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Addressing the risk domain in the long-term management of pediatric asthma*

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Impact statement: There is growing concern about the long-term risks associated with early and poorly controlled childhood asthma. This review focuses on risk assessment as an essential part of the management of all children with asthma. It examines the need to identify children at risk of poor outcomes, to monitor disease progression and design intervention strategies that can prevent or reverse asthma progression in children, in addition to focusing on day-to-day control of symptoms. Evidence suggests that individualized management strategies for children with asthma should take into account insights from spirometry, the use of biomarkers and methods needed to identify children at high risk of asthma attacks. These measurements should be integrated into routine clinical assessments of children with asthma.

Tweetable abstract: Risk assessment is essential in the management of all children with #asthma in order to improve #long-term outcomes

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Abstract

There is growing concern regarding the long-term outcomes of early and poorly controlled childhood asthma, either of which can potentially lead to the development of severe asthma in adults and irrecoverable loss of lung function leading to chronic obstructive pulmonary disease. These outcomes of inadequately controlled asthma should prompt a change in practice to better and/or earlier identify children at risk of adverse respiratory outcomes of asthma, to monitor disease progression, and to design intervention strategies that could either prevent or reverse asthma progression in children. The careful follow-up of spirometry over time—in the form of lung function trajectories, the application of biomarkers to assist in the diagnosis of early asthma and medication selection for these patients, as well as methods to identify patients at risk of asthma attacks—can be used to develop individualized management strategies for children with asthma. It is now time for asthma specialists to communicate this information to patients, parents and primary care physicians, and to incorporate them into routine clinical assessments of children with asthma. In time, these concepts of risk management and prevention can be refined to provide a more comprehensive approach to asthma care so as to prevent adverse respiratory outcomes from poorly controlled childhood asthma.

Keywords: asthma; children; risk assessment; risk management; biomarkers; spirometry; disease management; disease progression; early intervention.

Introduction

Recent asthma guidelines[1-4] have emphasized achieving asthma control, defined within two domains: impairment and risk. The term “risk” draws attention to the assessment of the potential for asthma attacks, adverse effects of medications and progression of the disease. We have a unique opportunity to significantly reduce the worldwide burden of asthma in children and impact consequent respiratory outcomes in adults. However, this will require directing more attention to methods that can alter the natural history of asthma, reduce asthma attacks and prevent long-term adverse outcomes of childhood asthma.[5,6]

There is growing concern regarding the long-term outcomes in many cases of early and poorly controlled childhood asthma, such as progression to severe asthma, irrecoverable loss of lung function and chronic obstructive pulmonary disease (COPD) in later life.[7] We surely need to direct attention to identifying patients at risk of these long-term adverse respiratory outcomes while not neglecting day-to-day symptom control. Also, we need to monitor disease progression, and to design intervention strategies that could either prevent or reverse asthma progression in children.

With the rapid advancement in technology, and the introduction of new medications and new biomarkers, we will be able to move toward a more individualized treatment plan and technology-oriented monitoring. New strategies to reduce asthma attacks could have a long-term impact on the life course of asthma in individual patients; severe asthma attacks, particularly those where inhaled corticosteroids (ICS) are neither prescribed nor utilized, are associated with an impaired lung growth trajectory.[8,9] This review will summarize information related to the importance and clinical implications of routinely following lung function trajectories in the life course of asthma that begins in childhood, the application of biomarkers to assist in the diagnosis and management of early childhood asthma,[10] and the importance of incorporating an assessment of risk for an asthma attack. While there is much information already available to support the application of these techniques to reduce risk, continued research will be important to refine our approach to managing childhood asthma and thus minimize adverse respiratory outcomes in adulthood.

Lung function deficits among children with asthma and wheeze

Wheezing symptoms are highly prevalent among children, particularly in the first 3 years of life. This is exemplified in the European multicenter PASTURE/EFRAIM birth cohort. Of the 1,133 enrolled children, 84% had complete data on presence or absence of wheeze at no less than 5 of 6 yearly intervals.[11] The parent-reported prevalence of wheeze in the previous 12 months amounted to 30.6% at 12 months of age and then gradually decreased to 15% at 6 years of age. Other birth cohort studies (such as Avon Longitudinal Study of Parents and Children [ALSPAC]) have shown even higher rates.[12]

