ASTHMA IN CHILDREN AND ADULTS – WHAT ARE THE DIFFERENCES AND WHAT CAN THEY TELL US ABOUT ASTHMA?

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ASTHMA IN CHILDREN AND ADULTS – WHAT ARE THE DIFFERENCES AND WHAT CAN THEY TELL US ABOUT ASTHMA?

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EDITORIAL
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Editorial: Asthma in Children and Adults – What Are the Differences and What Can They Tell Us About Asthma?

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Editorial on the Research Topic

Asthma in Children and Adults – What Are the Differences and What Can They Tell Us About Asthma?

In the 1970s, asthma was an enigmatic condition with no agreed definition or diagnostic test, but which was nonetheless diagnosed and treated every day. Fast forward 50 years and the situation is mostly unchanged. Uncertainty about what asthma is has hampered development of new treatments. The care for other non-communicable diseases such as diabetes, leukemia, epilepsy, and inflammatory bowel disease has leapt ahead, whilst most patients with asthma are receiving the same treatment their parents were prescribed a generation ago, i.e., short acting beta agonists and inhaled corticosteroids. New treatments options have emerged for severe asthma treatment, but these impact on a relatively small proportion of people with asthma.

The subjective nature of asthma diagnosis causes both under- and over- diagnosis. This uncertainty results in preventable morbidity firstly due to treatment side effects where "asthma" is not present and secondly where effective treatment is not given.

It is now widely accepted that what is currently recognized as "asthma" is a syndrome (1) which describes a range of different pathologies which share common symptoms (i.e., wheeze, shortness of breath and cough) and common physiology (i.e., reversible airway obstruction). Over the years attempts to prise apart these different facets of asthma by stratifying have proven unhelpful; examples of well-meaning but ultimately unhelpful categorizations include atopic vs. non-atopic asthma, intrinsic vs. extrinsic asthma and intermittent vs. persistent asthma. Well-crafted efforts to describe asthma (or wheeze) phenotypes have proved convenient but ultimately flawed. For example, terms such as viral wheeze, multi trigger wheeze and the Asthma COPD Overlap Syndrome have been used to try and capture the potential overlap between "asthma" and other wheezing syndromes which are present early and later on in the life course. In children, viral wheeze and multi trigger wheeze are unstable phenotypes (2) (i.e., over time individuals viral wheeze develop multitrigger wheeze and vice versa) and in adults the "Dutch hypothesis" (3) remains hotly debated. The observation that viral wheeze (aka wheezy bronchitis) and asthma are both risk factors for COPD (4) further dampens enthusiasm for these phenotypes.

One phenotype which seems durable and appears in most attempts at cracking the asthma puzzle is childhood onset asthma (5–7). From a genetic perspective there are different variants associated with childhood onset asthma compared to other phenotypes (8) or adult onset asthma (9). "Childhood onset" is generally considered to include up to age 12 years but the persistently low lung function trajectory associated with asthma is present by 6 years of age (10, 11), and this

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suggests that "childhood onset" might be refined to onset by 5 years of age. Further recognition that asthma may be different between adult and children is seen in asthma guidelines which have different approaches to diagnosis and management of asthma in children and adults. When adult chest physicians and pediatric pulmonologists meet at international conferences, local educational events and transition clinics, there are often differences in approaches for adults and children. For example, adult physicians believe that they can improve asthma symptoms with treatment for rhinitis and gastro esophageal reflux, but this is not clearly seen in children. Aspirin-sensitive asthma is almost exclusively seen in adults. Children inhale lots of environmental exposures at school but do not demonstrate an equivalent of occupational asthma. Steroid-resistant asthma is much more commonly seen in adult than in children and severe asthma in preschool children is very uncommon (and likely to be a manifestation of something other than asthma). Adult-onset, eosinophilic asthma with nasal polyps in the absence of atopy is a well-recognized entity in adults, but is rarely seen in children.

Has the elusive first key to unlocking the asthma conundrum been staring us in the face all along? Could childhood-onset asthma vs. adult onset asthma(s) be the obvious first way to start dissecting asthma?

We challenged experts in asthma from around the world to compare and contrast asthma in adults and children. The author's challenge was not to simply reproduce the many guidelines for asthma diagnosis and management. Each article compared and contrasted asthma in adults and children within the following 11 domains: epidemiology (causation) (Dharmage et al.); epidemiology (life-course) (Trivedi and Denton); genetics (including gene environment interactions) (Morales and Duffy); diagnosis (Saglani and Menzie-Gow); monitoring (Gallucci et al.); treatment (chronic symptoms) (Chung and Paton); treatment (acute symptoms) (Chavasse and Scott); dysfunctional breathing (Connett and Thomas); severe asthma (Fleming and Heaney); primary care (Kaplan et al.); and transition (Withers and Green). Authors of each article included an adult chest physician and a pediatric pulmonologist (with the exception of primary care). After submitting their article, authors were asked to give a "score of similarity" from the perspective of their article using the following scale:

0 Asthma is a totally different condition in children and adults
1 There is ∼10% overlap between childhood asthma and adult asthma
2 There is ∼20% overlap between childhood asthma and adult asthma
3 There is ∼30% overlap between childhood asthma and adult asthma
4 There is ∼40% overlap between childhood asthma and adult asthma
5 There is ∼50% overlap between childhood asthma and adult asthma
6 There is ∼60% overlap between childhood asthma and adult asthma
7 There is ∼70% overlap between childhood asthma and adult asthma
8 There is ∼80% overlap between childhood asthma and adult asthma
9 There is ∼90% overlap between childhood asthma and adult asthma
10 Asthma is the same condition in children and adults.

TABLE 1 | This describes the 11 domains of asthma in which each article associated with this article compared and contrasted asthma in adults and children.

Domain	Nationality of authors	Score of similarity
1. Epidemiology (causation)	UK Australia	7
2. Epidemiology (life course)	US, Australia	4
3. Genetics (including gene environment interactions)	Spain, Australia	4
4. Diagnosis	UK	7
5. Monitoring	Italy	*
6. Treatment (chronic)	Australia UK	7
7. Treatment (acute)	UK	8
8. Dysfunctional breathing	UK	7
9. Severe asthma	UK	5
10. A primary care perspective	Canada, UK, Singapore	7
11. Transition from pediatric to adult services	Australia UK	†

The table also states the nationality of authors and the authors "score of similarity" which rates the overlap between asthma in adults and children from the perspective of their article (higher score indicating greater overlap, see text for definition of score).
**A score was not available. † A score was not sought since the age range at transition is so narrow.*

The resulting scores ranged between 4 and 8, **Table 1**. The domains of epidemiology (life-course), genetics and severe asthma were rated as having only 40–50% overlap between childhood and adult asthma. In contrast, all other domains which were scored were considered to have 70–80% overlap.

So do these different perspectives give us any insight into how we can start to solve the asthma enigma? Well yes and no. The international experts who considered adult and childhood asthma from these different perspectives are consistent in believing that there are some areas of common ground, but also a clear distance between adult and childhood asthma; the experts differ on how much clear distance there is. If asthma is perceived as a single entity which is treated with the same medications as guidelines advocate (12, 13), then there will be an inevitable bias for diagnosis and treatment to be considered mostly homogenous across all ages. Similarly, it is not unexpected that childhood and adult asthma will be considered more heterogenous conditions when perceived from a life course perspective. Perhaps the notable differences are genetics and severe asthma. Hereditary factors are considered to explain up to 70% of asthma causation (14), so from a purely genetic perspective childhood and adult asthma are more different than similar. Severe asthma, as evidenced by persistently poorly controlled asthma despite adequate medication, is vanishingly rare in preschool children

and 70% of asthma deaths occurred in individuals whose diagnoses was made in adulthood (15). Recent years have seen the development of targeted therapies such as monoclonal antibodies that are transforming severe asthma management in adults (16).

Perhaps adult and child asthma may be the most useful (or least useless) method of phenotyping asthma. At the time of writing, 3 months after the last article was published, there have been almost 42,000 views of the articles, so the perspectives seem to have struck a chord. Looking forwards, endotypes, and using non-hypothesis driven artificial intelligence may prove more accurate means to tease apart the strands we know are within the heterogenous entity we call asthma. A uniform definition of asthma and a diagnostic test would be very helpful. In the meantime, we carry on diagnosing and managing asthma across the life course, but in the hope that we can do it better in the near future.

AUTHOR CONTRIBUTIONS

ST wrote the first draft. ST and JU made meaningful contributions to the final manuscript.

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REVIEW
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Dysfunctional Breathing in Children and Adults With Asthma

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Asthma occurs across the life course. Its optimal treatment includes the use of personalized management plans that recognize the importance of co-morbidities including so-called "dysfunctional breathing." Such symptoms can arise as a result of induced laryngeal obstruction (ILO) or alterations in the mechanics of normal breathing called breathing pattern disorders. Whilst these two types of breathing abnormalities might be related, studies tend to focus on only one of them and do not consider their relationship. Evidence for these problems amongst childhood asthmatics is largely anecdotal. They seem rare in early childhood. Both types are more frequently recognized in the second decade of life and girls are affected more often. These observations tantalizingly parallel epidemiological studies characterizing the increasing prevalence and severity of asthma that also occurs amongst females after puberty. Exercise ILO is more common amongst adolescents and young adults. It should be properly delineated as it might be causally related to specific treatable factors. More severe ILO occurring at rest and breathing pattern disorders are more likely to be occurring within a psychological paradigm. Dysfunctional breathing is associated with asthma morbidity through a number of potential mechanisms. These include anxiety induced breathing pattern disorders and the enhanced perception of subsequent symptoms, cooling and drying of the airways from hyperventilation induced hyperresponsiveness and a direct effect of emotional stimuli on airways constriction via cholinergic pathways. Hyperventilation is the most common breathing pattern disorder amongst adults. Although not validated for use in asthma, the Nijmegen questionnaire has been used to characterize this problem. Studies show higher scores amongst women, those with poorly controlled asthma and those with psychiatric problems. Evidence that treatment with breathing retraining techniques is effective in a primary care population including all types of asthmatics suggests the problem might be more ubiquitous than just these high-risk groups. Future challenges include the need for studies characterizing all types of dysfunctional breathing in pediatric and adult patient cohorts and clearly defined, age appropriate, interventional studies. Clinicians caring for asthmatics in all age groups need to be aware of these co-morbidities and routinely ask about symptoms that suggest these problems.

Keywords: asthma, dysfunctioal breathing, paradoxical vocal fold motion, hyperventilation, breathing pattern disorders, inducible laryngeal obstruction, exercise inducible laryngeal obstruction, breathing retraining exercises

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INTRODUCTION

For most of the time breathing occurs sub-consciously. A network of brain stem neurones at the level of the medulla and pons forms the respiratory center which initiates rhythmic contraction of the respiratory muscles whilst co-ordinating these movements with other activities, such as speaking and swallowing (1). As humans we are able to override this otherwise automatic process, for example by breath holding to dive underwater or to forcefully blow out candles. Breathing can also be impacted upon by emotions. For example, bouts of laughter can harmlessly interrupt normal respiration. However, in some people physiologically inappropriate hyperventilation, in response to feelings of agitation and anxiety, can lead to disabling symptoms and become a chronic problem (2). In others abnormal dysfunctional breathing patterns, such as trying to breath through an obstructed larynx, rapid, shallow breathing, irregular breathing and predominant upper-chest breathing might also lead to troublesome symptoms with or without associated hypocapnia. Identifying such problems as a co-morbidity complicating asthma can be difficult as there is considerable overlap in the types of symptoms that occur and a complex interrelationship (3).

In this article we will review how the asthma phenotype might be impacted upon by dysfunctional breathing problems throughout the life course.

DEFINITIONS AND TERMINOLOGY

Dysfunctional breathing might usefully be regarded as an overarching term that is inclusive of problems that are either thoracic or laryngeal in nature (4). Whilst both types are reported as occurring amongst asthmatics, there are no studies addressing the extent to which they both occur within individual patients. This is despite prevalence studies suggesting that both are common and that therefore there should be considerable overlap. Unfortunately the use of the term dysfunctional can be stigmatizing for patients and especially in children where it might have inappropriate connotations about dysfunctional families and elements of abuse or neglect. To address such issues, breathing pattern disorders is a recently recommended term describing functional abnormalities in the mechanics of the diaphragm and intercostal muscles that result in inefficient breathing. Similarly, a joint task force addressing upper airway problems has recommended the term inducible laryngeal obstruction (ILO) rather than laryngeal dysfunction or paradoxical vocal cord motion to denote extrathoracic airway problems. ILO usefully encompasses obstruction occurring at supraglottic as well as glottic (vocal fold) levels as characterized at laryngoscopy (5).

The most commonly recognized breathing pattern disorder and the first to be described was hyperventilation in adults (6). More recently however, breathing pattern disorders have come to encompass a wider spectrum of breathing abnormalities. These include periodic deep sighing, thoracic dominant breathing, forced abdominal expiration and thoracic-abdominal asynchrony (7, 8). The extent to which these other problems occur amongst asthmatics is unknown.

PATHOPHYSIOLOGY

The pathophysiology of dysfunctional breathing disorders is incompletely understood. It has been suggested that the occurrence of a characteristic complex of symptoms that can include breathlessness, chest tightness, sighing, yawning, chest discomfort, general fatigue, anxiety and abdominal bloating, might usefully be regarded as a learnt conditioned response to some sort of emotional distress that has taken on physical manifestations (9). Those affected often do not recognize that their symptoms are arising in this way and that they might be "catastrophising" their health fearing serious underlying illness. The resulting interference with normal automatic control probably occurs at a sub-conscious level.

Somatisation symptoms typically resemble those of an illness the affected person is aware of, has, or has had in the past. In this context, it is well-recognized that those patients presenting with acute hyperventilation, commonly also have undetected co-existing asthma (10). Amongst known asthmatics however, the situation is far more complex because of the difficulties distinguishing true asthma from asthmatic symptoms induced by dysfunctional breathing. Hyperventilation for example, occurs in the vast majority of acute asthma attacks as demonstrated by low arterial carbon dioxide tensions (11). The mechanism whereby this happens might include stimulation of irritant and stretch receptors, anxiety mediated effects on cholinergic bronchosconstriction (12) and a hyperventilatory response to the perception of increased airways resistance (13). Hyperventilation *per se* might then further worsen true asthma through bronchosconstrictive cooling and airway dehydration.

ILO, the involuntary narrowing of the upper airway during inspiration, is similarly complex and multifactorial. Anxiety and psychological disorders are thought to be major contributory factors in the majority of adults who are affected and particularly when symptoms occur spontaneously at rest (14). Amongst younger asthmatics, exercise induced laryngeal obstruction (EILO) is more common and should usefully be regarded as a separate condition. It can co-exist with exercise-induced asthma and psychological co-morbidities are less predominant than in ILO. Causal factors include the aerodynamic effects of high inspiratory flow rates, neurally mediated laryngeal hyper-reactivity and environmental factors, such as inhaling cold air. Gastro-esophageal reflux has been implicated but this is very common in unaffected individuals of all ages and a causal relationship has not been proven (15). Upper airway symptoms of rhinitis and post-nasal drip might also be a contributory precipitant of upper airway closure but is also unproven (16).

EPIDEMIOLOGY

The findings of the main studies to determine the presence of hyperventilation in asthmatics are summarized in **Table 1**. These studies have used the Nijmegen questionnaire (**Table 2**). This

TABLE 1 | Prevalence studies of dysfunctional breathing identified by Nijmegen scoring in asthmatics.

Study setting	Age	Study size	Age differences; Mean (SD)	Prevalence and sex differences	Comments
UK General Practice ($N = 7033$) (17, 18)	17–65 years	71% of 307 asthmatics provided completed questionnaires	Dysfunctional breathers (DB) were younger: 44.8 years (14.7) vs. 49.0 years (13.8) $P = 0.05$	Overall prevalence; 29%. 35% of females and 20% of males Female:male, 73:27 ($P = 0.016$)	Patients were affected equally across all levels of severity. A follow up study found DB in 9.5% of non-asthmatics (14% of females and 2% males surveyed).
Greece Secondary care mild to moderate asthmatics (19)	20–68 years	162 participants; 94 female, 68 male	Not reported	Overall prevalence; 34% 46.8% of females and 14.7% males Female:male, 81:19	DB was more common in asthmatics that were moderate (72.9%) vs. mild (27.1%) and uncontrolled (81.4%) vs. controlled (18.6%).
Scotland secondary care "problem asthma clinic," 76% of patients on BTS step 4 or 5 (20)	13.5–83 years	102 participants; 72 female, 30 male	Not reported	Overall prevalence 64%	Nijmegen scores were related to poor asthma control but more significantly related to quality of life measures.
Romania secondary care asthma clinics (21)	Mean age 35 years	91 participants; 47 female, 44 male	No significant age difference: 37.9 years in DB vs. 34.4 years	Nijmegen score prevalence: 29.7%, progressive exercise test prevalence: 17.6% 38% of females and 7.3% of males Female:male, 82:18	Severe asthma, lack of control and anxiety all associated with DB
Sweden secondary care clinic (22)	Mean age 47 years	25 participants; 19 female, 6 male	Not reported	Nijmegen score positive: 20%	Patients had well-controlled asthma
Spain secondary care clinic (23)	Mean age 47 years, 15–69 years	157 participants; 96 female, 61 male	DB were older: 49 years (24) vs. 42 years (17) $P = 0.014$	Overall prevalence 36% 47% of females and 19.6% of males Female: male, 79:21	Patients with DB experienced all asthma symptoms more acutely. They had more anxiety but no difference in overall asthma severity
Italy school setting (25)	11–14 years	120 asthmatics identified amongst 760 children (15.8%) 47 female, 73 male	No differences	Overall prevalence 25.8% 36.2% of females and 19.2% of males Female:male, 55:45	Asthma was more common amongst males. Amongst non-asthmatics, DB was found in 2.5% (4.1% of females and 0.9% of males surveyed).
Netherlands secondary care asthma clinic (26)	Mean age 10.4 years	206 consecutive asthmatics seen; 96 female, 144 male	No differences	Overall prevalence 5.3% 12% of females and 2.1% of males Female:male, 73:27	Asthma was more common amongst males. There was a strong dose dependent association between DB and asthma control

TABLE 2 | The Nijmegen Questionnaire, Please circle the number in the column that best represents what you have felt recently*.

	Never	Rarely	Sometimes	Often	Very often
Chest pain	0	1	2	3	4
Feeling tense	0	1	2	3	4
Blurred vision	0	1	2	3	4
Dizzy spells	0	1	2	3	4
Feeling confused	0	1	2	3	4
Faster or deeper breathing	0	1	2	3	4
Short of breath	0	1	2	3	4
Tight feelings in the chest	0	1	2	3	4
Bloated feeling in the stomach	0	1	2	3	4
Tingling fingers	0	1	2	3	4
Unable to breathe deeply	0	1	2	3	4
Stiff fingers or arms	0	1	2	3	4
Tight feelings round mouth	0	1	2	3	4
Cold hands or feet	0	1	2	3	4
Palpitations	0	1	2	3	4
Feelings of anxiety	0	1	2	3	4
Subtotals					
Total					

A total score of 23 or more has been used to screen for dysfunctional breathing in a UK community setting (17). Cut-off scores to detect "abnormality" will depend on a comparison with normal values in the same setting and culture in which the questionnaire is used.

was originally developed as a screening tool for symptomatic hyperventilation syndrome and subsequently used as a continuous measure of the benefits of interventions to regulate breathing through capnographic feedback methods (24). Although the questionnaire has not been validated for use in adults with asthma (27) or in children, it does appear to be able to detect a cluster of symptoms that can be characterized as relating to the breathing-related effects of stress and anxiety.

Hyperventilation, as identified with this tool, is recognized as being common and occurs across the whole spectrum of asthma severity. It is more common in those with more severe disease and those with poor control (19, 26). Those studies that have investigated psychological co-morbidities, report that stress and the increased perception of more typical asthma symptoms occur more commonly in hyperventilators (21, 23). Such patients were also more likely to have acute asthma attacks.

All studies report that hyperventilation is more common amongst females vs. males and this sex difference tends to increase through childhood into early adult life. The only study in which asthma was more common amongst boys included a younger age group but, as in all other studies, the percentage of girls with asthma who also had hyperventilation was much higher than boys with asthma and hyperventilation (25).

It is not clear whether hyperventilation is more common in adults. A school study from Italy (25) produced comparable data to that in adult primary care, but a secondary care study from the Netherlands found far less dysfunctional breathing compared with adult data (26). Societal differences in reporting might be an important factor limiting the extent to which the Nijmegen questionnaire identifies abnormalities globally and might also limit the generalisability of such findings (28).

EILO is more common in adolescents and younger adults. It has been described in 26.9% of pediatric referrals to secondary care respiratory services, who were thought to have exercise induced asthma (29). Two population based studies suggest that it can occur in between 5.7 and 7.5% of none asthmatic adolescents (30, 31). Most studies also suggest a female predominance (15).

Adult studies have characterized a very severe phenotype of ILO in which symptoms typically occur without provocation. Amongst a hospital based series of 95 cases, 56% were diagnosed as also having asthma and 28% had suffered episodes needing endotracheal intubation to control symptoms (32). Two studies of adult asthmatics attending secondary care services report prevalences of 19 and 50% (33, 34). The study in which half of the asthmatics had this problem were identified using a novel computerized tomography imaging technique to none invasively assess laryngeal movements.

Poor discrimination between exercise induced inspiratory symptoms and exercise induced bronchoconstriction in adolescents and young adults, might be contributing to the over diagnosis of asthma in these age groups.

DIAGNOSTIC CONSIDERATIONS (SEE TABLE 3)

Symptoms relating to dysfunctional breathing need to be differentiated from symptoms due to other causes. These include undiagnosed respiratory, cardiac or metabolic diseases associated with breathlessness, a lack of physical fitness, panic disorders whereby symptoms are more obviously a part of direct manifestations of anxiety, simply reaching physiological limits when exercising and the less common occurrence of wilfully fabricated or induced illness either by the patient or by proxy during childhood.

Increasing breathing difficulties with prolonged inspiration, throat tightness, stridor and wheeze in the cervical region is highly suggestive of ILO in all age groups. A lack of response to more conventional asthma treatment is also indicative. Clinical clues suggesting the possibility of breathing pattern disorders include chest pain or discomfort with no other obvious cause, very short expiratory breath-holding times (e.g., $<$20 s), feelings of not being able to take a deep breath, the abrupt onset of breathlessness with no obvious cause and the recognition that getting anxious is a trigger of respiratory symptoms (7).

Lactic acidosis after high doses of beta-2-agonists can of itself cause hyperventilation and further complicate a picture of acute asthma made worse by associated tremor and tachycardia which might compound feelings of anxiety (35).

Unfortunately there is no agreed diagnostic work up for this group of conditions. Screening tools for ILO have been suggested but these have largely been developed to distinguish ILO from asthma rather than recognize the two conditions as co-morbidities (36, 37). The medical history can be usefully

TABLE 3 | Dysfunctional breathing in asthma: adults vs. children.

