom onset. A 25-year follow-up of 5115 participants of the US Coronary Artery Risk Development in Young Adults (CARDIA) study,[73] indicated that by the age of 40 years, adult-onset asthma in women becomes the dominant phenotype. Obesity, non-atopic state, and smoking further increased the proportion of adult-onset symptoms in women. For men, no such associations were found.[73] This outcome was further supported by data from the TAHS[43] and the TCRS,[55] in which the highest risk for adolescent and adult onset asthma symptoms was a high BMI in girls.

In summary, the risk for adult onset asthma symptoms is increased for women, for individuals who are sensitised or have an allergic comorbidity, for smokers, and potentially for people with pre-existing airway hyper-responsiveness or impaired lung function, possibly reflecting antecedent airway pathology.

Conclusions

Asthma is multifaceted, and treatment is approached in different ways by physicians in paediatric or adult health care. Certain forms of asthma might persist from infancy into adulthood with regards to symptoms, but also to sustained impaired lung function and airway inflammation. Thus, asthma symptoms might remit in some patients between childhood and adulthood, but then reoccur at later ages, whereas asthma might truly be healed in others. Moreover, true adult-onset asthma might still occur.

Several rather crude descriptive traits, such as atopy, airway hyper-responsiveness, eNO concentrations, and lung function deficits, together with disease severity, have been found (figure 2). This poor insight could partly be attributable to an absence of better endotyping. If asthma endophenotypes are in reality a conglomerate of many underlying mechanistic pathways, then determinants in epidemiological studies will reflect this mix of more or less the same atopy, airway hyper-responsiveness, and lung function deficits. An improved description of baseline endophenotypes that involves underlying mechanisms might allow more targeted follow-up studies to better delineate true persistence and remission, which will more efficiently distinguish between the different levels of underlying airway pathology, intermediate traits, and overt symptoms in the future. Consequently, remission is loosely defined as it could reflect a small aspect of a larger problem: although symptoms might disappear for unknown reasons, underlying pathology could persist giving rise to relapse for equally unknown reasons. The only environmental trigger for symptom relapse that has been clearly identified is active smoking.

Whether mechanisms that determine childhood asthma have any similarities with mechanisms that result in adult asthma is unclear. Alternatively, childhood and adult asthma might have less in common than expected and different mechanistic pathways might be involved from childhood across to adulthood and in the context of the developmental perspective. We therefore propose that future asthma research should integrate identical standardised molecular approaches in paediatric and adult populations and in longitudinal studies.

Contributors

OF and TB contributed equally, performed the literature search, and designed the figures; OF, TB, KFR, and EvM contributed to the manuscript and approved its final version.

Declaration of interests

We declare no competing interests.

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