Not all who wheeze progress to atopic allergic asthma. A number of birth cohort studies have shown different temporal patterns of wheeze over time. The first report from the Tucson Children's Respiratory Study (TCRS) showed that some children with early wheeze lose their symptoms around 3 years of age and do not show features frequently associated with asthma, such as atopic dermatitis, allergic sensitization, eosinophilia, or a family history of asthma and atopy.[13] This temporal pattern has been termed "transient wheeze" and has been replicated in numerous other prospective studies using investigator- or data-driven definitions by latent class analyses. Transient wheeze has, however, repeatedly been associated with diminished lung function early in life, at school age and into adulthood.[11,13,14] The progression of asthma over school age and adolescence is related to the early development of atopic sensitization. In the German Multicentre Allergy Study (MAS) cohort, children who developed allergic sensitization up to the age of 6 years were at risk of persistent symptoms and decreased lung function at 6–13 years of age compared with non-atopic children.[15] Not all types of allergic sensitization mattered, but the early manifestation of sensitization to perennial indoor allergens in the first 3 years of life was the most important, whereas sensitization to pollen allergens or development after the age of 3 years was unrelated to lung function deficits. Likewise, in the Manchester Asthma and Allergy Cohort, multiple early aeroallergen sensitization was the strongest determinant of asthma symptoms, asthma attacks and hospitalizations, whereas other atopic patterns were less indicative.[16]

In the PASTURE/EFRAIM birth cohort, latent class analysis of atopic sensitization revealed a severe atopy class that was related to signs of a dysbalanced immune response.[17] Moreover, severe atopy determined high asthma risk and impaired lung function. Importantly, children with persistent wheeze, frequent asthma attacks and multiple early atopy not only have diminished lung function, but also are at risk of a progressive loss of lung function from 3 to 11 years of age, as elegantly shown in the Manchester Cohort.[8]

Other determinants of low lung function in children

There is compelling evidence that maternal smoking and second-hand tobacco smoke exposure affect lung function. While the effects may seem minor at the general population level, strong harmful effects have been reported in children at risk. In the German cross-sectional International Study of Asthma and Allergies in Childhood (ISAAC) study, deficiency in glutathione S-transferase enzymes, which are involved in the detoxification of environmental tobacco smoke, was assessed through genotyping and related to lung function in children.[18] In utero exposure to maternal smoking was mostly harmful in those with the genetic deficiency, which amounted to a very significant loss in maximal mid-expiratory flow of more than 30%. In contrast, in those without genetically determined deficiency, maternal smoking had no significant impact on lung function. Maternal and paternal asthma are also associated with adverse long-term outcomes in the child.[19] Among children at risk, significant reductions in lung function, particularly of small airways measures, were found.

As part of the ESCAPE project, data from a number of European birth cohort studies that had measured lung function at 6–8 years of age (n=5,921) were analyzed.[20] Estimated levels of nitrogen oxides (NO), absorbance of particulate matter with aerodynamic diameters <2.5 µm ($PM_{2.5}$) and $PM_{2.5}$ at the current address were associated with small decreases in lung function; however, genetic susceptibility was not taken into account. Importantly, long-term PM_{10} and nitrogen dioxide exposures were associated with small but statistically significant reductions in lung volume growth in children of elementary school age in the Manchester Cohort.[21]

Early life origins of COPD

The Tasmanian Longitudinal Health Study (TAHS) is a population-based cohort study with multiple assessments of lung function over childhood into adulthood (ages 7, 13, 18, 45, 50 and 53 years).[22] Six trajectories of forced expiratory volume in 1 second (FEV_1) were identified, three of which carry an increased risk of COPD at 53 years of age (Figure 1). These three trajectories were determined by events early in life such as childhood and parental asthma, bronchitis, pneumonia, hay fever, eczema and maternal smoking. Personal smoking and active adult asthma increased the impact of maternal smoking and childhood asthma.

Trajectories of FEV_1 from early school age to adolescence were also studied in the Manchester Cohort and replicated in ALSPAC using data from school age to early adulthood.[23] Four FEV_1 trajectories were identified, of which the “Persistently Low” trajectory was likewise associated with early-life factors including recurrent wheeze with severe asthma attacks, early allergic sensitization and tobacco smoke exposure. These findings not only suggest that COPD may have its roots in childhood, but also that prevention of COPD may have to begin early in life through reducing maternal smoking and uptake of active smoking, particularly in those adolescents whose parents smoke or who already have poor lung function. Given that nicotine has definitely been proven harmful, vaping (inhaling nicotine by vapor) should also be discouraged. Furthermore, patients and their families should be made aware by their physicians of potential long-term sequelae of non-optimal asthma control resulting in reduced lung function, which is a significant risk factor for adult disease, particularly COPD.