	Children/young people	Adults
Breathing pattern disorders	Girls more often affected and more common in those with psychological co-morbidity	Present across all asthma types and age groups. Women more often affected and those with more severe asthma and/or poor control and/or psychological co-morbidity.
Exercise inducible laryngeal obstruction	Exercise induced breathlessness poorly responsive to asthma treatment. Adolescents of either sex but more commonly girls who are elite athletes or "A" grade students but usually little in the way of psychological co-morbidity	Young adults predominantly as described in adolescents.
Inducible laryngeal obstruction	Limited evidence, but cases similar to that seen in adults have been described and occurring in increasingly younger age groups.	More common in women. Unprovoked asthma, treatment resistant, acute attacks resulting in escalation to high levels of treatment. High levels of physical and psychological morbidity.

informative about EILO. Although psycho-social stressors are less of a feature amongst young people with this condition compared with those who have unprovoked symptoms, they are typically "A" grade individuals, high performing athletes and commonly striving to fulfill parental or peer group expectations. Symptoms crucially peak during exercise or just after stopping, whereas exercise induced bronchospasm typically comes on 3–15 min after exercise. Whilst abnormal spirometry might be indicative of upper airway problems, it is poorly sensitive and should not be used in isolation for diagnosis (38). Typically there is inspiratory flow limitation, but there might also be a plateau in the expiratory flow rate (39). Laryngoscopy, performed during increasing levels of exercise to provoke symptoms, is regarded as the gold standard test, but diagnostic facilities are not widely available and can be difficult to perform in younger age groups (40).

Getting patients to perform voluntary over breathing challenge tests were recommended as a means of reproducing symptoms to support a diagnosis of hyperventilation (41). Initially, this was thought to occur through induced hypocapnia. However, subsequent studies have suggested that, in the majority of patients, alterations in feelings of anxiety and their central effects on neuro-muscular control of breathing are more important determinants of symptoms than respiratory alkalosis and such tests are no longer in common use (42, 43).

Hyperventilation is commonly screened for in asthma clinics using the Nijmegen questionnaire. The questionnaire matches up fairly well with more sophisticated diagnostic testing, such as graded exercise challenge tests (21). The creators of the questionnaire suggest that when used in clinical practice, it should be in conjunction with more objective measures of assessment (44). However, breathing assessments can be difficult as the use of mouthpieces and breathing circuits can directly alter breathing patterns. New technologies, such as structured light plethysmography, might help to better define breathing patterns in the future (45).

In an out-patient setting, there is usually little to find on clinical examination. If symptoms are present, it might be possible to differentiate upper from lower airway obstruction, but this can be difficult. Observing an abnormal breathing pattern might also be usefully informative, but young children in particular commonly breathe in strange ways when their chest is auscultated. Getting the patient or their family to use a mobile phone to capture episodes of abnormal breathing can sometimes be useful (4, 46).

TREATMENT

An essential pre-requisite to treating dysfunctional breathing is to ensure optimal control of underlying asthma. This can be challenging given how similar respiratory symptoms occur in both problems and the need to contain the over use of medication.

Once problems, such as EILO and hyperventilation are identified, a clear explanation and reassurance about the nature of the problem can sometimes be effective in ameliorating symptoms. In the case of EILO, recordings of the larynx at endoscopy or direct visual feedback at the time of the procedure can be highly effective in explaining the cause of symptoms and the use of measures to overcome them (15). The optimal approach to ongoing treatment of (E)ILO is unclear (47). Many interventions have been suggested, but have only been studied in small, uncontrolled trials (48). The prognosis is also far from clear with conflicting case reports although those who have symptoms with no identifiable physical triggers (ILO) appear to do poorly (49). Most reviewers recommend the input of speech therapy services that have developed an interest and expertise in treating this problem and the use of inspiratory muscle training exercises. One retrospective study including adults and children suggested the benefits of inhaled anticholinergic agents in preventing exercise related problems (50). Laser supraglottoplasty has been used in highly selected cases with favorable results (40).

The intervention most commonly used for breathing pattern disorders is breathing retraining exercises. Pediatric studies are limited to reports of case series (51), but a large adult clinical trial in which asthmatics were taught by a trained physiotherapist or used a self-help online programme, reported significant improvements in quality of life scores compared to placebo (52). A smaller randomized controlled trial also reported positive results (53). A number of adult studies evaluating yoga and including yoga breathing techniques have shown small improvements in quality of life in unselected populations of asthmatics (54).

A pediatric service has reported a case series using individualized field testing protocols to characterize exercise related breathing problem in asthmatics and included the use of laryngoscopy to identify EILO as well as breathing pattern disorders thus facilitating individually tailored care plans (55). A pediatric respiratory physiotherapist led clinic designed to specifically address dysfunctional breathing problems has reported significant improvements in quality of life outcomes in support of this approach to treatment (56).

Whilst there is a good scientific rationale for psychological interventions to treat dysfunctional breathing, it is difficult to carry out well-designed studies in this area and there is little supporting evidence for this approach in any age group (57, 58). Suggestion therapy has been shown to be highly effective in young children with habit cough using a bed sheet as a bandage to strap and heal the chest, but a similar device has not been used for dysfunctional breathing in asthma (59).

Evaluating how psychotherapy might impact on dysfunctional breathing is compounded by the many ways in which environmental stressors might result in airway symptoms and associated confounders, such as poor adherence and poor lifestyle choices. These problems typically increase during adolescence and continue into early adult life. Stress increases the individual sensitivity to changes in airway caliber (60). It has also been shown to induce clinically significant bronchoconstriction in up to 40% of asthmatics under experimental conditions and asthmatics have been shown to develop increased indices of airway inflammation as a direct result of stress inducing challenges (61, 62). Research into psychological interventions in adults with asthma is inconclusive (63), but there are suggestions that interventions, such as cognitive behavioral therapy and mindfulness based stress reduction might improve both anxiety scores and asthma control. There is even less evidence for this type of psychological intervention in children and adolescents and high quality clinical studies with clearly defined outcomes are needed in this area (64).

CONCLUSIONS

The diagnosis and treatment of dysfunctional breathing has mostly evolved through observational experience and a growing realization about the importance of this problem in all age groups. Further studies might usefully identify the extent to which the increasing emergence of this clinical problem is impacting on asthma morbidity and in particular during adolescence and early adult life. Recent epidemiological studies have characterized how asthma becomes more prevalent and severe after puberty and particularly in women (65). These changes parallel the emergence of dysfunctional breathing as an increasing problem in asthmatics.

Further studies are needed to help define the optimal approach to treatment in all age groups and to clearly delineate the long-term outcomes for different types of dysfunctional breathing across the lifecourse. Controlled trials have shown that many adults with asthma can benefit from breathing retraining programmes, most probably as a result of correcting breathing pattern disorders. Similar trials are urgently needed to assess the effectiveness of such interventions in children and adolescents.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Use of Symptoms Scores, Spirometry, and Other Pulmonary Function Testing for Asthma Monitoring

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Asthma is a global problem affecting millions of people all over the world. Monitoring of asthma both in children and in adulthood is an indispensable tool for the optimal disease management and for the maintenance of clinical stability. To date, several resources are available to assess the asthma control, first is the monitoring of symptoms, both through periodic follow-up visits and through specific quality of life measures addressed to the patient in first person or to parents. Clinical monitoring is not always sufficient to predict the risk of future exacerbations, which is why further instrumental examinations are available including lung function tests, the assessment of bronchial hyper-reactivity and bronchial inflammation. All these tools may help in quantifying the future risk for each patient and therefore they potentially may change the natural history of asthmatic disease. The monitoring of asthma in children as in adults is certainly linked by many aspects, however the asthmatic child is a future asthmatic adult and it is precisely during childhood and adolescence that we should implement all the efforts and strategies to prevent the progression of the disease and the subsequent impairment of lung function. For these reasons, asthma monitoring plays a crucial role and must be particularly close and careful. In this paper, we evaluate several tools currently available for asthma monitoring, focusing on current recommendations emerging from various guidelines and especially on the differences between the monitoring in pediatric age and adulthood.

Keywords: asthma, guidelines, asthma monitoring, lung function tests, children, adults

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INTRODUCTION

Asthma is one of the most widespread diseases in the world and affects about 300 million patients (1). Despite the high prevalence of asthma in industrialized countries, overall asthma control is still not completely satisfactory. In Europe, only 15% of patients under steroid treatment achieve adequate disease control (2, 3). These findings highlight the importance of optimizing the asthma management in order to improve disease control. Asthma monitoring is an essential step of disease management, which cannot disregard the understanding of the asthma pathogenesis. The main goals of an effective management is the achievement of an optimal control and the prevention of serious exacerbations and impairment of lung function. Achieving control is ensured by monitoring.

The tools for monitoring asthma include the assessment of frequency and severity of symptoms (patient/parents reported or through specific scores) and the use of objective measurements such as spirometry, airway hyper-responsiveness and inflammatory markers.

During the pediatric age, the asthma monitoring must take into account that children are "growing subjects" with the need for continuous treatment adjustments related to the different stages of development not only physical but also psycho-relational. Moreover, healthcare providers do not face a patient but a family unit that must take care of the problem, with all the implications related to school and sports activities.

All guidelines recommend periodic follow-up visits, the interval between visits depends on initial assessment and treatment. Despite the availability of several asthma guidelines, detailed recommendations on asthma monitoring in children and young people (aged 5–16) are poorly defined.

The 2007 American National Asthma Education and Prevention Program (NAEPP) guidelines focuses their attention on the concepts of "impairment and risk" to determine the levels of asthma control and severity, assessed through symptom frequency and measures of lung function among children 5–11 years of age (4). NAEPP guidelines introduced a categorization of asthmatic patients defining them as having "persistent asthma" if they have experienced two or more exacerbations treated with oral corticosteroids (OCS) in the previous 6 months, with a consequent increased future risk. More recently, GINA guidelines state that a previous severe exacerbation in the last 12 months, a history of access into an intensive care or intubation are major independent risk factors for exacerbations (4, 5).

Others factors that increase the future risk in children and adults include the following: socioeconomic or psychological problems, comorbidities such as obesity, chronic rhino-sinusitis, food allergy, exposure to smoke or allergens, low FEV1, higher bronchodilator reversibility, high SABA use, inadequate treatment, sputum or blood eosinophilia and elevated FeNO (5).

The latter two performed before and after the preventive therapy are useful in the assessment of response to medical treatments.

Therefore, the need to quantify the "future risk" for each patient, led the scientific community to search for specific indicators of future exacerbations, such as biomarkers, individual characteristics and genetic factors. These indicators could play a crucial role in asthma monitoring, although some methods are not yet standardized or used in clinical practice.

Scottish Intercollegiate Guidelines Network (SIGN) recommends the monitoring of asthma in children mainly through the assessment of symptoms, number of exacerbations, school absences, evaluation of therapy adherence and inhaler technique, measurement of height, and weight at least annually (6).

Abbreviations: NAEPP, American National Asthma Education and Prevention Program; BDR, bronchodilator reversibility; BHR, bronchial hyper-responsiveness; GINA, Global Initiative for Asthma; FeNO, fractional exhaled nitric oxide; IOS, impulse oscillometry; FOT, technique of forced oscillations; COPD, Chronic Obstructive Pulmonary Disease.

A close monitoring of asthma should include also an early detection of the impairment in lung function as well as the presence of bronchial hyper-responsiveness and bronchial inflammation. These findings are even more relevant in patients at risk, especially in those at high risk of exacerbations or with poor/inadequate disease control (7).

Ideally, a successful management should minimize both daily symptoms and risk factors for exacerbations/complications.

As recommended by the most recent published guidelines (GINA, NICE, SIGN/BTS) the follow up of asthmatic patients should be centered on continuing patients self-monitoring and periodical ambulatory visits for the assessments of the clinical status and lung function parameters (5, 6, 8).

The frequency of follow-up visits depends on asthma severity and the need of treatment adjustments. According to GINA recommendations, the lung function should be recorded at diagnosis, 3–6 months after starting treatment and "periodically" thereafter.

Among pediatric population, an adequate parents training can have a role in reducing the frequency of follow-up visits (9–11).

The main purpose of this article is to compare recommendations of various guidelines about asthma monitoring but also highlighting the differences between recommendations for pediatric and adult patients. In particular, we focus our attention on the availability of clinical tools for assessment of frequency and severity of symptoms, the use of lung function tests and inflammatory markers and the early detection of comorbidities and risk factors for severe asthma.

Monitoring asthma also means investigating the causes of poor medication adherence as well as comprising practical difficulties in using inhaler devices and understanding therapeutic plans especially in adult patients with comorbidities. The lack of awareness and detailed information regarding the importance of treatment adherence, avoidance of triggers, proper inhaler technique significantly contributes to the poor disease control.

Many tools are currently available for clinical and instrumental asthma monitoring, some of these can be performed by patients or caregivers (e.g., PEF), others (such as FeNO, spirometry, or asthma scores) can be made by general practitioners and/or by pulmonologists while some other (such as sputum analysis and oscillometry) only by pulmonologists.

In this paper, we will analyze each of these tools by evaluating different applications in the disease monitoring and comparing different guidelines.

CLINICAL TOOLS

Asthma Control Scores

The clinical history is crucial to assess the asthma control and should include simple key questions and specific asthma scores to collected information about exacerbations, limitations of daily activities, nocturnal awakenings and reliever medication use.

For young children, asthma control should be determined with help from the child's parent through.

TABLE 1 | Main Asthma control scores in children and adults.

	Children	Adults	Normal value/Note
Asthma Control Questionnaire (ACQ) (7 questions) (9)	Validated in adults and children older than 5 years		Well controlled ≤0.75, Inadequately controlled ≥1.5 Minimal important difference 0.5
ACQ shortened (5 five question symptoms only)	Validated in adults and children older than 5 years		More accurate for subjects with normal or near-normal FEV1
Asthma Control Test (ACT) (5 questions) (6)	Validated in children aged for 4–11 year olds	Validated in adults	Reasonably well controlled 20–24; under control 25
Mini Asthma Quality of Life Questionnaire (AQLQ) (32 questions) (10)	–	Validated in adults	Symptoms assessed over the preceding 2 weeks
Pediatric Asthma Quality of Life Questionnaire (PAQLQ) (23 questions) (12, 13)	Validated for age range 7–17 years	–	Higher scores indicate better quality of life
Royal College of Physicians (RCP) (3 questions) (11)	Not validated in children	Not well validated in adults	Probably useful in day-to-day clinical practice
Asthma Therapy Assessment Questionnaire (ATAQ) (20-item) (14)	Mainly used in research	Not used in adults	Include 4 different domains on symptom control, behavior and attitude barriers, self-efficacy barriers, and communication gaps

Both in adult and children, GINA guidelines distinguishes between controlled, partly controlled and poorly controlled asthma based on level of symptoms during the past 4 weeks (5).

This categorization take into account the presence of daily symptoms (>2 per week), any night awakenings, reliever needed (>2 per week) and any activity limitation due to asthma, therefore, controlled asthma is defined by minimal daily symptoms and need of short acting bronchodilator, no nocturnal symptoms and no limitation of activities.

Further and more specific tools to assess the asthma control include quality-of-life measures such as questionnaires applicable in both adults and children (**Table 1**).

The Asthma Control Test (ACT) and the Asthma Control Questionnaire (ACQ) are recommended by all Guidelines and have been studied and extensively validated for both adults and children (the childhood ACT for children 4–11 years of age and the ACQ for children older than 5 years).

ACT includes 5 questions, 3 related to symptoms, 1 related to medication use, and 1 about overall control during the past 4 weeks with separate sections for parent and child; a score $\leq$ 19 indicate a poor symptoms control (15–17).

The C-ACT include seven items and it is divided into two parts. The first part is addressed to the child and consists of four questions on perception of asthma control, limitation of activities, coughing and awakenings at night. The second one is completed by parents and consists of three questions (daytime complaints, daytime wheezing and awakenings at night) with six response options. The score ranges from 0 (poorest asthma control) to 27 (optimal asthma control). ACT and ACQ are useful to assess the response to longer-term treatment.

The ACQ includes 7 questions, 5 related to symptoms, 1 on rescue treatment use and 1 on FEV1 finding; the control is assessed over the preceding week. For children with normal FEV1 a version of five-point questionnaire is preferable (12).

Other available scores include the Mini Asthma Quality of Life Questionnaire, validated for adults (its counterparts for patients 7–17 years of age is the Pediatric Quality of life Questionnaire) and the Royal College of Physicians 3 Questions (13, 14). The first values the control over the preceding 2 weeks and could be used to assess response to longer-term treatment trials. The latter although not well validated in both adults and children, could be used in day-to-day clinical practice thanks to his simplicity.

In the pediatric setting, GINA guidelines also include the Test for Respiratory and Asthma Control in Kids (TRACK) and the Composite Asthma Severity Index (CASI) both including the assessment of exacerbations. The TRACK is the first validated questionnaire designed to assess asthma control exclusively in young children (<4 years). This score may be more sensible in children since it reflects the changes in asthma control over a short follow up period and take into account the assessment of exacerbations (18, 19). Nevertheless, children may experience more exacerbations during one season vs. another while most of the clinical scores investigate trends over the last month, so they may not be totally indicative of asthma control in children with seasonal wheezing (20).

SIGN guidelines also recommend the use of the Pediatric Asthma Quality of life Questionnaire (PAQLQ) to assess health-related QoL in children with asthma and including 23 questions that investigate 4 domains (symptoms, activity limitations, emotional function, and environmental stimuli), validated for the age range 7–17 years (21, 22).

A further questionnaire is the Asthma Therapy Assessment Questionnaire (ATAQ), a 20-item parent-completed questionnaire, developed to assist clinicians to identify children at risk for adverse outcomes of asthma and including 4 different domains on symptom control, behavior and attitude barriers, self-efficacy barriers, and communication gaps (23).

TABLE 2 | Positive test threshold of objective tests in children (aged 5 years and over) and adults.

	NICE (8)		GINA (5)		SIGN (6)	
	Children	**Adults**	**Children**	**Adults**	**Children**	**Adults**
Obstructive spirometry	FEV1/FVC ratio <70% (or below the lower limit of normal if this value is available)		FEV1/FVC ratio <0.90	FEV1/FVC ratio <0.75–0.80	FEV1/FVC ratio <70%	
Bronchodilator reversibility test	Improvement in FEV1 of 12% or more	Improvement in FEV1 of 12% or more and increase in volume of 200 ml or more	Improvement in FEV1 of 12% or more	Improvement in FEV1 of 12% or more and increase in volume of 200 ml or more	Improvement in FEV1 of 12% or more	Improvement in FEV1 of 12% or more and increase in volume of 200 ml or more**
Peak expiratory flow variability	Variability over 20%		>13%*	>10%*	Variability over 20%***	
FeNO	35 ppb or more	40 ppb or more	FENO >50 ppb has been associated with a good short-term response to ICS		35 ppb or more	40 ppb or more
CHALLENGE TEST						
Methacholine and histamine (both non-specific direct broncho-provocation tests)	n/a	PC20°: 8 mg/ml or less	n/a	Fall in FEV1 of 20% or more with standard dose from baseline	n/a	C20 8 mg/ml or less°
Mannitol	n/i	n/i	n/a	Fall in FEV1 of 15% or more from baseline, with standard dose	Fall in FEV1 15% or more at cumulative dose of 635 mg	
Exercise challenge	n/i	n/i	Fall in FEV1 of >12% predicted , or PEF >15%	Fall in FEV1 of >10% and >200 ml from baseline	n/i	n/i

*Comparison between the different guidelines. n/a, not applicable; n/i, not included. *Calculated from twice-daily readings (best of each time): (HighestPEF-LowestPEF)/mean of the day's highest and lowest PEF, and averaged over 1–2 weeks. **School children using a threshold of 9% change. ***Monitor peak flows for 2–4 weeks. °PC20: provocative concentration of methacholine causing a 20% fall in FEV1.*

A new score defined Severe Asthma questionnaire (SAQ) is being validated in adults; it can be used to detect the impact of both asthma symptoms and treatment on quality of life (24).

Usually, in daily practice, the possibility of using asthma control questionnaires and above all quality of life measures is significantly higher in the pediatric clinical routine.

Certainly, in the pediatric age the supervision of parents ensures a further control and makes these scores more reliable than those compiled by asthmatic patients. Moreover, in the adulthood comorbidities play an important role in the care management, often with reduced time to apply these clinical tools by healthcare professionals.

Concluding, we believe that asthma control scores are simple and useful monitoring tools, but the most of these refer to a short previous period and are often influenced by the subjective (or caregivers') symptom perception, for this reason they should be combined, when possible, with more objective tests such as pulmonary function tests or a careful clinical follow-up.

Patients and Parents Self-Monitoring

Patients as well as parents should be encouraged to keep track of symptoms consequently healthcare practitioners should adequately train them on this issue.

As recognized by several guidelines, many patients can benefit from a written action plan in which, according to the disease control, the patient is instructed to recognize the need for action (e.g., to step up therapy or seek medical advice) (5, 25).

A detailed education program for both adults and pediatric patients should cover: training on treatment adherence and correct use of medication, recognition and avoidance of triggers and risk factors for exacerbations or worsening of symptoms (such as exposure to allergens, influenza virus or rhinoviruses, smoke both active and passive or other environmental factors, including workplace related factors) (25, 26).

Among adults, educational programs have been repeatedly proven effective in improving symptoms control, quality of life and treatment compliance therefore they potentially can prevent or reduce severe exacerbations conducive to urgent visits and hospital admissions (4, 5).

A recent prospective randomized controlled trial including 160 adults with asthma showed that a single 10 min, educational session provided by a respiratory specialist, could substantially improve asthma control determined by the ACT score after 3 months. The educational program included basic information about asthma treatment and instructions on inhalation technique for about 10 min (27).

More recently, new tools for the self-assessment of asthma control are available such as applications for smartphones, often produced by respiratory societies, which can often be obtained for free (28, 29).

These applications enable patients to enter in their profile daily data such as symptoms and their frequency, ACT, PEF values etc. The app can therefore calculate the level of asthma control. Some apps have up to date pollen maps and calendars, or have personalized acoustic memos to remind patients to take the inhaled therapy (30).

Vasbinder et al. in their randomized controlled trial e-MATIC (e-Monitoring of Asthma Therapy to Improve Compliance in children), proposed the use of the "real-time medication monitoring (RTMM)" for improving adherence to inhaled corticosteroids. The study failed to prove a significant improvement in asthma control, quality of life or asthma exacerbations with high costs in the intervention group, although RTMM with tailored SMS reminders improved adherence to ICS (31).

Nevertheless, e- devices may be precious tools for monitoring, especially in adolescence. Teenagers, in particular, may experience age-related difficulties as they accept responsibility for self-management from their parents; the negative impacts of asthma are largely preventable if adolescents engage in self-management behaviors, including symptom prevention as treatment adherence and trigger avoidance or symptom monitoring. It has been proved that the use of "asthma apps" can positively influence adolescents' self-management behaviors through increased self-observation, self-judgment and increased self-efficacy (32).

The availability of these new promising resources certainly opens up new possibilities in the management and monitoring of asthma, even though a recent Cochrane meta-analysis (including 21 studies in adults and children), concluded that tele-healthcare for asthma did not seems to improve QoL or reduce exacerbation rate in children (33). Therefore, further evidences and studies will be needed to routinely recommend the use of these tools in the clinical practice.

LUNG FUNCTION TESTS AND INFLAMMATORY MARKERS

Spirometry

The functional hallmark of asthma is a reversible airway obstruction and its detection is often required for the diagnosis of the disease. The severity of obstruction is a known risk factor for exacerbations, therefore functional monitoring is essential in order to achieve optimal control.

Moreover, severity of obstruction does not always correlate with symptoms: a significant bronchial obstruction may be present also in asymptomatic children and adults. It has been shown that children with chronic obstruction are less likely to perceive the symptom of dyspnea than children with an acute obstruction (34). For this reason, children with poor perception of chronic obstruction are at risk of developing severe exacerbations, associated with poor lung function. Therefore, a regular assessment of lung function is crucial.