In summary, assessing lung function trajectories is important for predicting the life course of respiratory disease. It is also important to communicate this information to primary care physicians, parents and patients in order to engage them in strategies to not only improve pulmonary function, but also to avoid circumstances that pose further risks for loss of pulmonary function, such as smoking, vaping, occupational hazards and environmental exposures. It is also important to stress adherence to ICS therapy if the child has had prior asthma attacks. For adolescents, this is also an excellent opportunity to discuss career counseling, and choices of location for higher education and future living conditions. It will also be important to determine whether biologic therapy might offer the potential to alter the course of airway remodeling. When a low lung function trajectory is identified, the next step is to understand whether there is evidence of active inflammation, and then to assess the nature of that inflammation through the use of relevant biomarkers.

Biomarkers in the early diagnosis and management of childhood asthma

Currently, the word “asthma” is used in many different ways, and diagnostic imprecision has led all too frequently to therapeutic confusion. A recent Asthma Commission published in *The Lancet* defines asthma as a clinical syndrome consisting of wheeze, breathlessness, chest tightness and sometimes cough.[24] As such, the use of the word “asthma” is the start, not the end, of the diagnostic journey. The next question is: what sort of “asthma” does the patient have? Leading on from this, we need to use biomarkers to define treatable traits, of which the most important in pediatric airway disease are bronchodilator-responsive variable airflow obstruction (treated with inhaled β_2-agonists), eosinophilic airway inflammation (treated with ICS) and airway bacterial infection (treated with antibiotics).

This principle extends to other airway diseases; thus, rather than asking, for example, whether survivors of preterm birth have “asthma”, the questions become (a) whether they have an airway disease, and (b) if so, what treatable traits are present? So, in the case of survivors of prematurity, there is evidence of bronchodilator reversibility but no type-2 inflammation;[25-28] hence β_2-agonists are indicated rather than ICS.[29] Unfortunately, instead of using biomarkers such as blood eosinophil count and aeroallergen sensitization (below), we have relied on a history-based diagnosis of asthma, which is frequently wrong,[30,31] resulting in children who do not have any airway disease being overtreated. The Asthma Commission stressed the importance of making measurements before making a diagnosis or instituting treatment, something that is all too often neglected.[24]

Ultimately, we need to move to more objective ways of making a diagnosis, such as gene signatures, as has been done so successfully in the field of infectious diseases.[32-34] Indeed, a gene signature has been proposed as a specific diagnostic test in red cedar asthma,[35] for which, of course, there is a gold-standard conventional diagnostic test.

Personalizing asthma therapy with biomarkers

We often ask “at what age can we diagnose asthma?”, instead of asking “how do we diagnose eosinophilic airway inflammation at any age?”[36] The INFANT study showed that two simple biomarkers—blood eosinophil count >300/µL and aeroallergen sensitization—could be used to target ICS in preschool wheeze.[37] The group recruited 300 children, and, in a blinded three-way cross-over design, compared regular ICS, intermittent ICS and regular montelukast treatment using a composite outcome of asthma control days and time to an exacerbation for which oral corticosteroids were prescribed. They found that 42% were aeroallergen sensitized and 60% had a positive modified asthma predictive index. In support of this approach, Jochmann et al. have shown good agreement between peripheral blood and bronchoalveolar lavage eosinophil count in a smaller group.[38] Hence, we can progress beyond symptom-driven therapy to using biomarkers to personalize treatment.

Clearly, as with every test in clinical pediatrics, biomarkers must be used critically. Most children who have eosinophilic airway inflammation are atopic, but many atopic children do not have airway disease. We know that fractional exhaled NO (FeNO) is elevated in atopic eosinophilic asthma, but may also be elevated in atopy without airway disease, and that multiple measurement factors (e.g. performing spirometry) affect the readings.[39,40] The response of FeNO to steroid therapy is variable:[41,42] blood eosinophil count correlates with airway eosinophilia in some children, and thus with likely responsiveness to ICS, but may also be elevated in non-airway atopic disease (e.g. eczema) and with parasite infections. This may be particularly relevant in some low- and middle-income countries (LMICs), and emphasizes the need to test the utility of biomarkers in local settings before they are applied clinically.