The spirometry is the main test for detecting and measuring airway obstruction in children over 5 years old and adults and it has some precision for predicting future attacks.

Reference values of the lung function tests suggested by several guidelines are reported in **Table 2**.

The presence of expiratory airflow limitation should be valued at diagnosis or at the beginning of treatment (in order to evaluate increase in treatment dose), after 3–6 months of controller therapy and then periodically depending on clinical course, although SIGN and GINA guidelines do not indicate clear recommendations on monitoring FEV1 in children (5, 6).

NICE guidelines specify to perform a spirometry for monitoring asthma at each visit or at least after 3 or 6 months from the beginning of therapy and then every 1–2 years (8).

Spirometer parameters should be adjusted according to sex, age, and ethnicity. According to GINA guidelines, the FEV/FVC ratio cut-off of normality is 0.90 in children and 0.75–0.80 in adults (5). Different guidelines often diverge in the choice of this cut-off (according to NICE guidelines, it is 0.70 in both pediatric and adult age) (8) (**Table 2**).

In general, a fixed threshold might lead to an overestimation of obstruction in elderly patients and an underestimation in young ones (35).

In **Table 3** we reported the main lung function tests used in our clinical setting in monitoring asthma.

FEV1 is the most widely used functional index in the asthma follow up; in particular, among asthmatic children a FEV1 $<60\%$ is a risk factor for exacerbations and its decrease is associated with increasing asthma severity (36). Children with FEV1 $<60\%$ of the predicted seem to have a double risk of asthma exacerbations in the following year compared to those with FEV1$>$ 80% (4, 37).

In order to compare spirometry findings in children, Global Lung Initiative recommend that the spirometry values should be expressed in z score, even though these recommendation is poorly applied worldwide (5).

Adults with an accelerated FEV_1 decline ($>$30 ml/year) may be either steroid-resistant/difficult-to-treat asthmatics or not adequately treated principally due to under-perception or poorly adherence to maintenance therapy (38).

Some authors have argued that other indices, such as FVC, should be also considered, as some patients with severe obstruction respond to bronchodilators with a significant increase in FVC but not FEV1 (39).

In order to compare spirometry findings in children, Global Lung Initiative recommend that the spirometry values should be expressed in z score, even though these recommendation is poorly applied worldwide (8).

It is well known that the confirmation of the diagnosis requires a positive reversibility test (according to GINA guidelines improvement in FEV1 $\geq$12 in children, $\geq$12% together with an increase in volume $\geq$200 ml in adults). American Thoracic Society recommendations define a significant bronchodilator response (BDR) as an increase in FEV1 $\geq$12% and/or 200 ml in both adults and children (40).

TABLE 3 | Main lung function tests used in our clinical setting in monitoring asthma.

	Children >5 years	Adults	Normal value	Note
Spirometry	Values widely available, usually within normal range in adults and children with asthma		FEV1/FVC >0.90 in children >0.75–0.80 in adults	Less applicable in acute severe asthma
Positive bronchodilator (BD) reversibility test from baseline suggestive for asthma	++	++	Children FEV1 <10% Adults FEV1<12% and <200 mL	In children sometimes also suggestive also FEV1 >10% In adults more robust FEV1>15% and >400 mL
Peak expiratory flow (PEF) average diurnal variability over 2 weeks	Not routinely used	+	<8% with twice daily readings	Confirmed airflow limitation by variability
AIRWAY RESPONSIVENESS				
Exercise test	Used preferentially for diagnosis and not to monitor disease		Children <12-% adults <10%	Not applicable in patients with impaired lung function (i.e., FEV1/FVC <0.7 and FEV1<70% predicted)
Exhaled nitric oxide (FENO)	Used only in specific protocols for diagnosis and monitoring		<25 ppb at exhaled flow of 50 ml/sec	>50 ppb highly predictive of eosinophilic airway inflammation and positive response to corticosteroid therapy
Eosinophil differential count in induced sputum	–	+	Normal range <2%	Close relationship between raised sputum eosinophil count and corticosteroid responsiveness

+, dubious role in asthma monitoring; ++, potentially useful in asthma monitoring.

Some studies showed that in children, this cut-off may be too high and then less sensitive to assess airway obstruction, suggesting that a lower cut-off (8%) should be used to improve the diagnosis of asthma (41).

The assessment of bronchodilator reversibility (BDR) can be useful not only to confirm the diagnosis but also in the asthma monitoring. In severe pediatric asthma, the spirometry should be always performed with a bronchodilator test to detect airway obstruction and its reversibility since it has been shown that these children have an increased bronchodilator response that may be associated with higher risk of impairment of lung function (42, 43). A persistent BDR may also be associated with poor therapy compliance or wrong inhaler technique and seems to correlate to some indices of airway inflammation, such as the exhaled nitric oxide fraction (FeNO), therefore it might be predictive for a positive response to inhaled corticosteroids (ICSs) (44).

Regarding the most appropriate setting to perform lung function tests, although spirometry performed in the primary care setting may be a useful tool in asthma monitoring, concerns have been raised about the quality and standardization of this procedure compared to hospital-based or laboratory spirometry. The spirometry provides objective data of lung function, but the outcome is often dependent on the operator. Therefore, in our opinion, expert personnel that spurs the patient to an optimal execution should perform it.

Peak Expiratory Flow

Home monitoring of peak expiratory flow (PEF) may be use as an additional functional test in the monitoring of asthma. There is still lack of evidence that PEF monitoring over time might result in better disease control. PEF measurement can be used to document the variability of bronchial obstruction in asthma even if PEF is not related to FEV1 values and may underestimate the degree of airflow limitation and air trapping. Moreover, PEF values vary depending on the meter used therefore it is advisable to compare its measurement with the best personal value (obtained during the disease control phase or during maximum treatment) using the same meter. PEF "personal best" has proved to be useful in improving the progression of asthma, but the patient needs to be adequately trained since measures are effort dependent (45, 46).

According with most of the guidelines, PEF measurement should not be routinely used to monitor asthma in children, unlike in adults where it is recommended for subjects with severe asthma or with poor perception of airflow limitation (5, 6, 8). Certainly, PEF measurements do not give information about the obstruction characteristics (obstructive or restrictive) or site. Nevertheless, NICE guidelines recommend a monitoring of peak flow variability for 2–4 weeks in children and young people (aged 5–16) if there is "diagnostic uncertainty after initial assessment with a normal or obstructive spirometry, irreversible airways obstruction (negative BDR) and a FeNO level of 35 ppb or more" (8). NICE guideline also recommend considering a value of more than 20% variability as a positive test. Even GINA guidelines in the diagnostic assessment of asthma include the use of diurnal PEF variability calculated from twice daily over 2 weeks; for children diurnal variability >13% is considered excessive [unlike in adult where the cut-off of PEF variability is >10% (5)] (**Table 2**).

The ease of execution even in pediatric age and the possibility of being performed at home and during acute phase make this test easy to handle and reproducible, even though its monitoring does not improve asthma control in addition to clinical scores in adults and children (6, 47). For this reason, PEF assessment is not recommended in pediatric age in asthma monitoring.

Impulse Oscillometry, Forced Oscillations Technique, and Expiratory Flow Limitation

During childhood, impulse oscillometry (IOS) and the technique of forced oscillations (FOT) may be used as an alternative technique to assess lung function, since measurements are made from tidal breathing and younger children are able to comply compared to spirometry. IOS measures respiratory resistance and reactance by analyzing responses to pressure waves of different frequency. The assessment of airflow resistance can be an indirect indicator of airway caliber, while spirometry mainly reflects airflow characteristics. IOS is easily performed during tidal breathing therefore it only need a partial collaboration of small patients, even though it is not available in all centers and in some cases, it is difficult to interpret. ERS/ATS guidelines give practice information about the test modality and its analysis (48).

Several studies showed a significant association between findings of the IOS and those of spirometry. In asthma, IOS has been used to assess the bronchodilator response and the therapeutic response to different treatments. In studies utilizing both IOS and spirometry, the first one has proved to be more useful than spirometry in early detection of asthmatic children from normal cohorts (49).

Many evidence showed that peripheral airways (PAW) in children as in adults are the initial site of inflammation and obstruction in asthmatic disease (50).

IOS can evaluate peripheral airways more accurately than spirometry identifying a PAW impairment before symptoms and spirometric abnormalities occur. For these reasons, it could be used to guide an early therapeutic approach to prevent clinical symptoms and further lung damage (51).

In adulthood, excluding patients with severe chronic asthma and marked airway obstruction, an expiratory flow limitation (ELF) at rest is seldom observed, unless under severe and prolonged bronchoconstriction.

One way to value EFL is by the forced oscillation technique (FOT) through the application of negative pressure at the mouth during tidal expiration (NEP).

When the oscillatory pressure applied at the mouth does not reach alveoli during expiration due to a flow-limiting segment in the bronchial tree, the reactance signal, instead of reflecting the mechanical properties of the lung parenchyma and airways, is influenced only by those of the airways and becomes much more negative with a clear distinction between inspiration and expiration.

This application of the FOT is useful to identify flow limitation during tidal breathing, but the closure of intrathoracic airways eventually occurring at end expiratory lung volume (EELV) must be considered as an important limiting factor of this technique, since the distortion of the reactance signal is similar (52, 53).

In addition, when EFL originates in the peripheral airways, it is mainly due to the viscous, density-independent, flow-limiting mechanism, while the speed wave, density-dependent, flow-limiting mechanism is substantially involved when the EFL originates in the central airways.

Despite several potential applications of FOT and oscillometry, larger longitudinal studies will be needed to confirm the usefulness of these techniques as routinely monitoring tools in asthma.

Blood and Sputum Eosinophils

As indicated in the recent ERS/ATS guidelines, the assessment of asthma phenotype (eosinophilic or non-eosinophilic) may play a crucial role in the management of patients with severe disease (54). The ideal tool for this purpose is represented by the cell count on BAL during bronchoscopy. The invasive nature of the procedure has obviously limited the number of subjects studied, therefore the scientific community has sought surrogates that allowed the identification of different asthma phenotypes such as eosinophils count in induced sputum and the peripheral eosinophilia.

Based on the sputum analysis, patients with asthma can be grouped in four different inflammatory phenotypes: eosinophilic asthma, neutrophilic asthma, mixed granulocytic asthma, and paucigranulocytic asthma. Eosinophilic asthma defined as a sputum eosinophil count of 2–3% or higher, represents almost half of the asthmatic population (55).

Several studies have found higher levels of sputum eosinophils in uncontrolled asthmatics, therefore sputum analysis may be a useful method of objectively monitoring asthma (56). Moreover, the short-term response to inhaled corticosteroids depends on the amount of eosinophils present in the sputum therefore this technique may be a guide for modulating steroid therapy (57).

A recent study by Fleming et al. included 55 children with severe asthma and showed that incorporating the control of sputum eosinophils into the management algorithm reduce exacerbations in the short term even though did not significantly reduce overall exacerbations or improve asthma control (58).

It is difficult for children to collect sputum because they tend to swallow more than expectorate.

Among pediatric patients with bronchial hyperactivity, induced sputum, through stimulation with hypertonic saline, may allow to understand the type of inflammation, the presence of cells and lower respiratory tract mediators (59–61).

Several studies have evaluated the safety of sputum induced in asthmatic children aged 6 to 16, demonstrating how moderate bronchospasm occurs in 10% of children and resolves with the administration of the bronchodilator (62, 63).

In clinical practice, the use of these tools for the diagnosis and monitoring of asthma certainly has limitations, however among pulmonologists and also in our center these may be a precious help for the assessment of the type of inflammation, the diagnostic confirmation and the adjustment of the preventive therapy.

In asthma, blood eosinophil are considered a good surrogate marker for sputum eosinophil count (over 2–3% with a cut-off of 220 cells per mm^3 or 3% among adults). High eosinophil count in peripheral blood is a recognized risk factor for disease severity and for future exacerbations (58, 64). During childhood, the asthma predictive index (API) also include blood eosinophils within minor criteria as predictor of future recurrent wheezing (65, 66).

Nadif et al. showed that patients with high blood eosinophilia (>250 cells per mm^3) had lower FEV1 values and worse asthma control than those with eosinophils in normal range (67).

For these reasons, the bronchial and peripheral eosinophilia could be considered a potentially useful biomarker for the selection of patients who will respond to anti IL5 therapy, a monoclonal antibody used in patient older than 12 years with refractory eosinophilic asthma.

Fractional Exhaled Nitric Oxide (FeNO)

As already mentioned, the detection of different asthma phenotypes guided the scientific community searching for specific biomarkers that could guide and improve the disease monitoring and the therapeutic approach. The monitoring of asthma should also include the determination of minimally invasive inflammatory markers.

Fractional exhaled nitric oxide (FeNO) measurement correlates with eosinophilic airway inflammation and therefore with the most common asthma endotype, independently of gender, and age. FeNO levels are higher in asthmatic children compared to non-asthmatic children and in one study values rose further during exacerbations and rapid decline after oral steroid treatment (68–70). British guidelines recognize that a FeNO <20 ppb in children under 12 years may have a role in identifying patients who can step down corticosteroid treatment (5). This relationship is lost in adults smokers (superior cut off in children >35 ppb, in adults >50 ppb) (6) (**Table 3**).

Agency for Healthcare Research and Quality (AHRQ), recently conducted a systematic review (including 175 studies) about the role of FeNO in the diagnosis, treatment and monitoring of asthma. Both in adults and in children FeNO results can predict which patients will respond to inhaled corticosteroid therapy, therefore the use of this marker in long-term managing of treatments can reduce the frequency of exacerbations. Moreover, the review showed that FeNO diagnostic accuracy was modestly better in steroid-naïve asthmatics, children and non-smokers than the overall population. Nevertheless, regarding the asthma monitoring in preschooler children authors concluded that there is insufficient evidence supporting the use of FeNO in this category for predicting a future diagnosis of asthma (69).

Two recent Cochrane reviews, including both pediatric and adulthood studies, showed that tailoring asthma medications based on FeNO levels decreased the frequency of asthma exacerbations but did not impact on day-to-day clinical symptoms or inhaled corticosteroid dose (71–73).

In conclusion, FeNO role in asthma management has not been concretely proven due to incomplete evidence therefore it is not routinely recommended in all patients, at least in monitoring, even though it may be useful in subjects who respond poorly to inhaled corticosteroids (73).

Nevertheless, the use of biomarkers as tools for phenotyping asthma and personalizing therapy is certainly attractive but it has not yet entered clinical practice.

AIRWAY HYPERRESPONSIVENESS

Bronchial Provocation Tests

A hallmark feature of asthma is increased responsiveness of the airways to inhaled stimuli. The assessment of bronchial responsiveness through provocation tests can be useful for both research purposes and clinical practice. Bronchial provocation tests include the direct inhalation of different substances such as methacholine, histamine, mannitol, inhalation of allergens or the use of "stimuli" such as exercise, inhalation of cold air and hyperventilation with dry air (74).

Monitoring of bronchial hyper-responsiveness (BHR) is not routinely recommended in current guidelines, since its role is more typically confined to the diagnostic process.

However, some data seem to indicate a potential usefulness of BHR among asthmatic adults, as an indicator of exacerbation risk and inhaled corticosteroid response (75, 76).

Bronchial provocations tests are not usually performed in asthmatic children and several papers support this recommendation including one clinical trial (77). Nevertheless, BHR assessments could have a role in asthma monitoring among children with exercise limitations or with reduced perception of symptoms (78).

Within the pediatric population, the exercise test may be a precious tool for the evaluation of indirect BHR (79). A reduction in post-exercise FEV1 compared to the baseline is considered a sign of bronchial obstruction induced by exercise. GINA guidelines recognize that the exercise challenge may provide information about airway hyper-responsiveness but "only undertake a challenge if it is otherwise difficult to assess asthma control." A positive exercise challenge for children is considered for a fall in FEV1 >12% of predicted or PEF >15% (for adult a fall in FEV1 >10% and >200 ml from baseline).

NICE guideline clearly recommend of "do not use challenge testing to monitor asthma control," while SIGN group state that "regular monitoring of airway responsiveness not proven to improve asthma control in children" (6, 8) (**Table 2**).

COMORBIDITIES AND RISK FACTORS

Both for adults and children, the detection of potentially modifiable risk factors for exacerbations may be useful in asthma monitoring and includes the exposure to specific allergens, smoking, high SABA use, poor adherence to therapy and incorrect inhaler technique. As already mentioned, GINA guidelines state that a previous sever exacerbation in last 12 months and a history of access into an intensive care or intubation are major independent risk factors for exacerbations (5).

Moreover, the asthma monitoring cannot be separated from an early identification and management of associated comorbidities (**Table 4**).

This term defines factors and/or pathological conditions, which can coexist with asthma, contribute to its severity and to poor control.

Comorbidities are obviously more frequent in adults and may significantly complicate the management of asthma throughout

TABLE 4 | Principal asthma comorbidities.

	Children	Adults	Note
Anxiety and depressive disorders	++	+	Especially during adolescence
Gastro-esophageal reflux disease	+	++	More common in adults, although empiric treatment of asymptomatic GERD in asthmatics does not seem useful (68)
Obesity	++	+++	Asthma is more difficult to control in obese patients
Food allergy/anaphylaxis	+	+	Food allergy is a rare trigger but the association with asthma is a risk factor for anaphylaxis
Allergic rhinitis/Sinusitis	+	++	Often coexist
Nasal polyps	–	++	Exacerbated by aspirin or NSAIDs
Pregnancy	–	+	Change asthma control
Perimenstrual asthma	±	++	Possible role during adolescence
Respiratory infections	+++	++	Often exacerbation factors
Tobacco smoking and environmental exposure	++	+++	Chronic mechanism
Cardiovascular diseases	–	+++	Frequent in elderly
Chronic pulmonary diseases	–	+++	Frequent in elderly

–, not relevant; ±, some relevance; ++, relevant; +++, very relevant.

all its stages, from diagnosis to treatment. All guidelines present this point as relevant in the workup of asthma. The most frequent comorbidities among adult population include upper airway diseases (rhinitis, chronic rhinosinusitis), obesity, COPD, gastro-esophageal reflux disease (GERD), bronchiectasis; in elderly patients, heart failure is very common.

From an epidemiological point of view, rhinitis, and rhinosinusitis are the most frequent comorbidities of asthma for all ages and the former seems to be associated with an increased risk of exacerbations (80). The presence of GERD is associated with worse asthma symptoms and poorer quality of life while obesity can worsen asthma by compromising lung function, inducing corticosteroid insensitivity and systemic inflammation (81–83).

All these conditions often exacerbate or simulate symptoms of asthma causing a poor response to treatment. For these reasons, it is essential to assess and carefully monitor these comorbidities also by implementing integrated care pathways.

Other conditions that may present with elevated blood eosinophilia and a clinical picture mimicking a severe refractory asthma, such as chronic eosinophilic pneumonia, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis (ABPA), should be taken into account during asthma monitoring (84).

Finally, a subset of adult patients (usually over 40 years of age) present a combination of both asthma and COPD features which is known as Asthma-COPD overlap syndrome (ACOS), likely resulting from different phenotypes of airway disease. They are often smokers, but may have allergies and a family or personal history of asthma with a not completely reversible airway obstruction (5).

Additional diagnostic findings include eosinophilic airway inflammation, a good response to corticosteroid therapy, and high concentrations of exhaled nitric oxide, which should be assessed in the monitoring of these patients (85). Since ACOS outcome is generally worse than asthma with higher treatment needs, the management should be especially careful therefore it might be advisable to refer these patients to specialized center.

ASTHMA ACTION PLAN

The asthma action plan helps asthmatic adults and/or caregivers recognize worsening asthma and gives clear instructions on what to do in response. Each asthmatic patient is different, so each action plan will be too.

An accurate action plan should cover every of these points:

- What medicines to take and when
- A list of potential triggers
- Early symptoms of flare-ups and what to do if they happen
- Know how to manage a full-blown flare-up
- When to get emergency care

The asthma action plan should be based on symptoms trend or peak expiratory flow (PEF) measurements and is individualized according to the pattern of the patient's disease. In children, symptom-based plans are preferred.

Inclusion of PEF measurements in the asthma action plan can be beneficial for adults with more severe or difficult-to-control asthma and those with poor symptoms perception. When PEF is used, the asthma action plan should be based on personal best rather than on predicted values.

Regular review of the asthma action plan is an important part of asthma monitoring since the level of asthma severity and control may change over time (86, 87).

CONCLUSION

An ideal asthma monitoring should provide a personalized approach for each asthmatic patient.

The personalized asthma care should use specific monitoring tools for different patients, preferably with different fields. This assumption therefore represent a fundamental part of comprehensive asthma management.

In light of reported evidences, it may be noted that some advice in monitoring of asthma may apply to both adults and children.

1. The categorization of asthma based on disease severity, which is crucial for the therapeutic planning, require an accurate combination and evaluation of the clinical and functional status.
2. The assessment of risk factors for exacerbations and for severe asthma should be carefully investigated.
3. Moreover, the estimation of future risk allows identifying patients who require a closed follow-up in order to prevent

acute exacerbations and to detect an early impairment of lung function.
4. The use of a written and simple action plan (clear indications on which drugs to take every day, how to spot if asthma's getting worse, and what to do if you have an asthma attack) for both adults and children is advisable and it should be reviewed during each control.
5. At each visit, the patient's adherence to the treatment and correct use of inhaler devices should be assessed and reviewed. For patients who monitor their PEF at home, is advisable to review periodically the correct use of the instrument.
6. Pediatricians should always remember that a careful monitoring of growth and possible side effects of therapy is essential among asthmatic children.
7. Self-management tests associated with monitoring tools for the assessment of pulmonary function and measures of airways inflammation must be appropriate for pediatric age.

Ideally, the follow-up of asthmatic patients should have as its objective a responsible self-monitoring associated with a periodic outpatient check of the clinical status and lung function findings.

As healthcare professionals, we should arouse awareness and self-management. Particularly among adolescents, we should implement a shared decision-making and find ways to connect with them effectively.

The use of new technologies in monitoring asthma is inevitable and may help us to provide great opportunities to monitor patients remotely and to improve the communication.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and the supplementary files.

AUTHOR CONTRIBUTIONS

MG and PC performed the literature review. AP, SN, and EdP contributed to data collection and interpretation of the literature data. GR coordinated the writing group. All authors critically reviewed the manuscript, read and approved the final version.

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REVIEW
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The Differences in Acute Management of Asthma in Adults and Children

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Acute asthma or wheeze is a common presentation to emergency services for both adults and children. Although there are phenotypic differences between asthma syndromes, the management of acute symptoms follow similar lines. This article looks at the similarities and differences in approaches for children and adults. Some of these may be age dependent, such as the physiological parameters used to define the severity of the attack or the use of age appropriate inhaler devices. Other differences may reflect the availability of evidence. In other areas there is conflicting evidence between adult and pediatric studies such as a temporary increase in dose of inhaled corticosteroids during an acute attack. Overall there are more similarities than differences.

Keywords: asthma, attack, adults, children, treatment

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INTRODUCTION

Asthma is the commonest chronic condition in the UK with a UK lifetime prevalence of patient-reported clinician-diagnosed asthma of 15.6%. In 1 year asthma results in 6.3 million primary care consultations and 93,000 hospital in-patient episodes. The costs of asthma are estimated at £1.1 billion 12% of which is accounted for by hospital care and 14% for primary care consultations (1). Many physicians in both adult and pediatric medicine across the whole healthcare economy will therefore be expected to manage patients who may present with an acute attack of their disease so knowledge of this area is very important for good patient care. Guidelines for the management of an acute asthma attacks are documented in a number of national and international publications (2–4). Management of an acute attack may start with treatment at home and may progress to treatment in primary care, the emergency department and on the hospital wards including intensive care. This article looks at similarities and differences in the management of acute management between adults and children of varying ages.