Biomarkers and adverse effects of asthma and its treatment

The assessment of asthma control is routine, but the domain of risk is also important, including risk of adverse effects of treatment. There is some evidence that ICS side effects relate not to the absolute dose, but to whether the prescribed dose is excessive. In an important study by Brutsche et al., clearance of an intravenous dose of fluticasone was the same in asthmatics compared with non-asthmatics, but systemic absorption of inhaled fluticasone was much greater in non-asthmatics, implying that adjusting ICS dose according to the degree of inflammation may be beneficial.[43] We speculate that titrating the dose of ICS against FeNO—or preferably, but much less practically, to measure induced sputum eosinophils—may allow dose reduction without loss of benefit whilst reducing the risk of adrenal suppression. In the future, more specific markers of ongoing airway type-2 inflammation that are responsive to treatment would be an even better option.

Another risk in asthmatics is impaired airway growth;[7] however, the mechanism is unclear and we have no childhood biomarkers for this risk. This is a really important issue, because failure to attain the normal plateau of airway function at 20–25 years of age[44] is associated with a 26% incidence of early-onset COPD,[45,46] and increased all-cause mortality as early as the third decade of life.[47,48] In preschool children, impaired lung growth is predicted by multiple early aeroallergen sensitization and severe wheeze attacks.[8] In adults, accelerated lung aging (which carries a lesser, but still significant risk of COPD) is associated with both a raised blood eosinophil count >400/µL,[49] elevated FeNO and elevated CD3, CD4 and CD8 cells in the airway mucosa.[50,51]

Future role of biomarkers

Currently, we are focused on phenotypes, defined as the set of observable characteristics of an individual resulting from the interaction of their genotype with the environment (for example, eosinophilic versus non-eosinophilic asthma). Provided that phenotyping leads to beneficial action, this is an improvement on patient history and physical examination, but it results in relatively non-specific treatments. We need to move to endotypes, defined as a subtype of a condition defined by a distinct pathophysiologic mechanism. This should result in pathway-specific treatments, which are essential as more and different monoclonal antibodies become available. So, for example, airway eosinophilia is not synonymous with type-2 inflammation.[52-54] However, we still have a long way to go. In the U-BIOPRED adult cohort, Th2-high asthma, as defined by bronchial epithelial cell transcriptomics, was best predicted by sputum eosinophilia; blood eosinophilia and FeNO were also moderately predictive, but serum periostin was entirely useless.[55]

In summary, we have some initial biomarkers to work with that should lead to the discovery of new ones to help diagnose and manage asthma appropriately. We should currently be using exhaled nitric oxide and peripheral blood eosinophil count as an aid to asthma diagnosis, at least in a developed world setting. Similarly, at least in this setting, we can reduce the prevalence of asthma attacks by titrating ICS dose using exhaled nitric oxide measurements.[10] Induced sputum is likely to be too time-consuming a tool to use routinely in pediatric asthma, and the evidence for benefit in children is less compelling than in adults. There is an increasing trend towards using gene signatures diagnostically, and we need to move in that direction. Unfortunately, we are not even at the stage of phenotypes in most cases, let alone where we need to be, with endotypes in the era of the multiplicity of novel biologics. In the years to come, we need to move to biomarker-driven, objective diagnosis, risk stratification and treatment decisions.

Predicting asthma attacks

For good reason, the Global Initiative for Asthma and other national and international asthma guidelines describe the "reduction of the future risk" as one of the two main targets for asthma therapy.[2,56] An important future risk in this context is frequent and severe asthma attacks, above all accounting for a constant threat for children and their families. Despite considerable advances in asthma therapy and management, including introduction of pediatric guidelines and education programs, acute asthma attacks occur more or less frequently in many patients from various causes, and may result in serious outcomes such as hospitalization, intubation or even death.