The definition of asthma is difficult and there is no gold standard, and it is increasingly recognized that asthma as a condition is made up of a number of phenotypes (5, 6). The use of phenotypic variations is more likely to inform and modify chronic management, rather than the acute management of a crisis at the present time. The first recognized presentation of asthma is not uncommonly an acute attack, particularly in children, and therefore may present a diagnostic challenge.

The British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN) asthma guideline precis the definitions of asthma as the presence of more than one symptom of wheeze, breathlessness, chest tightness and cough associated with variable airflow obstruction. Other definitions of asthma, in both children and adults, include airway hyper-responsiveness

and airway inflammation as components of the disease (BTS/SIGN) (2). The National Institute of Clinical Effectiveness (NICE) have suggested a diagnosis should not be made without objective evidence of airway obstruction or inflammation (3).

In younger children, particularly those <5 years of age, the diagnosis of asthma (or phenotypes of wheeze) is difficult and often controversial (7). Acute wheeze is however a very common presenting complaint to both primary and secondary care and may frequently be recurrent and troublesome. Whilst the intricacies of diagnosis is beyond the context of this piece, recognition of this difficulty is important. Asthma diagnosis and phenotypes are subjects covered elsewhere in this series of articles. As is not uncommon, the evidence for different treatments are less well studied in the younger age groups. For the purpose of this review it will be assumed that the diagnosis of asthma is secure and we will be comparing / contrasting the differences in children and adult asthma.

DEFINITION OF ADULTS AND CHILDREN

The definition of an adult will be taken as a person over 18 years, accepting there is a considerable cross over in the adolescent age group. In most hospital emergency departments, adolescents under 18 are usually managed in the pediatric area, and if necessary by pediatricians, although it is recognized that different healthcare systems may have different policies. Guidelines and clinical trials vary in their cut off ages with many studies including adolescents over 12 in "adult" studies. Age cut offs are clearly not as relevant to provision of care in primary care and the home environment, however the age and maturity of the individual patient should be considered when agreeing a management plan. For children there are differences in the approach to the young, preschool child (<5 years) and there is very little evidence for the management of asthma symptoms in children under 1 year of age.

DEFINITIONS & ASSESSMENT OF ACUTE ASTHMA

An acute asthma attack represents a deterioration in symptoms and lung function from the patient's normal status. Distinguishing between a lower respiratory tract infection and an asthma attack can be challenging, particularly in young children. This can include shortness of breath, wheezing, cough, and chest tightness (4). Attacks are marked by a decrease from baseline in objective measures of pulmonary function, such as peak expiratory flow rate and FEV1. Objective measures, such as FEV1 are less easy to perform in children and young persons, and PEFR can be unreliable in children and young persons if they have not used the technique before and are highly unlikely to be achieved in children <5 years of age (8). In some individuals, in particular those with poor adherence and/or more severe asthma, there can be a challenge in distinguishing between a mild asthma attack and long-standing poorly controlled asthma; the challenge in in part due to symptoms being common to both a mild asthma attack and poorly controlled asthma and in part due to guidelines not defining criteria for a mild asthma attack.

Pharmacological management is entirely dependent upon the severity of the attack which in turn is defined by a number of objective and subjective findings. These differ between adults and children, reflecting the age-related physiologic differences and the reliability of pulmonary function testing in children. Definitions from the BTS/SIGN and Global Initiative for Asthma (GINA) guidelines are outlined in **Table 1**.

PRE-HOSPITAL MANAGEMENT OF ACUTE ASTHMA

Adults are encouraged to have a personalized asthma action plan (PAAP) in place which empowers them to increase treatments in response to increasing symptoms or decreasing PEFR (9). The PAAP should advise them when to seek medical assistance. In children PAAPs advice only recommends increasing short acting beta agonist. A Cochrane database systematic review of 4 clinical trials in children concluded that symptom-based PAAPs are superior to peak flow PAAPs for preventing acute care visits (10). There was insufficient data to firmly conclude how symptom-based PAAPs were superior of the two. For example the observed superiority of symptom-based PAAPs may have been due to greater adherence to the monitoring strategy, earlier identification of onset of deteriorations, higher threshold for presentation to acute care settings, or the specific treatment recommendations (10).

Most adult PAAPs recommend the increased use short acting beta agonists at the onset of acute symptoms (11). Most pediatric management plans suggest a titrated increased dose of beta-2 agonist using doses between 2 and 10 puffs of a salbutamol (pressure dose metered dose inhaler and spacer device) up to every 4 h (12). Safety net advice to seek medical advice and call an ambulance if not responding to treatment should be included. Judicial use of rescue oral steroids at home is sometimes included, although there is no consistent evidence of benefit for this practice (13).

A second approach in adults may be the use of a single combination inhaler for both preventer and relief [Maintenance and Reliever Therapy: (MART)] which patients may titrate in accordance to their symptoms (14). Preparations are not currently licensed or in formulations for younger adolescents or children in the UK.

A recent study in adults suggested a 4-fold increase in inhaled steroid dose used early during an attack resulted in fewer severe asthma exacerbations than a plan in which the dose was not increased and this would be a reasonable self-management strategy in this situation (15). A similar pediatric paper suggesting a quintupled dose of ICS in children however showed no benefit (16). This may reflect a difference in causation of an attack, different responses by age or methodological differences between the studies.

Any patients with features of acute severe or life-threatening asthma should be referred to hospital immediately.

TABLE 1 | Comparison of symptoms and signs associated with levels of acute asthma severity in adults and children the BTS/SIGN (1) and GINA (4) asthma guidelines.

	BTS/SIGN		GINA	
	Adult	**Children**	**Adult & Children >5years**	**Children (0-5)**
Moderate	Increasing symptoms PEFR >50–75% best or predicted No "severe" symptoms	Able to talk in sentences SpO_2 ≥ 92% HR-≤140/min* or 125/min** RR-≤40/min* or 30/min** PEFR ≥50%** best or predicted No "severe" symptoms	Talks in phrases Prefers sitting to lying Not agitated Respiratory rate increased Accessory muscles not used Pulse rate 100-120 bpm SaO_2 in air 90-95% PEF >50% predicted or best	Breathless Agitated Pulse rate ≤200 bpm (0–3), ≤180 (4–5 years) SaO_2 ≥92%
Severe	Any one of: Inability to complete sentences in one breath PEFR: 33–50% best or predicted HR ≥ 110/min RR ≥ 25/min	Can't complete sentences in one breath or too breathless to talk or feed SpO_2 < 92% HR ≥ 140/min* or 125/min** RR ≥ 40/min* or 30/min** PEFR 33–50%** best or predicted	Talks in words Sits hunched forwards Agitated Respiratory rate >30 bpm Accessory muscles in use Pulse rate >120 bpm SaO_2 <90% in air PEFR ≤50% predicted or best	Unable to speak or drink Central cyanosis Confusion or drowsiness Marked subcostal and/or sub-glottic retractions SaO_2 <92% Silent chest on auscultation Pulse rate >200 (0–3 years) or >180 bpm (4–5 years)
Life threatening	Severe attack with any of: Altered conscious level Exhaustion Arrhythmia Hypotension Cyanosis Silent Chest Poor respiratory effort PEFR <33% best or predicted SpO_2 <92% PaO_2 <8 kPa Normal $PaCO_2$ 4.6–6 kPa	Severe attack with any of:Silent Chest Cyanosis Poor respiratory effort Hypotension Confusion Exhaustion SpO_2 <92% PEFR <33%** best or predicted	Drowsy Confused Silent chest	
Near fatal	Raised $PaCO_2$ and/or requiring mechanical ventilation			

**children 1–5 years; **children over 5 years.*

MEDICAL MANAGEMENT OF ACUTE ASTHMA IN HEALTHCARE FACILITIES

Oxygen

It is essential to monitor oxygen saturations when assessing an asthma attack. In adults there is evidence that hyperoxia may be detrimental plus there is also a possibility that the patient may have chronic obstruction so that the delivery of oxygen should be controlled to maintain an SpO2 level of 94–98% (17).

In children with saturations <92% in air after initial bronchodilator treatment it is advised that inpatient hospital treatment will be required as this reflects more severe asthma (18, 19). Oxygen should be administered to any child with acute asthma with SpO2 <94% via a tight fitting face mask or nasal cannula at sufficient flow rates to achieve normal saturations of 94–98%.

Short Acting Bronchodilators

The initial management of an acute asthma attack is usually given by the inhaled route. In adults it is recommended that in non-life threatening acute asthma, beta agonists can be given through repeated actuations of a pMDI via an appropriate large volume spacer. The recommendation is to give 4 puffs (400 mcg) as the initial dose and increase by 2 puffs every 2 min up to 10 puffs if needed. In life threatening asthma however wet nebulization of beta agonists with oxygen is preferable. Adult patients who do not respond to initial nebulization of beta agonist may be considered for repeated doses at 15–30 min intervals or continuous nebulization at 5–10 mg/h (2).

In Children, a pMDI and age-appropriate spacer device is the preferred option for delivering inhaled beta agonists with mild to moderate asthma as this is less likely to produce a tachycardia and hypoxia than using a nebulizer (20, 21). A facemask connected to the mouthpiece of a spacer is recommended in children <3 years old. In children drug dosing should be escalated as required from two puffs of salbutamol suitable for mild attacks up to 10 puffs for more severe attacks with 30–60 s between puffs. The inhalers should be activated into the spacer in in individual puffs and inhaled immediately by tidal breathing (for five breaths). In the hospital setting, with appropriate monitoring, doses can be repeated every 20 min over an hour if necessary. In children with severe or life-threatening asthma should receive nebulized

bronchodilators driven by oxygen. These can be given in combination with ipratropium bromide which is recommended if there is a poor response to salbutamol alone (22). Repeated doses can be given every 20 min over a 1–2 h period. In contrast to adult recommendations continuous nebulized beta agonists are of no greater benefit than the use of frequent intermittent doses in the same hourly dosage (2, 23, 24).

After the first few hours salbutamol can be tapered down to one to two hourly and ipratropium tapered to four to six hourly or discontinued. In adults ipratropium bromide is recommended in acute severe or life-threatening asthma but is not necessary in milder asthma attacks or after stabilization.

Steroids

For adults and children it is important to give steroids early during an acute attack. Steroid tablets are as effective as injected steroids and should be given for at least 5 days in adults or until recovery. Evidence for the ideal duration of oral steroid treatment is still required (25). Once recovery is achieved, steroids can be stopped abruptly and do not need to be tapered unless the patient is on maintenance steroids or if they have received a prolonged course of three or more weeks (26). Inhaled steroid treatment should continue during prescription of oral steroids (2).

In children, oral prednisolone is the steroid of choice for asthma attacks and intravenous corticosteroids are only indicated for children who are vomiting or who have very severe symptoms which prevent swallowing (27). Some studies using dexamethasone have shown potential equivalence to prednisolone with the potential to reduce the number of doses and therefore potentially improving treatment adherence (28). The use of oral steroids is more controversial in preschool children (age 1–5). This may reflect the presence of common symptoms in asthma and lower respiratory tract infection in this age group. Additionally there may be more than one acute asthma phenotype, but one study considered this and found no difference in outcome between children with "viral induced wheeze" with and without atopy (29). Different prednisolone dose schedules have been recommended from 0.5–2 mg /kg (30) and others recommend an age related dose schedule (2). In children recommendations are usually for 3 days of treatment but may need to be extended from 5 to 10 days to bring about recovery. Tapering is not necessary unless the course exceeds 14 days.

There is no evidence to support the use of Inhaled steroids as an alternative to oral steroids during an asthma attack of this severity but it is good practice to continue the usual maintenance inhaled steroids during an attack (2).

Second Line Treatments

Magnesium

There is some evidence that intravenous magnesium sulfate has bronchodilator effect during an acute asthma attack (31). In adults there is limited evidence that a single dose of iv magnesium may be some benefit in adults with a PEF <50%. This is felt to be safe and may improve lung function and reduce intubation rates in those with acute severe asthma. It may also reduce admission to hospital with asthma from ED in adults who have had little or no response to standard treatment. It should only be used following consultation with senior medical staff (2).

The use of IV magnesium has become more frequent in children with acute asthma. There is relatively little evidence compared to other intravenous therapies although there is one comparative study showing a more rapid improvement compared to IV salbutamol or aminophylline (32). It is generally safe with few side effects. It should be used if there is a poor response to first line therapies and is not recommended in mild to moderate asthma attacks.

The use of nebulized magnesium has been studied in one large UK based trial (33). Overall the benefits were small although did seem to offer some benefit when added to nebulized salbutamol and ipratropium in the first hour of hospital treatment in children presenting with a short duration of acute severe asthma symptoms presenting with an SpO2 <92% (34). At the time of writing, the role of nebulized magnesium in both adults and children is uncertain.

Aminophylline

In adults evidence suggests that the addition of intravenous aminophylline is unlikely to add any additional bronchodilation compared to standard care and side effects such as arrhythmias and vomiting are increased (35). However, patients with near fatal asthma with a poor response to initial therapy may gain additional benefit from IV aminophylline. It is advised that before its use consultation should take place with a senior member of medical staff as these patients are likely to be rare (2).

In children, aminophylline was previously considered the first line IV treatment following a poor response to initial management (bronchodilators and steroids) but now intravenous magnesium is recommended as first line due to reduced side effects and equal efficacy (2). There is some evidence of benefit in severe or life threatening asthma (36). The risk of side effects is high and ECG monitoring is recommended with the patient monitored in an HDU/PICU environment.

IV Salbutamol

There may be some benefit for the use of IV salbutamol in both adults and children who have not responded to first line treatments and IV magnesium (37).

In children an initial bolus dose (15 mcg/kg) may be given. In comparison with IV aminophylline (bolus and infusion) this has been shown to give equivalent results. Initially it was thought to cause fewer side effects compared to aminophylline but more recently nausea, tachycardia and lactic acidosis have been frequently recognized. There is very limited evidence for the use of a salbutamol infusion in children but is sometimes utilized in the PICU environment.

Antibiotics

In adults an infection precipitating an attack is most likely to be viral and therefore routine prescription of antibiotics is not indicated. Objective measures such as serum procalcitonin where available should be used to guide decisions on using antibiotics (2).

TABLE 2 | Summary of similarities and differences in the diagnoses, assessment and treatment of acute asthma in adults and children.

	Similarities	Differences
Diagnosis	Same symptoms	Challenge in distinguishing from lower respiratory tract infection may be greater in children
Assessment	The same physiological parameters are used in assessment (i.e., Respiratory rate, Heart rate, Oxygen saturations)	Physiological parameters differ numerically between adults and children. Achievability and reliability of PEFR and FEV_1 in children is lower than in adults
Stepping up treatment	Actions plans recommend using short acting beta agonists when symptoms occur	Only adult personal action plans (based on good evidence) recommend MART of quadroupling ICS dose for worsening control/minor asthma attacks
Supplemental oxygen treatment	Required when oxygen saturation are below 92% in all age groups	Aim for ceiling 98% in adults due to potential overlap with COPD
First line treatment	Same medications used	Doses differ in children and adults, e.g., initial short acting beta agonist 400 microg in adults but in children is 200 microg increasing to 1,000 microg
Second line treatment	Same medications used (i.e., intravenous magnesium, salbutamol and aminophylline)	No major differences at this level

In children the role of bacterial infection is also less common than a viral trigger. Antibiotics are not recommended. Procalcitonin is not routinely used at present in children. CRP is more frequently used but less specific.

Critical Care

In both adults and children with acute asthma and a poor response to standard therapy it is important to involve clinicians with the appropriate skills in airway management and critical care support early. There is little good quality evidence to guide treatment at this stage and a national audit of treatment for acute asthma in adults in the UK found a wide variation in clinical practice (38).

In adults admission to critical care is recommended in those requiring ventilator support and acute severe life-threatening asthma indicated by: deteriorating PEF, persisting or worsening hypoxia, hypercapnia, arterial blood gas analysis showing fall in pH or rising hydrogen concentration, exhaustion, feeble respiration, drowsiness, confusion, altered conscious state or respiratory arrest (2).

In children admitted to hospital with status asthmaticus two small studies have reported the use of non-invasive ventilation suggesting that it is safe and feasible but there was insufficient evidence of its effectiveness. In adults there has also been suggestions that the use of NIV can be safe and effective however the evidence is limited and inconclusive. One trial of NIV in a small number of patients showed improvement in hospitalization rates, discharge from emergency departments and lung function. Other trials have shown safety and feasibility of using NIV in treating acute exacerbations of asthma but little evidence of benefit in comparison with standard care. It is recommended that NIV should only be considered in adults in a critical care or equivalent setting (2).

Invasive ventilation strategies are beyond the scope of this article.

The BTS asthma guidelines are able to recommend the following advice for therapies at this stage. In both adults and children Ketamine may be considered as a potential bronchodilator although further prospective trials are required before conclusions about effectiveness can be drawn (39, 40).

In children the anesthetic gas Sevoflurane is potentially an option for correcting high levels of PaCO2 in mechanically ventilated children however its use would be limited to areas where appropriate scavenging facilities to extract gas are available (41).

There is an increasing trend in the use of Recombinant DNase in pediatric intensive care in children with acute asthma due to airway plugging. There is little or no published evidence to support this practice. A study in non-intubated adults with severe asthma showed no improvement in FEV1 (42).

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a form of cardiopulmonary life-support, where blood is drained from the vascular system, circulated outside the body by a mechanical pump, and then reinfused into the circulation. While outside the body, hemoglobin becomes fully saturated with oxygen and CO2 is removed. Oxygenation is determined by flow rate, and CO2 elimination can be controlled by adjusting the rate of countercurrent gas flow through the oxygenator. It is a highly specialized form of treatment and available in only a few centers in the UK. It has been shown to be useful and an option in severe asthma refractory to mechanical ventilation in both children and adults by providing adequate gas exchange and preventing lung injury. However, careful management is required to avoid complications (43).

Discharge and Follow Up

In adults it is recommended discharge can be considered when clinical signs are compatible with home management i.e., medical therapy can continue safely at home. Patients with PEF <75% best or predicted and diurnal variability of PEF >25% are at greater risk of early relapse and readmission therefore this should be borne in mind when deciding on timing of discharge. This is also true in children (2).

In both adults and children it is important to assess and attend to correct risk factors that may have lead to a loss of control of asthma leading to admission e.g., smoking or exposure to smoke in the household in children. Education prior to discharge is important including advice on inhaler technique, a review of the personal asthma plan and, if used, PEF record keeping. Tools

such as the BTS asthma discharge bundle are available to provide help with this process (44).

All patients both adult and children should have an appointment arranged with their primary care team within 48 h of hospital discharge. Secondary care review should be arranged within a few weeks.

CONCLUSION/SUMMARY

There are similarities and differences in the diagnoses, assessment and treatment of acute asthma in adults and children, and these are summarized in **Table 2**. The mainstay of management is to ensure early assessment of severity with appropriate use of bronchodilators with corticosteroids. There are some differences in the recommendations of how these medications are given and their associated doses but because the pathological processes are essentially the same the general principles of treatment are also the same. The more cautious use of oral corticosteroids in children may reflect concern over longer term side effects as well as questionable response in preschool children. The use of variable dose regimes of inhaled steroids may reflect the availability of suitable drug preparations and the difference between an individual feeling their own innate symptoms and a parent recognizing their child's symptoms.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Two Sides of the Same Coin?—Treatment of Chronic Asthma in Children and Adults

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Globally, asthma is one of the most common chronic conditions that affect individuals of all ages. When poorly controlled, it negatively impacts patient's ability to enjoy life and work. At the population level, effective use of recommended strategies in children and adults can reduce symptom burden, improve quality of life and significantly reduce the risk of exacerbation, decline of lung function and asthma-related death. Inhaled corticosteroid as the initial maintenance therapy, ideally started within 2 years of symptom onset, is highly effective in both children and adults and across various degrees of asthma severity. If asthma is not controlled, the choice of subsequent add-on therapies differs between children and adults. Evidence supporting pharmacological approach to asthma management, especially for those with more severe disease, is more robust in adults compared to children. This is, in part, due to various challenges in the diagnosis of asthma, in the recruitment into clinical trials and in the lack of objective outcomes in children, especially those in the preschool age group. Nevertheless, where evidence is emerging for younger children, it seems to mirror the observations in adults. Clinicians need to develop strategies to implement guideline-based recommendations while taking into consideration individual variations in asthma clinical phenotypes, pathophysiology and treatment responses at different ages.

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INTRODUCTION

Asthma Burden

Asthma is a chronic inflammatory disease of the airways with typical symptoms of wheezing, breathlessness and cough and variable airflow obstruction. The WHO estimates that some 235 million people currently suffer from asthma (1) and it is the commonest chronic disease of children worldwide. Asthma causes long term effects: it affects patient's quality of life, daily activities, their work and school attendance; it causes anxiety—to the patients themselves, and to their families and caregivers; it imposes a substantial economic burden on families and societies; and it causes death. Yet, with appropriate management most people with asthma can enjoy excellent symptom control and a good quality of life (1).

Control of asthma symptoms, reduction of future risk in terms of asthma attacks, and prevention of decline in lung function are recognized as the key goals of asthma management (**Figure 1**). These goals are relevant to all patients with asthma irrespective of age. Pharmacological therapies are the main tools for controlling asthma but non-pharmacological interventions such as allergen or

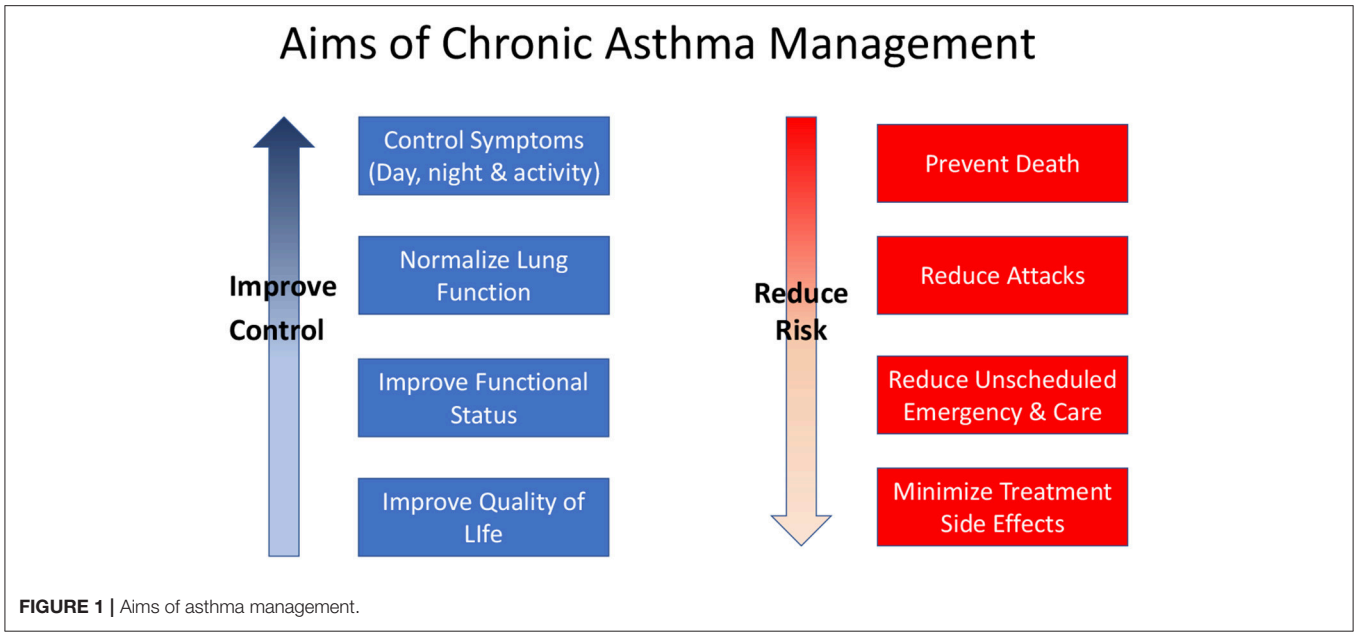

FIGURE 1 | Aims of asthma management.

irritant (especially tobacco smoke) avoidance, and education about the disease, inhaler device use and self-management strategies are also important.

Asthma Phenotypes

There is increasing recognition of different clinical and patho-physiological patterns of asthma ('phenotypes') in both children and adults.

The most striking asthma phenotype is found in young children who present with wheezing attacks associated with viral infection, particularly rhinovirus infection, often with no symptoms between attacks. For many of these children, the wheezing attacks stop in later childhood (2). In older children, a more classic asthma pattern of attacks with chronic interval symptoms usually with an atopic background emerges (3). However, these patterns overlap and are unstable, at least in early childhood, and may change from one to another over times scales as short as a year (4, 5). Lung function testing in young children is generally not possible and making a diagnosis of asthma without objective testing has been criticized (6). The implications for the choice of treatments of the different phenotypes is complex and has resulted in a wide variety of approaches often compounded by a lack of evidence (7).

In adults, the pattern of airway inflammation is more diverse and the clinical presentation is often clouded by co-existing comorbidities especially in those with severe asthma (8, 9). Currently an emerging concept, but an important focus of asthma management in adults is the identification and management of pulmonary, extrapulmonary and behavioral "treatable traits". The hope is that treatment of these modifiable elements (e.g., bronchodilator reversibility, eosinophilic airway inflammation, depression) even in the absence of a deeper understanding of the mechanisms of airway inflammation will improve patient outcomes (10). Although the concept of treatable traits has been developed in relation to adults it is also likely to be useful in children with asthma.

There are some patients, both adult and children, with "discordant" disease who suffer substantial symptom burden with little evidence of eosinophilic inflammation or those with high level of inflammation but few symptoms (11). However, the majority of patients will have asthma symptoms that parallel the degree of inflammation in which step-wise guideline recommended approach is likely to be effective.

This review summarizes evidence about differences in the approaches to asthma treatments in adults and children as currently recommended in commonly used asthma guidelines (12, 13) (**Table 1**).

GUIDELINE RECOMMENDED APPROACH FOR CHRONIC ASTHMA

Step 1: As Needed SABA

For patients of all ages, as needed short acting beta2 agonist (SABA) reliever therapy is highly effective for rapid relief of asthma symptoms. SABA as the sole treatment is now only recommended for those with the mild and intermittent symptoms (<2 per week and no nocturnal awakenings), no history of asthma attacks in the previous year and normal lung function.

Historically, there has been a perception that patients with intermittent symptoms are not at risk of asthma attacks, a view increasingly challenged. Evidence from adult studies showed that airways inflammation occurs at a very early stage of the disease even in patients with intermittent asthma, albeit at a lower level than in those with persistent asthma (14, 15). Furthermore, early introduction of once daily inhaled corticosteroid (ICS) in adults and children > 5years with mild asthma symptoms

TABLE 1 | Comparison of recommended treatments for chronic asthma in adults and children from widely used international guidelines (12, 13).

Asthma guideline treatment steps	Similarities in recommendations	Differences in recommendations, effectiveness or safety profile
Step 1	• As needed SABA effective for all ages • Consider early use of ICS for adults and children ≥ 6 years old	
Step 2	• Regular low dose ICS for all ages	• Potential concern for effect of ICS on linear growth in children • Intermittent ICS may improve symptom control in adults and adolescents • Intermittent ICS in children < 5 years with viral induced wheezing reduces the risk of severe asthma attacks.
Step 3	• Regular ICS recommended for all age groups • LTRA inferior to LABA or higher dose ICS in adults and children respectively • Allergen immunotherapy limited to carefully selected adults and children.	• Addition of LABA to low dose ICS as first preferred option in adolescents and adults • Moderate dose ICS preferred in children • Concern for LTRA-related neuropsychiatric effects in children and adolescents • ICS/formoterol as single maintenance and reliever therapy is another option for adolescents and adults; insufficient evidence for use in children <12 years old
Step 4	• ICS/LABA + SABA prn or ICS/fomoterol as single maintenance and reliever therapy recommended for adults and adolescents. • Higher dose ICS monotherapy provides little additional benefit in children and adults • Tiotropium is a safe, alternative add-on therapy for adults and adolescents; emerging supportive data for younger children • Theophylline no longer recommended for adults and children.	• Insufficient data for ICS/formoterol as single inhaler therapy use in children <12 years old • Specialist review recommended for children
Step 5	• Referral to specialist recommended for all ages • Review of medication adherence, comorbidities and risk factors important for all ages groups • Anti-IgE monoclonal therapy can be used for patients ≥ 6 years old • Anti-IL5 monoclonal therapy (mepolizumab) can be used in patients ≥18 years old and has been approved for use in children ≥ 6 years	• Use of anti-IL5 (mepolizumab) more extensively researched in adolescents and adults; use of younger children (≥ 6years old) approved based on extrapolated data. • Other advanced therapies such as macrolides and bronchial thermoplasty are recommended for adults; lacks data in children or adolescents.

ICS, inhaled corticosteroid; LABA, long acting beta2 agonist; LTRA, leukotriene receptor antagonist; SABA, short acting beta2 agonist.

reduced the risk of severe asthma exacerbation by almost half, with better asthma control although it did not affect lung function (16, 17).

This has led widely used international guidelines (12, 13) to update their recommendation for the consideration of ICS use as Step 1 treatment in all adults, adolescents and children over 6 years with mild asthma, even those with infrequent symptoms, to reduce the risk of severe, potentially life-threatening exacerbations (18–20).

Step 2: Regular Low Dose ICS Plus as Needed SABA

Adults and Children (Age >5years)

Regular low dose ICS significantly improves lung function, quality of life and reduces asthma exacerbations in both adults and children with mild persistent asthma (13, 18). O'Byrne et al showed that introduction of low dose budesonide reduced the risk of asthma exacerbation by 60% and improved asthma control days by half (19). Selected studies in adults also showed less rescue SABA use (18). It was suggested that duration of therapy of at least 4 weeks may be an important determinant of overall treatment response (18).

The greatest benefits of ICS in adults and children older than 5 years old have been achieved when ICS therapy was started within 2 years of symptom onset (21, 22); this effectively halved the overall risk of severe or life-threatening exacerbations (16, 17). After this time, higher ICS doses are required for adults and there is a negative correlation between duration of symptoms and maximal increases in lung function (22–24). Low dose ICS appears protective against potential long-term decline in lung function following severe exacerbations. Interestingly, this effect is only seen in adults and children but not adolescents (25). It is unclear if this is due to the relatively small number of adolescents studied or relates to the improvements in asthma that have been noted during adolescence (26). Early initiation of ICS also improves asthma control and diminished subsequent needs for additional maintenance therapy (24).

One important difference in children compared with adults is a persistent concern about the impact of regular ICS in

children on linear growth. As an example, in the START study Pauwels et al. reported that children aged 5–15years treated with budesonide showed reduced growth especially in the first year of treatment (16). However, other studies found that children attain normal projected adult height while on prolonged inhaled budesonide (21, 22).

The evidence on linear growth in children treated with ICS has recently been updated to take account of newer inhaled steroid molecules. The regular use of ICS at low or medium daily doses was found to be associated with statistically significant growth suppression during a 1-year treatment period in children with mild to moderate persistent asthma. The mean growth reduction was 0.48 cm/year in linear growth velocity and 0.61 cm change from baseline height during a one year treatment period. ICS-induced growth suppression appears to be maximal during the first year of treatment and less pronounced in subsequent years and appears to be more strongly associated with ICS molecule than with the device or dose in the low to medium dose range (27). A second review looking at dose response effects found a small but statistically significant group difference in growth velocity between low doses and low to medium doses, favoring the use of low-dose ICS (28). Thus the evidence confirms the relative safety of ICS in relation to growth effects but supports the use of the lowest effective dose of ICS, with regular monitoring of linear growth. It is surprising how many gaps still exist in the current evidence base about ICS and growth (29).

Preschool Children (Age <5years)

There is also strong and consistent evidence to support the use of daily ICS for preventing exacerbations in preschool children with recurrent wheeze, especially in those with persistent asthma symptoms (30). The effect of ICS appears to be stronger in those with a diagnosis of asthma compared with recurrent wheezing and is independent of age (pre-schoolers vs. infants), atopic condition, type of ICS, and mode of delivery (spacer vs. nebulizer) (31).

The evidence about growth suppression in pre-school children is limited. Nevertheless, because of concerns about side effects, an important question is whether ICS therapy can be targeted to those children most likely to respond? One recent study in children requiring step 2 treatment showed that while individual treatment responses were phenotypically diverse, children with aeroallergen sensitization and increased blood eosinophil counts responded best to a daily ICS as opposed to a leukotriene receptor antagonist (LTRA) or as needed-ICS. Daily ICS was associated with more asthma control days and fewer exacerbation (32). However, a very recent real-world study of large matched cohort analysis of anonymized UK medical record data found no evidence that stepping up therapy by adding ICS or monteleukast, compared with as-needed use of SABA, reduced wheezing/asthma attacks in a diverse population of preschool children with at least two documented prior wheezing episodes (33). In the absence of better tools to help target treatments, and in light of improved outcomes over time in preschool children a "wait-and-see approach" may be a clinically prudent approach for many with infrequent, intermittent attacks.

Alternative Options

Low Dose Combination ICS/Long Acting Beta2 Agonist (LABA)

For steroid-naïve adults and adolescents with mild persistent asthma, ICS/LABA works faster in achieving GINA-defined good asthma control compared to ICS alone. However, there is little difference in exacerbation rate between the two therapies. In practice, the additional cost for ICS/LABA compared to low dose ICS may be an important consideration for the individual patient (34). Data as to whether there would be similar benefits in children is not available.

Intermittent ICS Regimes

Regular use of ICS raises concerns from patients and clinicians about adherence and steroid side effects. Poor adherence to ICS potentially results in patients relying on SABAs to control symptoms, possibly resulting in overuse.

Recently, it was shown that adults and adolescents with mild asthma using as-needed combination ICS and fast acting LABA had better asthma symptom control measured by an electronic diary compared to as-needed SABA (35). However, the magnitude of effect was inferior to regular low dose ICS therapy. A second trial in a similar cohort reported no difference in exacerbation rate when comparing ICS/formoterol as needed vs. regular ICS (36).

There is less evidence about the use of as needed ICS treatment in children. One study in children from 5 years upwards with mild well-controlled asthma stepping down from daily ICS found ICS and SABAs as needed more effective at reducing attacks than SABA use alone (37). Liner growth was 1.1 cm a year less when ICS was used regularly but not when used on an as needed basis.

In children under 5 years, the most common asthma phenotype is intermittent viral triggered wheezing attacks with no interval symptoms. In this group, intermittent ICS, usually as high-dose ICS at the first sign of an URTI for 7 to 10 days led to a 35% reduction in severe attacks (30). Intermittent ICS were associated with greater linear growth of 0.41 cm per year (i.e., less growth suppression) compared with daily treatment (38).

Oral Leukotriene Receptor Antagonist (LTRA) in Preschool Children

Because of concerns about ICS side effects and difficulties using inhaled therapies in young children, oral montelukast has been widely prescribed as an alternative to regular ICS. While early studies showed it to be effective, the most recent review found no evidence of benefit from the use of montelukast, continuously or intermittently on the number of wheezing episodes, unscheduled medical attendance, or oral corticosteroid use in preschool children with recurrent wheeze (39). There is also little evidence of benefit for other secondary outcomes (7).

Step 3: One or two Maintenance Treatments Plus as Needed Reliever Therapy

For adults and adolescents with suboptimal symptom control or more than 1 exacerbation in the previous year despite treatment with low dose ICS, guidelines recommend low dose ICS/LABA

as maintenance therapy plus SABA or ICS/formoterol as single inhaler therapy (12, 13). In children, at present, moderate dose ICS plus as needed SABA is the preferred treatment for children.

ICS/LABA Maintenance Plus SABA as Required

Historically, there were concerns that LABA may mask airway inflammation leading to potential adverse events including asthma exacerbations. To the contrary, the addition of LABA to ICS significantly increases the odds of achieving good overall asthma control as defined by guidelines (34). Combination low dose ICS/LABA therapy was highly effective at reducing the risk of exacerbations needing oral corticosteroid (19, 40, 41) and hospitalizations (40, 42, 43) in symptomatic adults and adolescents with mild to moderate asthma compared to ICS alone. The addition of LABA also leads to improvement in lung function (especially in those with lower baseline FEV_1), proportion of symptom-free days (19, 44) and a slight reduction in rescue SABA use compared to same or higher dose of ICS (41, 43).

The advantages of adding a LABA have been less clear in children. In children with persistent asthma, the addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but it was superior for improving lung function compared with the same or higher doses of ICS. There were no differences in adverse effects, with the exception of significantly lower linear growth over a year in the children treated with a higher ICS dose, with a mean difference of 1.21cm/yr. A trend toward an increased risk of hospital admission with LABA, irrespective of the dose of ICS, was noted as a matter for concern (45).

ICS/Formoterol as Single Maintenance and Reliever Therapy

Combination of ICS with formoterol as fast acting bronchodilator allows patients to use their regular maintenance inhaler also for rapid relief of symptoms. Single inhaler therapy is more effective at reducing mild to moderate exacerbations while providing similar levels of asthma control compared with medium dose ICS monotherapy or fixed dose of ICS/LABA and as required SABA (46–50). It has been suggested that using single inhaler for both maintenance and reliever therapy may improve adherence but definitive data is lacking.

The role of single maintenance and reliever therapy in children age 12 years and below is unclear at present and requires further study. It is not currently licensed for use in this way in this age group.

Alternative Treatment Options

Higher dose ICS

At the population level, further escalation to higher dose ICS use in adults and adolescents provides little added benefit but rather greater adrenal suppression (51, 52). Higher dose of ICS is inferior to combination ICS/LABA in reducing the risk of exacerbations requiring oral corticosteroids. Combination therapy is also superior in improving lung function, symptom control, and use of rescue SABA than a higher dose of ICS alone (44, 47).

In the past, written action plans commonly included advice about a temporary increase in inhaled steroid dose—usually doubling—in the early stages of an asthma exacerbation to reduce the severity of the attack and to prevent the need for oral steroids or hospital admission. The accumulated evidence suggested that this doubling approach was not effective (53).

However, the concept of intermittent ICS dose escalation to prevent asthma exacerbations has recently been revisited in two large studies. In a pragmatic and unblinded trial, McKeever et al. randomized adults and adolescents ($N = 1922$) on ICS maintenance therapy to receive a personalized management plan that included a temporary quadrupling of ICS when asthma control started to deteriorate compared to remaining on their usual ICS dose (54). They showed that a temporary quadrupling at the time of worsening asthma control resulted in a lower rate of severe exacerbations of asthma than no increase in the dose (45% vs. 52%).

In contrast, Jackson et al. studied children 5 to 11 years of age ($n = 254$) with mild to moderate asthma already on low dose ICS therapy and reported no difference in rates of exacerbation in those treated with quintupled dose of ICS compared with their usual ICS dose at the earliest sign of asthma deterioration (55).

The reasons for the differences in outcomes between these two studies are not completely clear. Differences in the size of study cohort and fewer than expected exacerbations in the pediatric study may be one reason and there may be differences in pathophysiology during exacerbations between adults and children. A more plausible explanation may lie in the fact the study by McKeever et al. was a pragmatic open label study with no monitoring of compliance. Increasing the ICS dose at the start of an exacerbation may have merely resulted in the patients starting a treatment they had been poorly compliant with before. In contrast, Jackson's study was a randomized control trial with electronic diary recording of treatment. Diary completion was $> 70\%$ during usual treatment and rose to around 98% of the days during the treatment (55, 56). Thus there may have been no headroom for a further impact of the increased ICS dose.

Given the bioequivalence dose of inhaled to oral corticosteroid and subsequent potential effects on adrenal suppression, it is also debatable whether the very high steroid dose used in the quadrupling or quintupling approach is necessarily better than a standard course of oral prednisolone (57).

Leukotriene receptor antagonists (LTRA)

Leukotriene receptor antagonists inhibit the pro-inflammatory effect of leukotrienes not completely suppressed by corticosteroid therapy. The addition of LTRA to symptomatic adult asthmatics already treated with regular ICS monotherapy leads to reduced exacerbations, better asthma control and better lung function (58, 59).

It is unclear if LTRA is superior to higher doses of ICS monotherapy (58) except in adults with aspirin-intolerant asthma. However, asthma symptoms, lung function, and rescue medication use are improved when LTRA is added to high doses of ICS (60). In this specific patient cohort, aspirin desensitization is also a safe, and effective option (61).

The addition of LTRA is less effective than adding LABA to ICS when one looks at comparative benefits in lung function, asthma symptoms, rescue medication use, and asthma related quality of life (62). The effect on oral corticosteroid-treated exacerbation was statistically superior with the addition of LABA than LTRA to ICS but with only an absolute difference of 2% between groups. However, this meta-analysis was dominated by 16 trials that included 6872 adults and adolescents; only 2 studies included 336 children (age 6–17 years). As such, it is unclear which adjunct therapy is best for children.

An earlier Cochrane 2013 analysis concluded there was no difference in asthma exacerbations needing oral corticosteroid or hospitalization comparing LTRA to same or higher dose ICS in children and adolescents with mild to moderate asthma (63). The paucity of randomized trials and heterogeneity in study design and reporting of published studies make it difficult to support its use as add-on therapy in children with moderate asthma (step 3 treatment).

In preschool children, there are as yet no trials comparing LTRA, or LABA, as an add on therapy to ICS.

Neuropsychiatric side effects have been reported as not uncommon in young children started on montelukast. One study ($n = 106$) found montelukast had been stopped in 16% of children because of neuropsychiatric effects (irritability, aggressiveness, and sleep disturbance), mostly within 2 weeks of starting therapy (64). Long term use in adults is not recommended unless there is clear symptomatic improvement after a trial of therapy (65).

Allergen immunotherapy

Allergen immunotherapy (AIT) is still the only-disease modifying treatment strategy for IgE-mediated allergic disease (66). Studies using both subcutaneous (SCIT) and sublingual treatments (SLIT) have shown some benefit in reducing asthma symptoms and bronchial hyper-reactivity in adults and children.

GINA guideline recommend SLIT for adults with rhinitis and allergy to house dust mite with exacerbations despite ICS, provided FEV_1 is > 70% predicted (12). It reduces exacerbation rates in adults with moderate asthma but has minimal effect on asthma symptom control or quality of life (67). Its role in adults with compromised lung function requires further clarification. In a randomized control trial of subjects 14 years or older with mild to moderate asthma, those treated with sublingual house dust mite immunotherapy were able to reduce their ICS dose while maintaining asthma control (68).

In children, the most up to date evidence noted that there were no studies that evaluated asthma symptom using a validated tool and both study characteristics and outcomes were reported heterogeneously. There is moderate-strength evidence that SCIT may reduce long term asthma controller medication use in children with allergic asthma (68). Studies of SLIT have only studied children with mild/moderate asthma mono-sensitized to house dust mite. Local and systemic allergic reactions were common but anaphylaxis was reported rarely (69).

Current recommendations advise that allergen immunotherapy should not be given to patients with severe or uncontrolled asthma who are at increased risk for systemic reactions (70).

Step 4: Two or More Maintenance Therapies Plus as Needed Reliever Medication

For adults and adolescents whose asthma is inadequately controlled on low dose ICS/LABA maintenance therapy, the two recommended step-up approaches are low dose ICS/formoterol single maintenance and reliever therapy or medium dose ICS/LABA as maintenance plus as needed SABA (44). In contrast, for children < 12 years old because of concerns regarding medication side effects and the lack of sound evidence base, current guidelines recommend referral for specialist review (12).

Post hoc analysis of five large clinical trials suggests that ICS/formoterol as single maintenance and reliever inhaler may be the preferred option compared to guideline recommended treatment for various stages of asthma severity using low dose ICS monotherapy or same or higher fixed dose ICS/LABA regime (50). The magnitude of difference is more marked for those with more severe disease requiring GINA Step 4 treatment. Single maintenance and inhaler therapy prolongs the time to first exacerbation and reduces the overall risk of exacerbations at relatively low doses of ICS compared with higher fixed dose of ICS/LABA and as-needed SABA (46, 47, 50). The effect on hospitalization is less clear. Secondary outcomes such as lung function, rescue SABA use, symptom free days, and quality of life were also superior for single maintenance and reliever therapy than higher fixed dose ICS/LABA regime.

Again, the best option in children younger than 12 years old is unclear due to insufficient data.

Alternative and/or Additional Treatment Options

Several alternative options are available for adults and adolescents. However, robust data for their use in younger children is again currently lacking.

High dose ICS/LABA

While high dose ICS/LABA may be considered in adults and adolescents, the increase in ICS dose generally provides little additional benefit (34, 41, 71), and there is an increased risk of side effects, including adrenal suppression (72). A high dose is recommended only on a trial basis for up to 6 months when good asthma control cannot be achieved with medium dose ICS/LABA and /or a third controller (12).

Long acting muscarinic antagonist (LAMA)

The long-acting anticholinergic tiotropium, delivered once daily via a mist inhaler, is approved for the treatment of asthma in the EU and the USA with the license recently extended to include children with severe asthma over 6 years of age. The GINA guidelines currently position tiotropium as an add on therapy option at step 4 in patients aged ≥12years with a history of exacerbations (12).

For adults treated with ICS, LAMA prescribed as add on therapy has been shown to reduce the risk of exacerbations and improve lung function but made no difference in quality of life (73). In a study of 210 moderate asthmatics, tiotropium bromide added to ICS offered marginal improvements in peak flow and symptoms compared to doubling dose of ICS. The effect was considered non-inferior to salmeterol. However, there was the possibility of carry-over effects due to the cross-over design (74, 75). Cochrane analysis of 3 trials (76–78) comparing addition of tiotropium mist inhaler in adults with severe asthma already treated with ICS/LABA combination therapy showed definitive improvement in trough FEV_1 and fewer exacerbations (79).

In children over 6 years with symptomatic moderate or severe asthma, tiotropium treatment led to improvement in lung function and asthma control (80), similar to that found in adult studies. However, the data in children is less extensive and generally short term with the longest study lasting 48 weeks (81). In younger children, one small 12 week RCT of children aged 1–5years study showed tiotropium was safe, led to a reduction in asthma attacks but did not improve daily asthma symptom scores. These findings need to be confirmed in larger studies (82).

Both in adults and children tiotropium has a safety profile comparable to placebo.

Theophylline

The addition of slow release theophylline to low dose budesonide for moderate asthma is just as effective as high dose budesonide in improving lung function and reducing symptoms and rescue SABA use in adults but has little effect on exacerbation rate over 3 months duration (83). Theophylline is a less effective bronchodilator than beta2 agonists and associated with high risk of adverse effects.