A joint statement of the American Thoracic Society and the European Respiratory Society defined severe asthma "exacerbations" as (a) an asthma-related hospitalization or visit to the emergency department that leads to treatment with systemic (oral, intramuscular or intravenous) corticosteroids, or (b) use of systemic corticosteroids (or an increase from a maintenance dose) for asthma for at least 3 days.[57] A more general definition is provided by the position statement on asthma attacks and severe asthma by the European Academy of Allergy, Asthma and Clinical Immunology, which states that asthma attacks should be considered when an increase in a patient's asthma symptoms with increasingly impaired lung function requires increased medication and an unscheduled visit to a physician or hospitalization.[58] However, this definition could also encompass loss of asthma control, characterized by increased within-day peak flow variability, as well as an attack, which is different, being characterized by a steep fall in peak flow[24] and no change in within-day variability.

Asthma attacks and severe asthma are linked with high morbidity, significant mortality and high treatment costs: in the US, around 10% of all children with asthma experience one asthma-related hospitalization and at least one unscheduled visit to the emergency room. Frequent and/or recurrent asthma attacks are closely associated with a decline in lung function and, in childhood, are linked to the development of persistent asthma.[58] In order to achieve the treatment goal of future risk reduction, it is therefore mandatory to (a) (retrospectively) identify the patients at risk of frequent or severe asthma attacks and (b) to (prospectively) predict the patients at future risk through clinical signs or biomarkers.

Identification of patients at risk

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) 3-year observational study followed children (aged 6–11 years; n=637) with asthma,[59] and recorded hospitalization, emergency room and unscheduled doctor visits.[60] Firstly, besides the obvious relationship between poor asthma control and increased risk of asthma attacks, the authors found an imbalance in the risk between different ethnic and social groups, demonstrating a significantly higher risk for children with African American background.[59,60] It should be appreciated that this may not be the case in other healthcare systems in a developed world setting. Secondly, the study showed that children with high or multiple allergic sensitizations are especially susceptible to frequent asthma attacks,[59] pointing towards the important role of allergies, synergistic with viral infections,[61] in the context of childhood asthma. Finally, and maybe most importantly, TENOR and many other studies have shown a striking relation between the risks of future severe asthma attacks and the occurrence of recent asthma attacks. The Severe Asthma Research Program (SARP) was able to define different subtypes of children with severe asthma by cluster analysis, but also demonstrated that asthma attacks were frequent in all four clusters, independent of lung function or disease duration.[62] A systematic review of risk factors for asthma attacks summarizing 68 manuscripts has recently been published.[63]

More recently, a genome-wide association study identified a gene—cadherin-related family member 3—as a susceptibility locus for early childhood asthma with severe asthma attacks, demonstrating significantly increased risk of asthma hospitalization during the first 6 years of life in the presence of certain variants of this gene.[64] The putative mechanism of this association—a reduced barrier function of the airway epithelium against virus entry via a specific receptor (RV-C receptor)[65]—points towards another main risk factor for asthma attacks: virus infections.

In a study investigating children with acute asthma, Bizzintino et al. demonstrated that human rhinovirus (RV), in particular RV-C, accounted for the majority of asthma attacks and caused more severe attacks than other viruses.[66] Lower respiratory tract infections cause asthma attacks, especially in atopic children,[67] and act in a synergistic way in allergic patients by enhanced expression of pro-allergic cytokines (interleukin [IL]-4/IL-13) and high-affinity immunoglobulin E (IgE)-receptor, thus augmenting allergic inflammation in a “two-hit fashion”.[68,69] The susceptibility towards allergen-induced asthma attacks may also be genetically predisposed. A genome-wide differential gene expression study in response to dust mite allergen identified IL-9, a biologically plausible gene target that may interact with environmental dust mite, which may increase severe asthma attacks in children after allergen exposure.[70] In summary, many factors contribute to why and how children with asthma are at high risk of asthma attacks (Figure 2).

Predicting patients at risk of an asthma attack

In order to better treat, or even prevent, asthma attacks in asthmatic children, one would ideally be able to use a simple, non-invasive and inexpensive test to predict future risk. However, several issues hamper this: asthma attacks are often (although not necessarily) preceded by decreased asthma control, but frequently occur out of a seemingly stable situation. The use of a clinical score, e.g. the Asthma Control Test for Children (C-ACT), will reflect the actual situation of the patient, but is unable to predict the future risk. For the same reason, lung function measurements at a given time point have a very poor positive predictive value for acute asthma attacks. Furthermore, a single FeNO measurement was not predictive for asthma attacks in the following 12 months, and severe asthma attacks were not preceded by FeNO increase in the previous 2 weeks.[71] Other biomarkers, such as exhaled breath condensate, sputum eosinophilia, urine bromotyrosine, urine metabolome and serum vitamin D levels, are under investigation, but are currently unable to predict future asthma attacks.[72]