In the past, oral xanthines were used as a first line preventer treatment (at Step 2) for children with asthma. Although there is weak evidence that theophyllines were better than placebo, they are no longer used because ICS were shown to be more effective at improving symptoms and reducing asthma attacks (84). When low dose ICS fail to control asthma, oral theophyllines have been used as one of the available add-on options and there is weak evidence that adding theophylline to ICS treatment improves symptom control and reduces exacerbations (85). However, current recommendations are that theophyllines should only be tried when the addition of LABA and LTRA have both failed.

Theophyllines have adverse effects including headaches and nausea if therapeutic concentrations are exceeded. There are also significant interactions with some commonly used drugs which inhibit theophylline clearance e.g., erythromycin which can result in increased theophylline levels and resulting toxicity.

Step 5: Refer for Expert Review and Add-On Therapy

The great majority of adults with severe asthma not responding to high dose treatments are "difficult-to-treat" because of comorbidities and risk factors that mimic or worsen asthma control (86, 87) and the management of these other factors is as important as the asthma treatments in improving the outcomes of patients with severe asthma. The situation is similar in children where only the minority will have genuinely therapy resistant asthma (88).

Poor adherence with treatment is a particularly important cause of difficult to treat asthma in both adults and children. Improving adherence is difficult. A variety of interventions have been shown to lead to improvements including adherence education, the use of electronic trackers or reminders, simplified drug regimens and school-based directly observed therapy. However, because of uncertain and inconsistent impact on clinical outcomes such as quality of life and asthma control the clinical relevance of the improvements has been less clear with many studies affected by concerns about risk of bias and inconsistency (89). The most recent studies in adults and children have shown that a combination of electronic monitoring and biofeedback can improve adherence and asthma outcomes (90–92). In one adult study, a programme of adherence and inhaler technique assessment resulted in only 27% remaining refractory to their asthma treatment (92). Hence, such approaches may offer a more effective approach in the future.

A number of add-on options are available for those with severe therapy resistant asthma. But prior to the use of these therapies, it is important to follow a systematic approach in the assessment and management of "difficult-to-treat" severe asthma—to confirm diagnosis, address poor adherence and to identify and manage comorbidities and risk factors (93, 94).

The following add-on options are best reserved for well-phenotyped patients with "severe treatment-refractory" asthma. The bulk of the evidence for their use at present is in adults and adolescents.

Anti-IgE Monoclonal Therapy

Omalizumab can be used for adults and children over 6 years of age with inadequately controlled severe allergic asthma despite optimized therapies (12, 13). The published data mostly related to adolescents and adults with only 3 randomized studies exclusive to children or adolescents (95–97). Most of the published data included subjects with moderate to severe asthma where omalizumab appears equally effective across different ages at reducing the risk of exacerbations and hospitalizations (98–100). Benefits are also seen in asthma symptom control for adults and children whilst other outcomes such as quality of life and rescue medication use have mainly been assessed in adults with modest improvements.

In addition, omalizumab allows for reduction or withdrawal of inhaled corticosteroid use but the latter option must be considered with caution (98). In children with severe disease omalizumab can reduce the burden of corticosteroids (101) and might be an effective alternative to oral corticosteroids (OCS) although a large direct OCS-sparing trial in children is required to confirm this.

In clinical use in both adults and children omalizumab has proved safe with few serious adverse effects (98).

Anti-interleukin 5 (IL-5) Monoclonal Therapy

Newer therapies targeted at IL-5 (mepolizumab, reslizumab) or the IL-5 receptor (benralizumab) are effective for adolescents and adults with severe eosinophilic asthma at high risk of

exacerbations or with high symptom burden despite high dose ICS and another maintenance therapy (102). The effectiveness of subcutaneous mepolizumab (103, 104) and benralizumab (105, 106) in reducing exacerbations and hospitalizations is well-documented. They also improve asthma control, quality of life with modest gain in lung function and reduce the need for oral corticosteroid (106–108). Similar benefits were demonstrated with reslizumab only when administered intravenously which may impact its use in clinical practice (109, 110).

Randomized trials for all three anti-IL-5 therapies recruited patients over 12 years and included a few adolescents; studies using mepolizumab in children age between 6 and 11yr are underway. The EMA has recently approved mepolizumab for use in children 6–17years but this is based on an extrapolation of data from the efficacy and safety data from the Phase III studies in the mepolizumab severe asthma development programme for patients 12 and over.

Possible Alternatives for Adults Not Included in Guidelines: Macrolides, Bronchial Thermoplasty

Macrolides

Macrolides have antibacterial, antiviral and immunomodulatory effects and are shown to be effective in different asthma phenotypes (111). Adults with persistent asthma despite two or more maintenance therapies including ICS have fewer exacerbations and better quality of life when treated with azithromycin for 6-12months (111, 112). Macrolides are well–tolerated but microbial resistance is a potential concern with long term use. To date, there is no reported increase in infections related to macrolide use.

At present, there is no evidence that regular treatment with macrolides improves asthma control in children. Intermittent use of azithromycin in preschool children at the time of asthma attacks has been investigated. One study found that Azithromycin shortened the duration of episodes of asthma-like symptoms in young children aged 1–3years (113); in a second study in preschool children presenting to an emergency department, 5 days azithromycin (vs. placebo) neither reduced the duration of respiratory symptoms nor time to respiratory exacerbation in the following 6 months after treatment (114).

Bronchial thermoplasty

Bronchial thermoplasty is a non-pharmacological, endoscopic treatment for subjects aged ≥18 years with severe persistent asthma that is not well-controlled with ICS and LABA. Bronchial thermoplasty provides lower rates of exacerbations and modest improvements in quality of life but no difference in asthma control scores in patients with moderate to severe asthma (115–117). The procedure may be associated with temporary deterioration in asthma control needing hospitalization but is not associated with significant adverse respiratory effects on follow up out with the treatment phase. Its role in adult patients with severe asthma remains unclear especially in those with poor lung function. Based on current data, bronchial thermoplasty is not recommended by guidelines and it should only be used in carefully considered patients in the setting of a registry to allow independent data collection and in centers experienced in the technique. At present, there is no data on the use of bronchial thermoplasty in young people with severe asthma <18years of age.

Chromones (nedocromial sodium and sodium cromoglycate)

Chromones have favorable safety profile but low clinical efficacy compared to ICS in adults and children (118). The most recent Cochrane systematic review of studies in children judged there was insufficient evidence to be sure about the efficacy of sodium chromoglycate over placebo and was concerned that publication bias is likely to have overestimated the beneficial effects of sodium chromoglycate as maintenance therapy in childhood asthma in the past. They may have some role in those with exercise induced bronchospasm who are unresponsive to SABA pre-exercise and regular ICS for underlying asthma, as well as those intolerant of bronchodilators (119).

Approach to Adjusting Maintenance Treatment

Pharmacological management of asthma is based on continuous cycle of assessment, treatment and review to allow up or down titration of maintenance therapies to maximize patient outcomes using minimal treatment at various stage of the disease (12, 13).

Control Based Treatment Adjustment

Most guidelines recommend a change in management based on measures of symptom control with or without other risk factors such as compromised lung function or a history of exacerbations. Symptom based approaches are essentially all that is available in young children because of the fact they cannot co-operate with standard lung function tests.

For many patients in primary care, symptom control is a good guide to reduced risk of exacerbations. However, it is important to be mindful that in some patients, there may be discordance between responses in symptom control and asthma attacks. In preschool children, particularly, many children will have severe attacks of wheezing but no symptoms in between attacks.

Alternative Strategies for Adjusting Asthma Treatment Based on Eosinophilic Markers (Sputum Eosinophil Count or Exhaled Nitric Oxide)

Airways inflammation in asthma can be predominantly eosinophilic or non-eosinophilic. While ICS are the major preventer treatment to control symptoms, ICS are more effective in reducing symptoms in patients with eosinophilic inflammation than in those with neutrophilic inflammation (120). There has therefore been interest in whether tailoring asthma treatment based on objective eosinophilic inflammation improved asthma outcomes. Two approaches have been used to date: examination of eosinophil counts in induced sputum samples; or the measurement of exhaled nitric oxide.

The most up-to-date synthesis of the evidence concluded that children and adults randomized to either eosinophilic marker strategy were significantly less likely to experience

an exacerbation during the follow-up period (4.5–24months). The exacerbation rate was also lower in adults with either strategy compared to controls, but not in children. For both strategies in adults and children, there was no difference for all secondary outcomes (FEV_1, asthma control test score, asthma quality of life, beta agonist use). There was also no difference in the final ICS use in either adults or children for either strategy (121).

Exacerbations are one, albeit important, asthma outcome; other outcomes such as symptom control and lung function also need consideration. Why there is discrepancy between exacerbations and other asthma outcomes is not understood but it has been noted in other studies involving the newer monoclonal drugs targeted at eosinophilic allergic pathways such as mepolizumab (103).

Currently, sputum induction is restricted to laboratories and clinics with specific expertise. It is technically demanding and time consuming and not always successful, particularly in younger children. Universal use of FeNO would be a substantial extra cost if used for all asthma patients and there is a yet no evidence-based algorithm on how to adjust treatment based on FeNO levels. Such an approach is most likely to benefit those with frequent asthma exacerbations.

In studies limited to non-smoking adults, FeNO >50ppb was predictive of good short-term response to ICS (122). However, there are no studies examining the long-term safety with regard to exacerbations or withholding ICS in patients with low initial FeNO.

Asthma Treatment at Different Ages – Challenges to Asthma Guidelines

The evidence base for the management of children with asthma, particularly young children, is often quite limited and has been compounded by a number of problems. Children under the age of 5–6years are usually not able to co-operate with lung function test and as result objective outcomes are commonly not available. Trials of treatment are more problematic without objective outcomes. New drugs are usually not tested in children until they have been extensively tested in adult patients. Recruiting and retaining children and their parents into randomized studies is difficult and as a result trials are often more limited in scale and duration. The consequence is that the evidence base for asthma treatments is often much smaller than available for adults. However, when an evidence base does emerge it is surprising how often it mirrors the that from adult studies. The value of ICS in preventing asthma exacerbations in young children would be an obvious example.

Asthma Guidelines summarize "population level" evidence and provide broad and generalized recommendations about asthma management (12, 13). However, it is now accepted that asthma is a heterogeneous disease and adjusting asthma treatment that takes account of differing phenotypes is one of the most important current challenges.

Despite publication of many evidence-based guidelines and the availability of effective therapies, there is widespread concern that asthma control in adults and children often remains poor and that asthma attacks and even deaths from asthma are not improving (123, 124). This is largely because there is a need to take account of "patient level" factors and tailor treatments to individuals. Such factors include any individual characteristics, preferences, risk factors, comorbidities or phenotype that predict or influence a patient's likely response to treatment, together with practical issues such as ability to use a particular inhaler, adherence, and affordability. Finally, patients with asthma, including children and their parents, often have different treatment goals from their physicians and want to balance the aims of optimizing asthma management against the side effects or inconvenience of taking regular medication necessary to achieve asthma control (13).

CONCLUSION

Asthma can significantly impact on all facets of life for patients across all age groups. Effective management strategies are broadly summarized by local and international guidelines. Overall, the evidence for pharmacological approach are more extensive and more robust for adults than that for younger children. For milder disease, the use of ICS as the initial maintenance therapy and SABA as needed appears universally effective for children, adolescents and adults. However, the preferred choice of subsequent add-on therapies differs and the evidence base for advanced therapeutic options is mostly based on studies in adolescents and adults. Clinicians are currently challenged with the need to develop management strategies that best caters for individual differences in asthma presentation and management. Accounting for differences in pathophysiological mechanisms, asthma phenotypes and treatment responses at different ages remains one of the most significant of these challenges.

AUTHOR CONTRIBUTIONS

Both authors contributed to the conception and preparation of this manuscript. LC contributed to the first draft and the content relating to asthma management in adults. JP provided his summary and expertise on treatment of asthma in children. Both authors contributed to manuscript revisions, read and approved the submitted version.

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Approaches to Asthma Diagnosis in Children and Adults

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Although the hallmark features of asthma include reversible airflow obstruction, airway eosinophilia, and symptoms of recurrent wheeze associated with breathlessness and cough, it is a heterogeneous disease. The extent of the pathophysiological abnormalities are variable between patients. Despite this, until recently, asthma diagnosis had been made very simplistically predominantly from a clinical history and examination, and often a trial of medication such as short acting bronchodilators. The limitations of this approach have become increasingly apparent with evidence of inappropriate over diagnosis, under diagnosis and misdiagnosis. Although there is no gold standard single test to make a diagnosis of asthma, there are several objective tests that can be used to support the diagnosis including physiological measures such as obstructive spirometry associated with bronchodilator reversibility and airway hyperresponsiveness. In addition, non-invasive tests of airway inflammation such as exhaled nitric oxide or peripheral blood eosinophils are important to identify those with an allergic or eosinophilic phenotype. Diagnostic guidelines reflect the importance of using objective tests to support a diagnosis of asthma, however practical application in the clinic may not be straightforward. The focus of this review is to discuss the need to undertake objective tests in all patients to support asthma diagnosis and not just rely on clinical features. The advantages, challenges and limitations of performing tests of lung function and airway inflammation in the clinic, the difficulties related to training and interpretation of results will be explored, and the utility and relevance of diagnostic tests will be compared in adults and children.

Keywords: asthma diagnosis, spirometry, exhaled nitric oxide, guidelines, inflammation, paediatric asthma, lung function, objective tests

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INTRODUCTION

The essential components of a detailed history and examination remain central to making a diagnosis of asthma in both children and adults (1). Additional confirmative tests are recommended and will be discussed, but all guidelines emphasize the need to accurately establish the presence of a constellation of symptoms that align with asthma. This fundamental need to accurately identify a collection of symptoms that fit with asthma has recently been agreed by an expert consensus opinion from clinicians, researchers and scientists worldwide (2). It has been suggested that the term "asthma" should only be used as a descriptor that relates to a collection of symptoms. But no associated assumptions should be made about the underlying pathophysiological features driving the symptoms (2). It is suggested that this approach will prevent inappropriate treatments from

being used and will encourage increased emphasis on individualized therapy. The focus of this review is to discuss the key features that constitute a diagnosis of asthma and to explore the role of objective confirmatory or supportive tests, highlighting the elements that are common to adult and childhood disease and some components that differ according to the age of the patient. The key components that contribute to a diagnosis of asthma include airway inflammation, hyperresponsiveness, bronchial obstruction, and symptoms. Each of these will be discussed, highlighting the relevance in children and adults and also the role of objective tests and the potential pitfalls that may lead to misdiagnosis.

THE BASICS NEED TO BE CORRECT REGARDLESS OF PATIENT AGE

History and Examination

Asthma is characterized by symptoms including wheeze, cough, breathlessness and chest tightness (3), all of which may fluctuate over time. The symptoms are common to children and adults, and an essential component is to obtain objective confirmation of symptoms either as documented doctor observed symptoms, or by administration of an objective questionnaire. A key issue that often leads to misdiagnosis in children is the mistaken assumption that all noisy breathing equates to wheeze and therefore asthma. Epidemiological data rely heavily on questionnaire reported symptoms, which may not always be accurate and may result in very varied reports of prevalence rates (4). However, for the individual patient, an accurate record of documented wheeze and symptoms consistent with asthma is critical to prevent inappropriate diagnosis, but equally importantly, inappropriate treatment (5, 6).

INCORPORATING OBJECTIVE TESTS TO MAKE A DIAGNOSIS OF ASTHMA: IS IT NECESSARY?

The importance of a correct diagnosis for the individual is obvious, however, equally important is the impact on cost to the health service of avoiding inappropriate prescription of asthma treatments. Application of a secondary screening programme, incorporating objective assessments of lung function and airway hyperresponsiveness, to a population who had a physician diagnosis of asthma, identified 28% of patients with a misdiagnosis (7) of whom 71% were on asthma medication. Moreover, the additional costs of the objective tests were significantly less than the costs of a lifetime of prescription of inappropriate medication. One-third of Canadian adults who had asthma diagnosed in the previous 5 years no longer had current asthma, likely because of an initial misdiagnosis (8). Factors contributing to the misdiagnosis of asthma include failure to confirm reversible airflow obstruction, the relatively poor sensitivity of spirometry alone to absolutely confirm asthma (especially in children), the day to day variability of symptoms and the numerous phenotypes of disease (9). Consequences of misdiagnosis not only include inappropriate treatment, but also lost opportunity and time in making a correct diagnosis to explain the patient's respiratory symptoms. It is important to remember that misdiagnosis incorporates both wrongly labeling another condition as asthma, but equally missing a diagnosis of asthma and failed treatment. Both have significant consequences (9). Given the availability of objective tests that can help to confirm the diagnosis and the potential unwanted effects of inappropriate or wrong diagnosis, many diagnostic algorithms now incorporate the need for objective tests in the diagnosis of asthma.

An important change in the approach to diagnosis has recently been introduced in England, where the National Institute of Health and Care Excellence (NICE), whose purpose is to generate evidence based and cost effective guidelines, has recently been published [https://www.nice.org.uk/guidance/ng80]. It was claimed by NICE that up to 1.2 million of the approximately 4 million people with asthma in the UK were misdiagnosed and therefore being prescribed wrong or inappropriate medication (10). For the first time in England, it has now been recommended that both spirometry and exhaled nitric oxide tests should be used in all patients older than 5 years to help in the confirmation of the diagnosis. This guideline has resulted in much debate and discussion especially because of differences from the British Thoracic Society and Scottish Intercollegiate National Guidance (BTS/SIGN) which have been used by clinicians in the UK for over 2 decades (11). In the context of asthma diagnosis, the big contrast between the two guidelines includes the implementation of objective tests as being absolutely central and essential for making a confirmed diagnosis in adults, and very important, and whenever possible, essential for a diagnosis in children over 5 years in the NICE guidance. Although the BTS/SIGN guidelines recommend the use of lung function tests to support asthma diagnosis, implementation of this to date has been very variable and limited.

TESTS TO ASSESS AIRWAY INFLAMMATION IN ASTHMA DIAGNOSIS

Use of Exhaled Nitric Oxide to Diagnose Asthma—In Adults

The NICE diagnostic algorithm for adults includes the need for an accurate history and physical examination, including wherever possible, objective confirmation of wheeze, however, the critical change at this point is the clear message that a diagnosis cannot be made only on symptoms, without an objective confirmatory test. The first objective test to be used in adults aged 17 years and over is exhaled nitric oxide. If a value of 40 parts per billion (ppb) or higher is measured in a patient with suspected asthma, this is considered a positive result, and is strongly supportive of asthma. However, situations in which exhaled nitric oxide may be low, despite the presence of asthma, are highlighted, the most important for adult patients being cigarette smoking (12).

The upregulation of nitric oxide (NO) by inflammatory cytokines in central and peripheral airways can be monitored in exhaled air. Increased fraction of exhaled NO (FeNO)

reflects eosinophilic-mediated inflammatory pathways and likely steroid responsiveness moderately well in asthma (13). As the fundamental pathophysiology underlying asthma incorporates eosinophilic airway inflammation coupled with reversible airflow obstruction, exhaled nitric oxide is considered additive to measures of lung function as an indirect marker of airway inflammation. However, in addition to smoking, other factors, including atopy and current treatment with steroids influence measured exhaled nitric oxide. Therefore, although considered useful to help support a diagnosis of asthma, it is apparent that its clinical utility and accuracy is greatest for steroid naïve and non-smoking patients (14). It is because of the variability of exhaled nitric oxide that it must be remembered that although a high level is supportive of the diagnosis, a level below 40 ppb does not exclude asthma (15).

Use of Exhaled Nitric Oxide to Diagnose Asthma—In Children

Although the NICE guidance includes objective tests for children to help confirm a diagnosis of asthma, in contrast to the adult diagnostic algorithm, exhaled nitric oxide measurement is not a required test for making the diagnosis in those under 17 years. Exhaled nitric oxide measurements are only recommended if there is diagnostic uncertainty after lung function tests and assessments of reversible airflow obstruction have been made [https://pathways.nice.org.uk/pathways/asthma#path=view%3A/pathways/asthma/assessing-and-diagnosing-asthma-in-under-17s.xml&content=view-node%3Anodes-diagnostic-uncertainty]. A systematic review of the utility of exhaled nitric oxide for the diagnosis of asthma in children has shown that the measure may be informative for a diagnosis when used in conjunction with other tests, but importantly, that the cut-off for normal should be lower in children than adults (16). Several factors, of relevance to children have been shown to influence levels of exhaled nitric oxide, including age, height, gender, race and passive smoke exposure (16). Another key issue for children, even if only considering those aged 5 and above, is their technique and ability to perform an adequate maneuver that allows maintenance of a sustained exhalation flow rate and an acceptable recording. With these numerous factors that affect values of exhaled nitric oxide in children, the American Thoracic Society (ATS) guidelines suggest values in children below 20 ppb are very unlikely to be associated with eosinophilic airway inflammation, whilst those above 50 ppb suggest airway eosinophilia and a response to corticosteroids (13). The ATS suggest values between 20 and 35 ppb should be interpreted in light of the clinical context, taking into consideration the various factors that may affect exhaled nitric oxide. Several pediatric studies have used 20 ppb as a cut-off and shown high sensitivity (86%), specificity (89%), positive (92%), and negative (80%) predictive value for asthma in children (17, 18). A significant factor that must be considered for children when interpreting values of exhaled nitric oxide is the influence of atopy. Allergic sensitization alone, without any clinical manifestation of atopic disease or asthma is strongly associated with elevated levels of exhaled nitric oxide (19, 20). Moreover, there is an association between elevated exhaled nitric oxide and current exposure to the allergen that the child is sensitized to and multiple sensitization may result in higher exhaled nitric oxide levels (20, 21). Despite the data from the ATS guidelines suggesting a value >20 ppb may be of clinical relevance in children, the abnormal cut-off level that has been set in the NICE guidelines for children is above 35 ppb for those aged 5–16 years. The test is only recommended in those children with diagnostic uncertainty after initial assessment and those with normal spirometry, or airflow obstruction without evidence of reversibility. On balance, an assessment of exhaled nitric oxide is helpful in supporting a diagnosis of asthma in children aged 5 and above, providing the challenges associated with technical ability to perform the test and the factors that may either elevate or lower the value are considered (**Table 1**). As a result, exhaled nitric oxide is currently predominantly used in specialist centers, where the equipment is used frequently, technical expertise in obtaining measurements is reliable, where children with diagnostic uncertainty are seen, and results are interpreted in the context of the influencing factors.

Sputum Eosinophils

Currently, assessment of airway eosinophils is not a requirement for the diagnosis of mild to moderate asthma. The utility of induced sputum inflammation is predominantly recommended for patients thought to have severe disease (22). In practice, the use of sputum eosinophils to make an asthma diagnosis is challenging because of the time and expertise required for both the induction, processing and analysis of the sample. For this reason, the utility of less invasive biomarkers that may reflect airway eosinophilia are preferred. A meta-analysis of the diagnostic accuracy of minimally invasive biomarkers (exhaled nitric oxide, blood eosinophils, total serum IgE) has shown each of these markers only moderately reflect sputum eosinophils with a sensitivity and specificity of 0.66 and 0.76 for exhaled nitric oxide, 0.71 and 0.77 for blood eosinophils (23). These data highlight that no single biomarker accurately reflects airway eosinophilia and if used alone, there is a substantial risk of both false positive and false negative diagnoses. Overall, it appears that blood eosinophils and exhaled nitric oxide have similar

TABLE 1 | Factors, independent of asthma, influencing exhaled nitric oxide levels.

	Elevated/lower level
Age	Increases with age, lower normal values in children than adults
Height	Increase in taller children
Ethnicity	Higher in Black than Caucasian children
Smoke exposure (passive/active)	Lower with smoke exposure
Allergic sensitization	Higher in atopic patients
Gender	Higher in males
Respiratory infection	Lower with concurrent infection
Technique—maintaining exhalation flow rate	Inaccurate results if flow not maintained
Consumption of nitrite containing foods, caffeine, alcohol	Increased values

accuracy in reflecting sputum eosinophilia, regardless of the asthma phenotype, while serum IgE is less accurate (24). Given the difficulty in obtaining sputum samples and the restriction of its use to specialist respiratory centers, currently an assessment of sputum eosinophils is not routinely undertaken to make a diagnosis of asthma in adults or children.

In adult patients the main use of sputum eosinophils has been to guide management and tailoring of therapy to achieve a reduction in exacerbations, rather than to make the diagnosis of asthma (25). Unfortunately, to date, these results have not been reproduced in children, perhaps because of the longitudinal variability of sputum eosinophils counts within patients over time (26).

Blood Eosinophils

A blood test is easier and can routinely be performed in all clinical settings, thus making the utility of peripheral, rather than airway eosinophils, more attractive to help make a diagnosis of asthma for both adults and children.

In children, several factors need to be considered prior to the interpretation of a blood eosinophil count. Firstly, the cut-off for normal values change with age. The range for blood eosinophils in healthy children aged between 6 months and 13 years is between 500 and 700 cells/mcl (27). Thus, using cut-offs of >300/mcl as suggested in numerous adult studies may be entirely inappropriate. Another factor that must be considered in children is the presence of atopic disease without asthma which may result in elevated blood eosinophils without airway eosinophilia. Therefore, if blood eosinophils are relied upon as a biomarker in a child with eczema and wheeze, disentangling the reason for peripheral eosinophilia is difficult and may lead to a false positive diagnosis (28). Another issue is the impact of steroid treatment on peripheral eosinophil count. If a child is steroid naïve, an elevated blood eosinophil count may truly represent airway eosinophilia, but for children on inhaled corticosteroids, the peripheral eosinophil count may be low or normal, while an airway eosinophilia may persist, this is especially true for children with severe asthma (29). On balance, in school-age children with asthma, given the number of potential caveats that may give a result that does not truly reflect airway eosinophils and without a cut-off for the upper limit of normal yet being established, there is currently no evidence to support the use of blood eosinophils as a diagnostic marker for asthma. The utility of blood eosinophils in preschool children with wheezing to predict asthma development and response to inhaled corticosteroids, has been better evaluated and will be discussed below in the section on preschool wheeze and diagnostic markers. Another caveat to the use of peripheral blood eosinophils in children, is the data showing correlations with airway eosinophils are based on values during stable disease, not during exacerbation. It is unclear whether peripheral blood eosinophils would be helpful in making a diagnosis of asthma during an exacerbation, especially in children, since so many acute attacks are driven by infection, when peripheral or airway inflammation may be predominantly neutrophilic, not eosinophilic.

Unlike the paucity of data supporting the utility of blood eosinophils for a diagnosis of asthma in children, there is significant evidence in adults that blood eosinophils are useful to identify those patients who are more likely to respond to specific therapies such as steroids or the anti-eosinophilic monoclonocal antibodies, Mepolizumab (30) and Benralizumab (31). However, it must be remembered that elevated blood eosinophils only reflect a particular phenotype of asthma, that which is predominantly driven by Th2 mediators and is likely to be steroid responsive. Therefore, an absence of peripheral eosinophilia does not exclude asthma. The need to consider symptom pattern and lung function to help support a diagnosis remains important. The use of blood eosinophils in primary care and even as a point of care test is becoming increasingly feasible, whereby a finger prick point of care device has been shown to have close correlation with differential cell counts obtained from samples by venepuncture (32). However, the most important clinical message when interpreting blood eosinophils for asthma diagnosis, is very high counts (>500 cells/mcl) have a high certainty of an associated airway eosinophilia, but for values <410 cells/mcl the relationship between blood and airway eosinophils becomes less clear and it is important to consider the overall clinical picture and all possible factors that might affect blood eosinophil counts (30).

LUNG FUNCTION TESTS AND ASTHMA DIAGNOSIS

Use of Spirometry to Diagnose Asthma—In Adults

Perhaps the most easily accessible test that can be used to support a diagnosis of asthma is spirometry. The presence of an obstructive picture, with a ratio of FEV_1/FVC <70%, and associated reversibility following administration of bronchodilator is in keeping with asthma. Although it is assumed by most that spirometry is used to help confirm a diagnosis of asthma in adults, its use in primary and secondary care settings is limited. For this reason, the NICE guidelines that have been recently published in England include spirometry as a "must do" objective test for all patients over 5 years old with a suspected diagnosis of asthma (https://www.nice.org.uk/guidance/ng80). If an obstructive spirometry result is present, then it has been recommended that all adults, aged 17 and over, should undergo a bronchodilator reversibility test, and an improvement of ≥12% in FEV_1 and an increase in ≥200 ml is considered a positive test of reversible airflow obstruction. However, one of the key issues about the use of spirometry to help diagnose asthma is the absolute requirement for its correct use and interpretation (15). If this is not done, there is a significant risk of both under and over diagnosis (33). Interpretation of spirometry results varies even between specialist lung function laboratories, with lack of standardization in relation to definitions for the lower limit of normal (34). Another issue that affects the interpretation of spirometry in the context of an asthma diagnosis is that values may be normal when assessed during stable disease in the clinic. The majority of adults seen in primary care have mild disease with well-preserved lung function. Airflow obstruction defined as a ratio

of FEV_1/FVC <70% was found in only 21% of adult patients diagnosed with asthma in a primary care setting (35). In the case of normal spirometry results, the NICE guidelines suggest a two to 4 week period of peak flow monitoring and more than 20% variability in results as a positive test supportive of asthma. The American Thoracic Society and the National Asthma Education and Prevention Program, both recommend the use of spirometry for the diagnosis of asthma, these recommendations have been in place since 2007. However, an assessment of the implementation of this recommendation by physicians for patients with newly diagnosed asthma demonstrated that only 47% had spirometry performed within a year of the diagnosis being made (36). Moreover, rates of use of spirometry in primary care were only 23% and 78% of patients were prescribed asthma drugs without previous spirometry (36). Therefore, despite recommendations and guidelines having been introduced for over a decade, implementation and physician practice seems to have remained largely unaffected. This pattern seems consistent across countries, with approximately 50% of patients with a diagnosis of asthma ever having had spirometry in a secondary care or specialist setting, and this value reducing to approximately 25% in primary care (37, 38). Overall, there is agreement among respiratory physicians that spirometry is important in making a diagnosis of asthma in adults. However, in practice, it is difficult to find evidence that the guidelines are being consistently implemented. A combination of physician education to undertake spirometry to the required standards, emphasis of its importance and providing knowledge in interpretation and importantly, resources and incentives to undertake the test from primary through to specialist care, is likely the only way it will be adopted more widely (**Table 2**).

TABLE 2 | Advantages and challenges of the use of spirometry in making a diagnosis of asthma in adults and children.

Advantages	Challenges
Objective evidence of obstructive airways disease	Not reliable if technically inadequate maneuvers performed—skills to undertake procedure and calibrate and maintain equipment needed
Demonstration of variable airflow obstruction if bronchodilator reversibility also applied	Defined and agreed values for lower normal limit needed
Minimizes over diagnosis and misdiagnosis	Normal values do not rule out asthma—tests of airway hyperresponsiveness may be needed
Demonstration of reversible airflow obstruction provides objective evidence of asthma	Requires cooperation, cannot be reliably performed in children under 6 years, except in specialist centers
	Difficulties around agreement of lower normal limit—need to use reference values that allow for ethnicity
	Technical expertise in obtaining a satisfactory result is needed. Often best results obtained with incentive devices, which may not be available in primary care

Use of Spirometry to Diagnose Asthma—In Children

Although confirmation of reversible airflow obstruction is as important for a diagnosis of asthma in children as in adults, the practical application of spirometry in children is even more of a challenge (**Table 2**). This applies to all levels of care from primary to specialist, because of the significant challenges of technical expertise required to undertake reliable and reproducible tests in children and the training and education needed by physicians in the interpretation of the data. These issues are highlighted by American data, which shows that although 52% of physicians who provided primary care to children used spirometry, only 21% used spirometry according to the national guidelines and only 35% of physicians surveyed were comfortable interpreting the test results (39). In addition, 21% of spirometry readings were interpreted incorrectly (40), emphasizing the need for training and quality control prior to use of spirometry for children in primary care. The challenges of using spirometry to diagnose asthma in children and the improvements that can be made following training and education of healthcare staff have been discussed in detail elsewhere (41). Another critical issue for children, even more prevalent than in adults, is that when measured during stable disease, spirometry is frequently normal, even in those with severe disease (42). The significant issues that arise when relying on spirometry in children to make a diagnosis of asthma have been highlighted recently in a study that assessed the usefulness of the recent NICE guidelines in England to accurately make a diagnosis of asthma when applied to a cohort of children being regularly followed. Only two of 89 children aged between 13 and 16 years, who were symptomatic met the definition of asthma when assessed according to the NICE diagnostic algorithm (FEV_1:FVC <70%), but neither met the epidemiological, questionnaire based definition of asthma (43). Although a total of 10 children had FEV_1:FVC <70%, 8 of those did not have symptoms consistent with current asthma (43). The risks of using cut-offs for airway obstruction and lower normal limits extrapolated from adult studies have been highlighted as a significant pitfall for the application of the pediatric NICE guidelines in clinical practice (44).

As asthma is characterized by variable airflow obstruction, a reduced FEV_1/FVC ratio may not be present at all times, therefore, if clinical suspicion remains, spirometry may need to be repeated to demonstrate obstruction. Another way of recording variation in airflow obstruction is to undertake several measurements of peak expiratory flow rate (PEFR) at home for 1–2 weeks. Variation of >13% suggests variable airflow obstruction. However, correct technique must be ensured, and this relies on patient cooperation and adherence in undertaking the measurements (45). Demonstration of improvement in spirometry following bronchodilator may be more sensitive in children than detection of obstruction (46). Demonstration of reversibility after bronchodilator had good specificity for an asthma diagnosis (73%), but using a cut-off of 12% improvement for children carried poor diagnostic sensitivity (35%), while a cut-off of 8% was significantly better (47). Therefore, although demonstration of bronchodilator reversibility is important to

help confirm a diagnosis of asthma, but it may not be appropriate to use a strict cut-off for improvement in children.

Reference Values for Spirometry: the Global Lung Function Initiative (GLI)

Global, multi-ethnic all age reference equations are now available and have been endorsed by all major international respiratory societies (48). These are now considered the international gold standard and offer a unified approach to the interpretation and presentation of FEV_1 and other spirometry measures. It is essential that these reference equations are used, but specifically in the context of demonstrating airway obstruction in children, it must be remembered that older reference equations may produce lower predicted values, which result in an over-estimation of lung function when interpreted as %predicted. Therefore, the switch to GLI-2012 will result in lower median FEV_1 %predicted values overall, as well as age-specific and individual patient differences. Data for airway obstruction should be interpreted using the GLI-reference values as recommended by the NICE guidelines.

PERSISTENT AIRFLOW LIMITATION AND ASTHMA DIAGNOSIS

An important sub-group of patients thought to have asthma may have obstructive spirometry, but without evidence of bronchodilator reversibility. These patients have a post-bronchodilator FEV1 and/or an FEV1/FVC less than the lower limits of normal, or persistent airflow limitation (49). Although this is unusual in asthma, it may still be consistent with the diagnosis. A multi-center study of children with persistent airflow limitation on spirometry, showed 93% of all children had a diagnosis of asthma, this was even after other diagnoses and co-morbidities had been excluded (49). Similarly approximately one-third of adults screened in asthma clinics have been shown to have persistent airflow obstruction (50). Those with persistent airflow limitation may have more severe disease, but the most important element prior to labeling these patients as asthma is to refer to a specialist center to ensure other diagnoses have been excluded.

In adults, the most common airway disease associated with fixed airway obstruction is chronic obstructive pulmonary disease (COPD). However, it has now been proposed that there is a gray area of overlap between patients that have asthma (with reversible airflow obstruction) and those with COPD and fixed airflow obstruction. This has led to the diagnostic label asthma-COPD overlap (ACO). Although the term has been proposed as a valid entity, the definition and clinical features of patients that may fit this category have remained uncertain. It appears to be characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. There has been a published consensus definition which includes persistent airflow limitation in symptomatic individuals 40 years of age and older, a well-documented history of asthma in childhood or early adulthood and a significant exposure history to cigarette or biomass smoke (51). Overall, the diagnosis of ACO in adults remains uncertain and a challenge (52). This entity adds to the confusion, however, it brings back the importance of identifying a constellation of symptoms and looking for evidence of underlying pathophysiology, with the approach of targeting therapy in individuals according to "treatable traits" (2). Certainly, in children, the approach taken is that the presence of persistent airflow limitation in a child with presumed asthma should lead to referral to a specialist center and the search for alternative diagnoses. However, if no other diagnoses explain the child's symptoms and presentation, asthma with persistent airflow limitation is the diagnosis and the patient should be treated as such. It is important to remember, however, that therapy escalation to try to reach "normal" lung function may not be appropriate, especially if a child does not have evidence of eosinophilic airway inflammation. A trial of steroids to try to establish optimal lung function may be appropriate, but if there is no improvement and the child's symptoms are controlled, attempts to escalate steroid medication must be resisted in this exceptional scenario (53).

UTILITY OF LUNG FUNCTION TESTS OTHER THAN SPIROMETRY FOR ASTHMA DIAGNOSIS

The limitation of spirometry in children is prevalent because of the reliance on the ability of the child to adequately perform voluntary maneuvers. This is a particular challenge in the absence of computer aided incentive devices (54). Alternative effort independent lung function tests can therefore be used in children, but none of these are available in primary or secondary care and issues around technical competence and normal values are even more of an issue than for spirometry, even in specialist centers. As a result, the application of tidal breathing or effort independent tests is currently limited predominantly to the research setting and being tested mainly in preschool children being assessed at specialist centers. The assessment of airway obstruction in children with severe asthma has been reviewed elsewhere (55) and the utility of forced oscillation technique and impulse oscillometry for asthma diagnosis have also been reviewed (56).

Other lung function tests that can be used include plethysmography, multiple breath washout (to measure lung clearance index) and airway resistance using the interruptor technique (Rint). However, none of these are used routinely in clinical practice, certainly none are available for use in primary or secondary care. The test used most commonly in specialist centers is plethysmography, however this measures lung volumes, and the role of assessing lung volumes in asthma diagnosis remains controversial. Although there is evidence that lung volumes may be complementary to spirometry to assess asthma severity (57), plethysmography alone is not routinely used to make the diagnosis. Similarly, the other tests have been used in small studies, especially in populations where voluntary maneuvers cannot be reliably performed, but currently their use remains limited to research and specialist centers, without

obvious evidence for their role in routine clinical practice, in either children or adults.

ASSESSMENT OF AIRWAY HYPERRESPONSIVENESS TO DIAGNOSE ASTHMA

As spirometry is often normal during stable disease in patients with a clinical picture consistent with asthma, an indirect bronchial provocation test to assess airway hyperresponsiveness can be used to help diagnostic confirmation. Various challenge agents can be used to induce hyperresponsiveness including histamine, methacholine, allergens, adenosine, and mannitol. However, the importance of optimal delivery of the inhaled agents to the airways to ensure reproducible data are generated has been highlighted (58). Inhaled methacholine, a direct cholinergic agonist, to evoke concentration-dependent airway smooth muscle contraction can be used and bronchoconstriction at low concentrations of methacholine (typically <4 mg/mL) suggest increased airway hyperresponsiveness. A novel method to report responsiveness using dose rather than concentration has recently been proposed (59). However, allergen challenge tests can only be undertaken in specialist centers and so are not routinely used for asthma diagnosis, but should be undertaken in patients with a symptom constellation suggestive of asthma, without evidence of reversible airflow obstruction or eosinophilic airway inflammation and without response to therapy.

In addition to inhaled challenge tests, another scenario that may uncover bronchoconstriction, and may also be supportive of an asthma diagnosis, is exercise. Exercise is a frequent precipitant of asthma symptoms, however an exercise test is of particular importance if this is the only trigger for symptoms in order to obtain objective confirmation of true bronchoconstriction and diagnose asthma, (60) and to exclude any contributory upper airway symptoms including exercise induced laryngeal obstruction which may be prevalent in both children and adults (61, 62). Importantly, the presence of exercise induced bronchoconstriction alone may not equate to a diagnosis of asthma as it may occur in people without asthma, the need to assess the complete clinical picture and airway inflammation remains essential.

ASSESSMENTS OF ATOPY IN ASTHMA DIAGNOSIS

Often a diagnosis of asthma is made clearer in the presence of associated allergic diseases including eczema, allergic rhinitis or food allergy. In children, allergic asthma is the most common phenotype (63) and therefore assessments of allergic sensitization, in the absence of disease manifestation, are undertaken to help support the diagnosis. However, what remains uncertain is how best to include tests of allergic sensitization into diagnostic algorithms for asthma (64). The presence of allergic sensitization, particularly to aeroallergens is supportive of the diagnosis, but the absence of sensitization does not rule out the disease. In school children, non-atopic asthma is rare and should be diagnosed after careful exclusion of other differential diagnoses (65).

The phenotype of "adult-onset asthma" is often non-atopic (66) and therefore atopy is not as central to the diagnosis in adults as in children. However, it must be remembered that atopy is not an all or nothing phenomenon and must itself be quantified in terms of severity (67). An absence of elevated specific IgE to a limited range of allergens may not exclude atopy, moreover, low peripheral IgE levels may not reflect low pulmonary mucosal IgE levels as has been shown by a reduction in bronchial IgE and associated improved lung function following omalizumab therapy in "non-atopic" adult asthmatics (68). As for blood eosinophils and other objective tests, the presence of allergic sensitization and indeed associated clinical manifestation of allergic diseases certainly supports a diagnosis of asthma in a patient with the correct symptom constellation, but the absence of atopy does not exclude asthma.

SHOULD WE HAVE DIAGNOSTIC ALGORITHMS/GUIDELINES FOR ASTHMA?

Unfortunately, we do not have a gold standard confirmatory test for asthma, so although objective markers may be used, they still all only provide evidence that is supportive of, or less indicative of asthma. Ultimately, a diagnosis at present can only be made based using a constellation of clinical features, supportive objective tests and frequently an assessment of response to therapy. The absence of a gold standard test, and the recognition that asthma constitutes a disease with an array of etiologies, phenotypes and clinical manifestations has led to the proposal that we should now diagnose "asthma" based on symptoms, and then identify pathological and physiological "treatable traits" to allow targeted and personalized therapy. Although in England the NICE guidelines have attempted to overcome the lack of utility of any objective tests to make a diagnosis of asthma, they remain restrictive, as the objective tests used assume the presence of predominantly eosinophilic airway inflammation and reversible airflow obstruction are required for the diagnosis. This approach has the risk of being too restrictive and potential for under diagnosis as numerous phenotypes and endotypes of the disease display either non-eosinophilic inflammation, or airflow limitation without obstruction. The inclusion of objective tests is important, and it should be remembered that a single test may not be enough to make a diagnosis, and a combination of tests demonstrating variable airflow obstruction and airway inflammation are needed. When applied to a cohort of 13–16 year old children spirometry, bronchodilator reversibility and exhaled nitric oxide were all normal in 24 of 56 children (43%) with current asthma defined epidemiologically (physician diagnosed asthma, current wheeze and prescribed asthma medication) (43). Moreover, the data question the cut-offs proposed for obstructive spirometry in children, the order in which the lung function tests are proposed and the position of bronchodilator reversibility within the algorithm. The authors plainly state the

NICE algorithm should not be used for an asthma diagnosis in children until better evidence of its utility is available (43).

DIFFERENTIAL DIAGNOSIS

Even though patients may present clinically with acute symptoms of breathlessness and wheeze, the long list of differential diagnoses that may cause these symptoms must be considered before asthma is diagnosed (69). Features in the history that are supportive of asthma include a positive family history in a parent or sibling, a history of atopy, including eczema, allergic rhinitis or food allergy and, for children, a symptom pattern that incorporates symptoms with several triggers such as exercise, cold air as well as upper respiratory infections. The important "red flags" in the clinical history and examination that should question the diagnosis in both children and adults have been clearly summarized in the British Thoracic Society/ Scottish Intercollegiate Network Guidelines (https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-quick-reference-guide-2016/). The initial structured clinical assessment should be used to help decide whether asthma is of high, intermediate or low probability. If any doubts about the diagnosis arise, it is essential that referral to a specialist is made prior to any diagnostic label being applied as the high risk of misdiagnosis and over diagnosis with the resulting undesirable consequences to the patient and inappropriate use of resources has become increasingly apparent (8).

SHOULD A TRIAL OF TREATMENT BE USED TO DIAGNOSE ASTHMA?

Given the difficulties associated with the absence of a gold standard diagnostic test for asthma, and especially in children, difficulties around appropriate lung function tests and assessments of airway inflammation, it has been argued that the only way to confirm the diagnosis is to assess response to a trial of asthma medication. However, this approach carries a significant risk of a misdiagnosis with the associated problems of inappropriate therapy. This is even more of a concern now since the BTS/SIGN guidance for the management of asthma suggests as required short acting bronchodilators should not be the starting point of treatment, but all patients should be commenced on anti-inflammatory treatment with low dose regular inhaled corticosteroids (70). Whenever possible, the diagnostic tests that have been outlined thus far to try to identify "treatable traits" such as evidence of eosinophilic airway inflammation and reversible airflow obstruction should be undertaken. This applies equally to children and adults. The concern is that a response of symptoms to a trial of therapy does not make a diagnosis. Indeed, a trial of therapy is not part of the diagnostic algorithm proposed by NICE in England (71). If a child or adult presents acutely with wheeze, then it is a priority to treat the symptoms and not wait for objective tests. However, once symptoms have been controlled, even if empirical maintenance therapy such as inhaled corticosteroids have been commenced, it remains important to undertake some objective testing once the patient is stable to help to confirm the diagnosis.

SPECIFIC CONSIDERATIONS

Diagnosing Asthma at the Extremes of Age

Preschool Wheeze

Making a diagnosis of asthma in preschool children is a huge challenge because objective tests of airway inflammation and lung function are either invasive (broncho-alveolar lavage for inflammation) or require voluntary maneuvers and cooperation (spirometry). In addition, children under 5 years old have phenotypes of wheezing that are distinct from allergic asthma. Some only wheeze with respiratory infections in acute episodes and others may have persistent symptoms during and in between episodes. The diagnostic term preschool wheeze is therefore used in preference to asthma for children under 5 years old. Guidelines and recommendations for diagnosis and management have been published (72, 73). Diagnosis currently relies predominantly on confirmation of wheeze (doctor diagnosed wheeze), history and symptom pattern (which relies on accurate parental recall) and tests of atopy. However, the pitfalls of relying predominantly on subjective markers to make a diagnosis and direct management have been highlighted (74). Increasing efforts are being made to identify biomarkers to help guide management in preschool wheezers. The most promising is recent evidence of children with aero-allergen sensitization and elevated blood eosinophils as differential responders to maintenance inhaled corticosteroids (75). The role of respiratory infection (both viral and bacterial) and neutrophilic airway inflammation in mediating symptoms is being increasingly recognized in this age group (76), but biomarkers that distinguish children with predominant eosinophilic and allergic airways disease compared to those with infection driven disease are currently lacking.