Even in the case of a sudden loss of control, patients or caregivers do not always recognize this as an imminent threat, and adolescents especially fail to recognize the possible consequences. A child can present with normal lung function and good overall health status on one day and experience a severe asthma attack on the other. Predictors or biomarkers for imminent asthma attacks are more or less absent. The strongest clinical predictor of a general risk for future asthma attacks remains a previous asthma attack: 25% of children with a previous asthma attack had at least one subsequent asthma attack in the following 12 months.[73]

In an attempt to summarize this clinical risk, the Asthma Exacerbation Clinical Score (ECS)—ascertained from 17 questions in the four domains of symptoms, medication, healthcare utilization and medical history—was validated in a cross-sectional study and evaluated using data from the Childhood Asthma Management Program (CAMP). ECS was able to predict asthma attacks up to 1 year later with a sensitivity of 0.69; therefore, it may be a helpful tool in patients with increased risk.[74] In a similar approach, Bateman et al. evaluated a risk score for "exacerbation" (RSE) in 7,446 adult patients from three independent studies, using five dominant baseline predictors for a severe asthma attack. By using simple clinical assessments, RSE predicted the risk of uncontrolled asthma within 3 months and severe asthma attacks within 12 months with high sensitivity.[75] However, this approach has not yet been validated in asthmatic children. A retrospective analysis used data from two trials on inner-city asthma in children in the US to identify season-specific risk factors for asthma exacerbations, and developed a Seasonal Asthma Exacerbation Predictive Index (saEPI) consisting of eight variables to determine exacerbation risk during each season.[76] This index was validated in a separate trial designed to prevent fall exacerbations with anti-IgE/omalizumab therapy, showing that exacerbations were associated with a higher saEPI, higher markers of allergic inflammation, higher treatment steps and recent exacerbations.[77] Although saEPI was able to reliably predict those children unlikely to have an asthma exacerbation, there is still a need to develop better markers to predict poor response to therapy and high risk for exacerbations. The future will tell if the broader use of these, or yet-to-be-defined, scores in daily practice will be able to better predict and, importantly, better prevent, future asthma attacks. Of note, any such developed world scores will need to be validated in LMICs before being introduced in that context. Achieving this would be a major improvement in the management of childhood asthma.

In summary, focusing on the risk domain necessitates methods to predict and prevent asthma attacks. In the past, asthma attacks were largely unpredictable. Now we have information that identifies risk factors for an asthma attack, and this information should be used to develop strategies to prevent asthma exacerbations by implementing a detailed and focused assessment of the child, the asthma plan and the current treatment. In future, the application of technology could also be used to refine our ability to identify patients within a population that are at risk for an exacerbation (for example, with the application of machine learning techniques and personal monitoring) in order to enhance our ability to predict those at risk for an asthma attack and hopefully prevent that asthma attack.

Conclusion

In summary, an assessment of risk is an essential part of the management of all children with asthma. Table 1 provides a summary of key points in this review. The challenge for the future is to apply this information in the clinical setting both to identify emerging atopic, eosinophilic asthma early in life, and to monitor the life course of respiratory disease. This should start with measuring lung function in children with repeated episodes of respiratory distress as early as possible, and monitoring it from that point on. For those with evidence of persistent asthma symptoms, assessment of allergic sensitization, evidence of airway inflammation (such as blood or sputum eosinophilia) and measurement of FeNO can provide information on the type of airway inflammation. Spirometry should then be measured regularly to identify those on a low lung function track. Monitoring risk of future attacks obviously involves more than biomarkers. A previous attack, poor adherence to ICS, over-use of bronchodilators and failure to engage with regular follow-up are all markers of risk, but so is uncontrolled type-2 inflammation, which can be monitored using FeNO. Indices to calculate risk of asthma attacks based on prior asthma attacks, lung function, allergic sensitization and biomarkers should be used to inform treatment adjustment. In summary, asthma impairment and risk are separate (albeit to some extent overlapping) issues, and objective measurement of future risk must become part of routine clinical assessments of children with asthma.

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Table 1. Summary of key points

• Reduced childhood lung function is associated with transient wheeze in the first 3 years of life. This wheezing phenotype is unrelated to asthma but is a marker of risk of COPD later in life.
• Risk factors for reduced lung function in childhood are bronchopulmonary disease in premature infants, pneumonia in the first 3 years of life, childhood and parental asthma, severe attacks of wheeze, and environmental pollutants, in particular, maternal smoking and second-hand tobacco exposure.
• Lung function tracks from childhood to adulthood—and therefore many determinants of reduced lung function and COPD—are found in early life. Childhood determinants are aggravated by adult exposures, in particular, active smoking.
• We have several biomarkers available, such as blood eosinophils, exhaled nitric oxide and aeroallergen sensitization, to guide therapy, but more reliable biomarkers are needed.
• Gene signatures hold promise for the diagnosis of asthma, but need further validation.
• We need to move from phenotype-driven decisions to endotype-directed methods to discover and utilize biologics appropriately.
• Asthma attacks in children are frequent, and may account for future loss of lung function, development of persistent asthma, and high morbidity and costs.
• Previous asthma attacks are the best predictor for future severe asthma attacks, and should be a signal for specific management and care

for these patients.
• Novel predictive tools using clinical information, healthcare data and/or serial measurements of lung function are in current development. Accurate biomarkers are still missing.
• Adequate asthma control reduces the risk of severe asthma attacks in children and is one cornerstone for this goal.

COPD = chronic obstructive pulmonary disease.

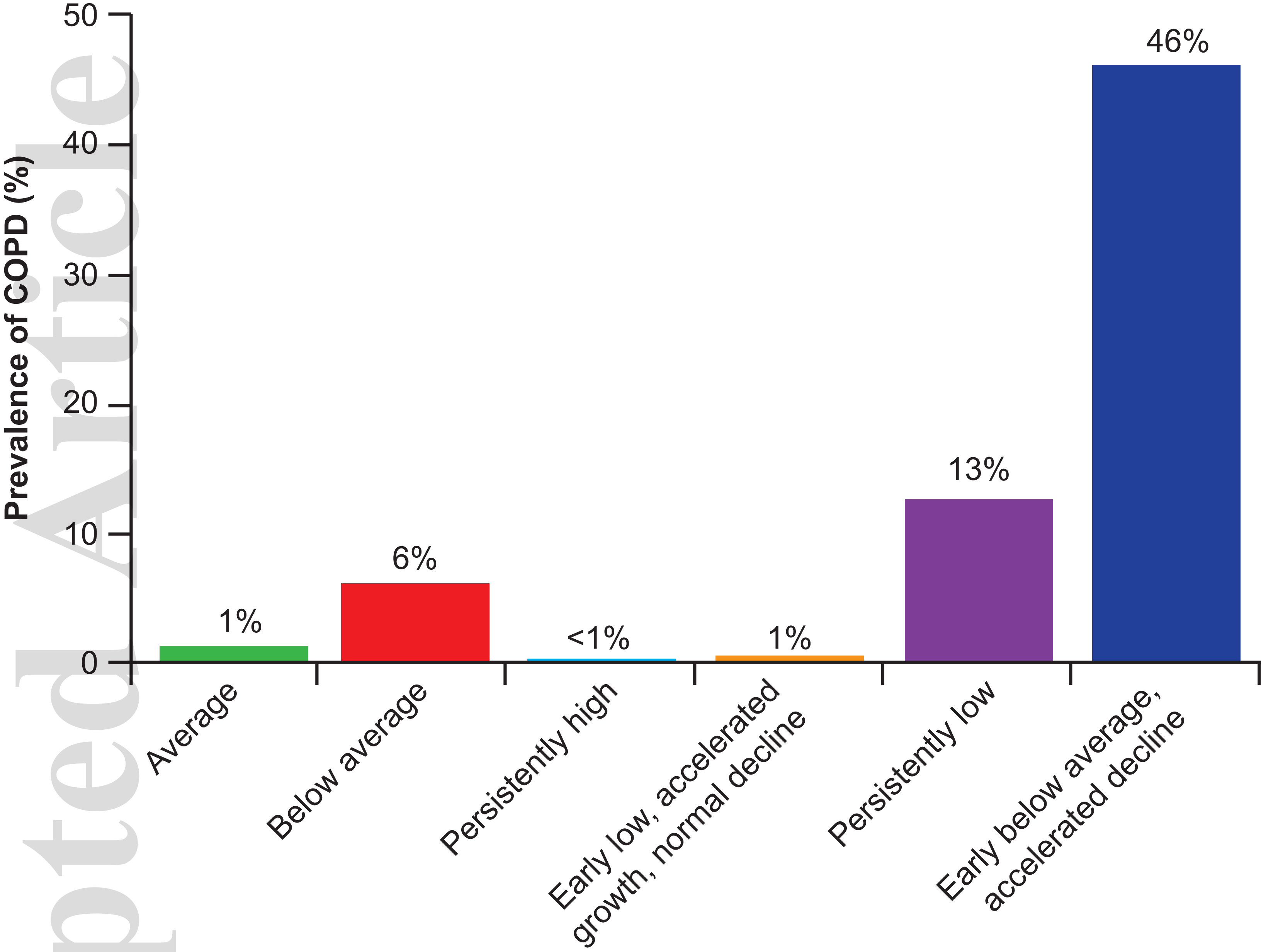
Figure legends

Figure 1. Prevalence of COPD in the six FEV_1 trajectories in the Tasmanian Longitudinal Health Study. Reproduced with permission from Bui et al. [22]

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second.

Figure 2. Asthma attacks may result from multiple causes and require an individualized approach to management and prevention.

ETS = environmental tobacco smoke; HRV = human rhinovirus.



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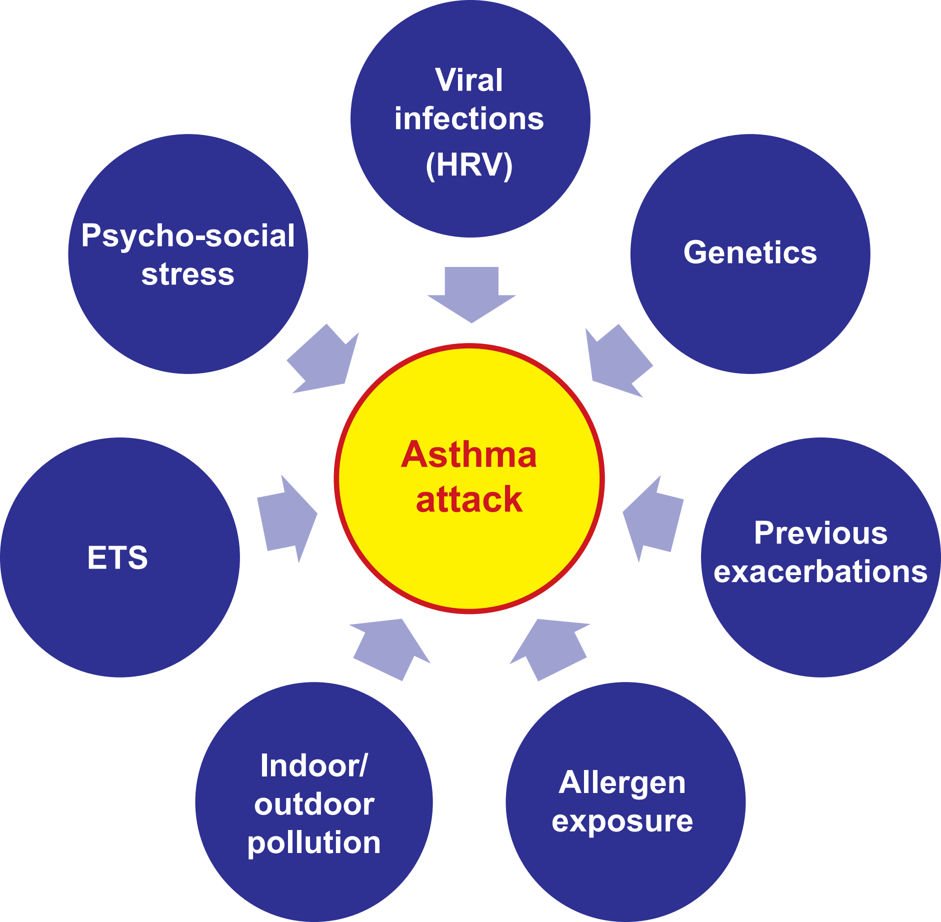
Viral infections (HRV)
Genetics
Previous exacerbations
Allergen exposure
Indoor/ outdoor pollution
ETS
Psycho-social stress
Asthma attack