Asthma in the Elderly

It is important to recognize the impact of aging on lung physiology when diagnosing asthma in the elderly. Specifically, because aging impacts respiratory mechanics, the fixed threshold of <0.70 for the ratio FEV_1 to FVC frequently misclassifies normal-for-age spirometry as airflow obstruction. Such misclassification can occur in otherwise asymptomatic never-smokers, starting at about age 45–50 (77). It is not fully understood how FeNO varies with age in healthy individuals. One study has demonstrated three distinct phases in the evolution of FeNO throughout the age range 6–80 years (78). FeNO values increased linearly between 6 and 14 years of age in girls and between 6 and 16 years of age in boys. After that, FeNO levels plateaued in both genders until age 45 years in females and age 59 years in males, when they started to increase linearly again. This increase continued until age 80.

Smoking and Asthma Diagnosis

A smoking history should always be obtained as regardless of the underlying disease smoking cessation advice should be given. Current or past smoking, conventionally at least a 20 pack

year history, opens up the potential diagnosis of a smoking asthmatic, COPD or ACO. To a certain extent these labels are arbritary and of more importance is the identification of underlying treatable traits (79). Active smoking will lower FeNO measurements (80) and any trial of treatment with either ICS or OCS may be affected by the impact of smoking on the mechanism of action of corticosteroids (81). Current smoking should not have any impact on blood eosinophils, spirometry, or bronchodilator reversibility.

Occupational Asthma

Asthma either caused by occupation or aggravated by occupation should always be considered in people diagnosed with asthma during their working lives. Studies have suggested that up to 10% of people diagnosed with asthma in adult life have an occupational cause (82). Occupational asthma can be simply screened for in primary care by asking whether asthma symptoms improve at the weekend or when on holiday (83). If the answer to either of these questions is yes then a full occupational history including exposures should be obtained. The diagnosis of occupational asthma is extremely important given that moving away from the relevant exposure may allow for their asthma to be cured, providing that this occurs in a timely fashion. Everyone with occupational asthma should be referred to a specialist occupational lung disease unit who will perform detailed peak flow monitoring, potentially skin prick tests for the relevant allergens and on occasion challenge testing.

SUMMARY

There is definite consensus among adult physicians and pediatricians that asthma is a heterogeneous disease underpinned by numerous pathophysiological mechanisms. It is no longer acceptable to make a diagnosis in a patient of any age simply from a history and physical examination and by assessing a response to a trial of therapy. Young preschool aged children may not be able to undertake tests of lung function and inflammation that require voluntary maneuvers, but they can have assessments of atopy and blood eosinophils to help make a diagnosis and guide therapy. Children and adults above 5 years should all have at least some objective confirmation to support the diagnosis using lung function tests and non-invasive assessments of airway inflammation using exhaled nitric oxide. These tests can be undertaken in a primary or secondary care setting providing adequate education and training in the use and interpretation of the equipment is made available to health professionals. There is no gold standard test, but we now know that to avoid under diagnosis, over diagnosis and misdiagnosis, it is essential to undertake objective tests to support a diagnosis of asthma and to identify treatable traits of the airway disease.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Asthma Across Age: Insights From Primary Care

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Asthma is a heterogeneous disease comprising of multiple phenotypes and affects patients from childhood up to old age. In this review, we summarize the current knowledge on the similarities and differences in asthma across different age-groups, with emphasis on the perspective from primary care. Despite the similar disease presentation, phenotyping studies showed that there are differences in the distribution of phenotypes of asthma presenting in childhood compared to that in adulthood. Whereas, asthma with early age of onset tends to be of the atopic phenotype, the disease shifts toward the non-atopic phenotypes at later ages. Studies within primary care patients aiming to elucidate risk factors for future asthma exacerbation have shown pediatric and elderly patients to be at higher risk for future asthma attacks compared to other adult patients. Regardless, both pediatric and adult studies demonstrated previous asthma episodes and severity, along with high blood eosinophil to predict subsequent asthma attacks. Differences in childhood and adult asthma are not limited to the underlying phenotypes but also extends to the challenges in the diagnosis, treatment, and management of the disease. Diagnosis of asthma is complicated by age-specific differential diagnoses such as infectious wheezing and nasal obstruction in children, and aging-related problems such as heart disease and obesity in the elderly. There are also age-related issues leading to decreased disease control such as non-adherence, tobacco use, difficulty in using inhalers and corticosteroid-related side effects which hinder asthma control at different patient age-groups. Several clinical guidelines are available to guide the diagnosis and drug prescription of asthma in pediatric patients. However, there are conflicting recommendations for the diagnostic tools and treatment for pediatric patients, posing additional challenges for primary care physicians in working with multiple guidelines. While tools such as spirometry and peak flow variability are often available in primary care, their usage in preschool patients is not consistently recommended. FeNO measurement may be a valuable non-invasive tool which can be adopted by primary physicians to assist asthma diagnosis in preschool-age patients.

Keywords: asthma, guidelines, primary care, children, adult, phenotypes, diagnosis, management

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INTRODUCTION

The term "asthma" encompasses1 heterogeneous phenotypes of conditions sharing similar symptoms yet different underlying causes and prognosis (1, 2). Depending on the age of presentation, symptoms of asthma may represent different phenotypes of the disease, each with its own challenges in the diagnosis, management, and treatment. A better understanding of the different subsets of asthma is hoped to assist us to better diagnose, manage, and treat this disorder.

Primary care represents the frontline of patient management and not all patients with asthma require referral to secondary care (3). Thus, this article aims to describe the age-related phenotypes of asthma and the challenges presented by asthma across different age groups, with emphasis on insight from primary care.

ASTHMA ACROSS AGES

Phenotypes of Asthma

The traditional method of asthma phenotyping involves grouping of asthma by characteristics such as the age of onset, trigger, atopic status, and presence of biomarkers, in a so-called "biased" approach to phenotyping (4–6). It is well-known that early-onset asthma represents a distinct phenotype compared to adult-onset asthma. Adult-onset asthma may also be further divided into long-standing asthma, asthma which remitted at childhood and subsequently relapsed, and new onset adult asthma (7).

Cluster analysis presents an unbiased statistical approach to phenotype asthma by grouping them into clusters with maximum similar characteristics within clusters and minimum similarity between clusters (**Table 1**). Haldar et al. conducted a cluster analysis from both patents with milder asthma presenting in primary care, as well as patients with refractory asthma diagnosed in secondary care (2). The study identified 3 and 4 separate clusters of asthma from the respective populations, 2 of which were identified from both populations. Two clusters denoted with early onset were both accompanied with positive atopic status, one of which had minimal signs of eosinophilic inflammation. Clusters of late-onset asthma include a cluster of obesity-related non-eosinophilic asthma predominant in females and a male-predominated cluster predominantly marked by active eosinophilic inflammation but fewer symptoms. Both late-onset clusters also consisted of lower proportion of patients with positive atopic status compared to the early onset clusters.

A cluster analysis which combined severe asthma and non-severe asthma patients recruited into the Severe Asthma Research Program (SARP) identified 5 clusters of asthma (8). Similar to the characteristics of the clusters identified by Haldar et al., clusters associated with early age of onset were also associated with higher atopic status while those with later-onset were less atopic. Another cluster analysis study was conducted on children (6–11 years) and adolescent to adult patients (>11 years) with severe or difficult-to-treat asthma from the TENOR (The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens) study (9). Five clusters were identified within both age-groups differentiated by demographics, a topic status, tobacco exposure (in children), and aspirin sensitivity (in adolescent to adults). Interestingly, in contrast to adolescent and adult patients, none of the five children clusters had significantly different asthma outcomes (within the next 12 months) among each other, though this is likely due to the population of the study being limited to severe asthma patients.

Results from both classic "biased" phenotyping studies and cluster analysis studies thus confirmed that early onset asthma is more likely to be atopic in nature, while adult-onset asthma tends to have non-atopic causes, primarily obesity. **Figure 1** illustrates a simple representation of this relationship between the atopic status of asthma and age as previously reviewed by Wenzel et al. (6).

Current asthma guidelines state that more research on the value of asthma phenotyping to guide treatment is required (10, 11).

Severe Asthma Across the Age

An estimated 5–10% of asthma patients suffer from a severe form of asthma (12). Despite the rarity, severe asthma poses high healthcare resource burden (13). The GINA (Global INitiatives for Asthma) guideline defined severe asthma as asthma which requires high dose ICS (inhaled corticosteroid)/LABA to prevent it from being uncontrolled or asthma which remains uncontrolled despite this treatment (10). Regardless, there is currently no universally accepted definition for severe asthma, preventing accurate estimation of its global prevalence, which is further contributed by the absence of a global registry for this subset of asthma until the recent creation of the International Severe Asthma Registry (14).

A recent review by Guilbert et al. highlighted the differences between adult and pediatric severe asthma (15). Compared to the adult counterpart, severe asthma in children had a more rapidly changing phenotype. They were also characterized with higher exhaled nitric oxide, IgE, and eosinophil levels. Despite the differences in pediatric and adult severe asthma, the current treatment guidelines for pediatric severe asthma is currently based on extrapolation from adult studies (15). Thus, there is a need for better guidelines on severe childhood asthma.

RISK PREDICTION OF ASTHMA

Asthma exacerbation is a major cause of quality of life disruption and healthcare resource consumption. Thus, a part of asthma management includes managing the risk for future asthma exacerbations/attacks on top of maintaining symptom control (10, 16). The GINA provides a guideline for assessment of asthma exacerbations in primary care setting (10). The guideline suggests documentation of symptom histories such as the onset, severity, potential risk factors, and current therapy, along with physical examination and objective measurements such as pulse oximetry and peak expiratory flow measurement (for patients > 5 year).

Numerous studies have been conducted to investigate potential risk factors for future asthma exacerbations (**Table 2**). Observational studies using primary care data have identified factors such as previous asthma attacks and medication usage in

TABLE 1 | Clusters of asthma phenotypes.

Population analyzed	Additional patient details	Clusters Identified
Haldar et al. (2)		
1. Primary care ($n = 184$)	Age range: 18–65 years	1. Early-onset atopic ($n = 61$) 2. Obese, non-eosinophilic ($n = 27$) 3. Benign ($n = 96$)
2. Secondary care ($n = 187$)	Age range: not specified	1. Early-onset atopic ($n = 74$) 2. Obese, non-eosinophilic ($n = 23$) 3. Early symptom predominant ($n = 22$) 4. Inflammation predominant ($n = 68$)
Moore et al. SARP study, 2010 (8)		
12–80 years old ($n = 726$), 304 fulfilled criteria for severe asthma	Primary/secondary: not specified	1. Early-onset atopic, normal lung function and low healthcare utilization ($n = 110$) 2. Early-onset atopic, higher medication requirement ($n = 321$) 3. Late-onset, less-atopic, obesity-related, lower lung function, and more daily symptoms and healthcare utilization ($n = 59$) 4. More severe, long-standing, early-onset, atopic, reversible lung obstruction, high ICS usage ($n = 120$) 5. More severe, long-standing, late-onset, less-atopic, less-reversible lung obstruction, high ICS usage ($n = 116$)
Schatz et al. TENOR study, 2014 (9)		
6–11 years old ($n = 518$)	Patients recruited from "managed care organizations, community physicians or group practices, and academic centers"	1. White race with no tobacco exposure ($n = 115$) 2. Female cluster ($n = 81$) 3. Non-atopic ($n = 162$) 4. Passive smoke exposed ($n = 87$) 5. Non-white race ($n = 73$)
≥12 years old ($n = 3,612$)		1. White female adult onset, low IgE ($n = 1262$) 2. High atopic cluster ($n = 659$) 3. Male cluster ($n = 664$) 4. Non-white cluster ($n = 596$) 5. Non-white race ($n = 431$)

ICS, Inhaled corticosteroid.

and biomarkers such as blood eosinophil to predict exacerbations in subsequent years (17, 18).

Knowledge of the risk factors for asthma attacks in children is scarce, and even less is known in preschool asthma, where exacerbation may have viral triggers (19). Swern et al. conducted a *post-hoc* analysis of 2–5years old patients ($n = 689$) previously enrolled in a randomized control trial (20) The trial included patients with physician-diagnosed asthma defined as ≥3 episodes of asthma symptoms in the past year including but not limited to cough, wheezing and shortness of breath. The study identified a combination of daytime cough, daytime wheeze, and night-time β2-agonist use to be predictive of exacerbation in the following day. However, this study did not report risks for exacerbations further than 3 days after the identification of risk factors.

A very recent study by Bloom et al. reported the exacerbation risks on the general asthma population across different age-groups including patients under 5 years old within the UK's national electronic healthcare records (3). Interestingly, patients ≥55 years and <5 years had the highest rate for exacerbations, in comparison to adolescents (5–17 year) and adults (18–54 years). Regardless of the age groups, higher asthma severity (as defined by the BTS [British Thoracic Society] treatment steps) was a significant predictor for annual exacerbation rate and time to next exacerbation, especially within the <5 years group.

Results on older children and adolescents confirmed the findings of the adult studies, i.e., recent asthma attacks and blood/systemic eosinophilia were consistently reported as predictors for future attacks (17, 18, 21–25). A recent observational study combining data from 2 primary care databases in the UK also reported recent asthma attacks, previous consultation for lower respiratory infections, blood eosinophils > 400/μL, and younger age to be indicative of high-risk for future asthma exacerbation in children 5–12 years of age (23). Another large observational study using general practice data of Dutch children 5–18 years old reported asthma exacerbations and asthma treatment in the preceding year and younger age to be risk factors for severe asthma exacerbations (24). While blood eosinophil level of ≥300 cells/uL was not a risk factor, children with heightened blood eosinophil had shorter time till exacerbation.

Interestingly, in contrast to adult population studies where older age was associated with increased risk (17, 18), studies in children reported younger age to be associated with higher risk for asthma attacks/exacerbations (23, 24). This confirms the observation by Bloom et al that patients at both ends of the age spectrum were at the highest risk for exacerbations (**Figure 2**) (3).

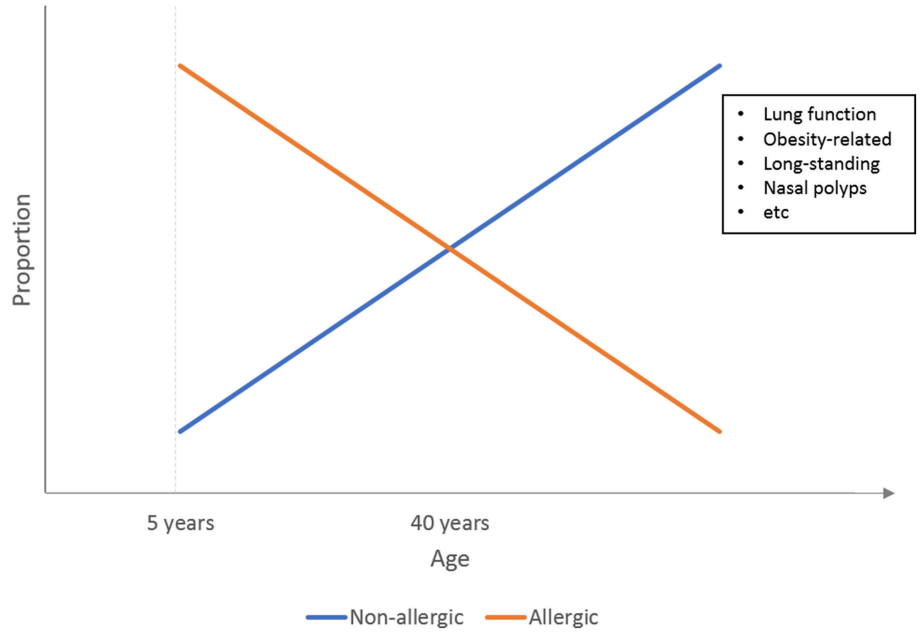

FIGURE 1 | Illustration of the relationship between asthma phenotypes and the age of onset. At younger age, asthma is predominated by the atopic phenotypes, which are gradually phased out by non-atopic phenotypes such as obesity-related asthma at adulthood.

DIAGNOSTIC CHALLENGES ACROSS AGE

There is still a very clear lack of understanding of asthma in children under 5 years, and diagnosis of asthma within the preschool age is challenging due to the lack of proper guideline and definition (26). In this age group, symptoms of wheezing and cough are very common but may be the result of acute respiratory infections instead of asthma (**Figure 3**) (27, 28). The Tucson birth cohort (USA) identified three distinct phenotypes of wheezing in the first 6 years of life: transient early wheezing, late onset wheezing and persistent wheezing (29, 30). The result from subsequent follow-up reported that not all children who wheezed developed asthma in later childhood, although children with atopic wheezing were the most likely (30). Thus, differentiating transient symptoms from symptoms of the more persistent asthma poses a challenge in early age.

The GINA (10) and CTS (Canadian Thoracic Society) (31) guidelines recommend consideration of symptomatology, potential triggers and family history to assist in clinical decision making for this age group of patients. The guidelines additionally recommend observing for signs of airway obstruction and reversibility with inhaled bronchodilators to assist in diagnosis. Similarly, the Australian Asthma Handbook (32) and NICE guideline (33) recommend treating preschool patients with suspected asthma based on clinical observation and conduct objective tests only after 5 years of age.

Objective tools recommended by the clinical guidelines to diagnose asthma across different age groups are summarized in **Table 3**. Lung function tests, primarily spirometry, are recommended to confirm asthma diagnosis in school-aged children and adults within primary care practice (10, 11, 16, 33–35). However, in many countries, spirometry is not available to primary care, and conducting lung function tests on patients <5 years old is challenging due to their inability to produce consistent lung function readings (**Figure 3**) (10, 26, 28, 36). The BTS guideline thus does not recommend lung function measurement to guide asthma management in this age group (16). A joint statement by the American Thoracic Society (ATS) and European Respiratory Society (ERS) suggested taking only one satisfactory measurement, instead of the ideal of at least two separate measurements to accommodate pediatric patients (36). The GEMA emphasizes the need for nursing supervision and suggested measurement of $FEV_{0.5}$ instead of FEV_1 in preschool children 3 years and above (11).

FeNO (Fractional concentration of exhaled Nitric Oxide) is an inflammatory biomarker which may indicate the presence of type 2 asthma (asthma characterized by Type-2 inflammation). The NICE (National Institute for Health and Care Excellence) (33) and GEMA (Spanish Guideline on the Management of Asthma) (11) guideline recommends FeNO measurement for asthma diagnosis. The GINA, on the other hand, do not recommend the usage of FeNO to aid asthma diagnosis in adults, with the argument that FeNO may be elevated in other respiratory conditions, and is not elevated in other asthma phenotypes such as neutrophilic asthma (10). However, the guideline recommends FeNO measurement in preschool-age patients. In agreement with this, a prospective study in a hospital setting reported elevated FeNO level during preschool to be predictive of school-age asthma (37). Additionally, a randomized control trial based on 24 primary care centers and one hospital showed that high

TABLE 2 | Risk prediction of future asthma exacerbations/hospitalization*.

References	Population	Age	Definition of asthma	Outcome	Predictive factors
PEDIATRIC					
Swern et al. (20)	Patient from double-blinded multicenter RCT	2–5 years	Physician-diagnosed asthma: At least 3 episodes of asthma symptoms such as cough, wheeze, shortness of breath	Asthma attacks	• Daytime cough • Daytime wheeze • Night-time β2-agonist
Bloom et al. (3)	Primary care	<5 years and 5–17 years	Patients with read codes for asthma	Annual asthma exacerbation rate and time to first exacerbation	• Higher asthma severity
Haselkorn et al. (21)	Severe asthma children recruited from "Managed care organizations, community physicians or group practices, and academic centers"	6–11 years	Diagnosed with severe asthma or mild/moderate asthma considered to be difficult-to-treat by site specialist.	Future severe exacerbation	• Recent exacerbation • Non-white race (vs. white) • 3-4 allergic triggers • Poor asthma control
Covar et al. (22)	Patient from double-blinded multicenter RCT	6–14 years	Mild-moderate persistent asthma: Diary-reported symptoms or β-agonist use (not including pre-exercise), or mean morning and evening peak flow < 80%.	Asthma exacerbation	• Baseline exacerbation
Turner et al. (19)	Primary care	5–12 years	Read Code for asthma diagnosis.	Asthma attack in 1 year follow-up	• Higher GINA management step • Consultation for LRTI • Blood eosinophil >400/μL • Baseline asthma attacks • Younger age • Lower peak expiratory flow
Engelkes et al. (24)	Primary care	5–18 years	Algorithm-validated from list of patients with ICD code and free-text of asthma	Severe asthma exacerbation	• Younger age • Exacerbations in the previous year • Use of any asthma medication
				Time until next exacerbation	• Younger age • Female gender • Exacerbations in the previous year • Respiratory infection in the previous year • Asthma specialist visit in the previous year • ICS prescription • Blood eosinophil >300/μL • Comorbid eczema
ADULTS					
Bloom et al. (3)	Primary care	18–54 years and ≥55 years	Patients with Read Codes for asthma	Annual asthma exacerbation rate and time to first exacerbation	• Higher asthma severity
Kerkof et al. (25)	Primary care patients with secondary care data linkage	≥5 years	Active asthma defined as having diagnostic Read Codes for asthma, no code for resolved asthma, and at least 2 prescriptions for asthma.	Asthma-related hospital readmission 1 year after discharge	• Blood eosinophil count ≥0.35 $\times 10^9$ cells/L
Blakey et al. (17)	Primary care	12–80 years	Active asthma defined as having diagnostic Read Codes for asthma, no code for resolved asthma, and at least 2 prescriptions for asthma.	Asthma exacerbations in 2 years follow-up period	• Baseline (1 year) asthma exacerbations • Older age, female gender, current smoking, overweight • Co-morbid rhinitis, eczema, GERD, nasal polyps, or anaphylaxis • High blood eosinophil count • Higher daily SABA dose • NSAID, LTRA or LABA prescriptions

(Continued)

TABLE 2 | Continued

References	Population	Age	Definition of asthma	Outcome	Predictive factors
					• More acute OCS course • More asthma-related hospitalization • More primary care visits • Lower PEF%
Price et al. (18)	Primary care	12–80 years	Patients with recorded physician-diagnosis for asthma and no other chronic respiratory diseases.	≥2 severe asthma exacerbations in 1 year follow-up	• Older age, female gender, current smoker, overweight, • Blood eosinophil >400/μL • Co-morbid anxiety, diabetes, eczema, GERD, rhinitis • NSAID prescriptions • Higher asthma treatment step (BTS-SIGN) • General practice consultation for LRTI • Outpatient asthma attendance • Having acute OCS courses • >400 μg/day SABA dose • >800 μg/day ICS dose (FP equivalent)

**Studies which analyzed pediatric and adult patients as a single group are categorized as adult studies. BTS, British Thoracic Society; FP, Fluticasone propionate; GERD, Gastroesophageal reflux disease; GINA, Global Initiatives for Asthma; ICS, Inhaled corticosteroid; LABA, long-acting β-agonists; LRTI, Lower respiratory tract infection; LTRA, Leukotriene receptor antagonists; NSAID, Nonsteroidal anti-inflammatory drugs; OCS, oral corticosteroid; PEF, Peak expiratory flow; SABA, short-acting β-agonist; SIGN, Scottish Intercollegiate Guidelines Network.*

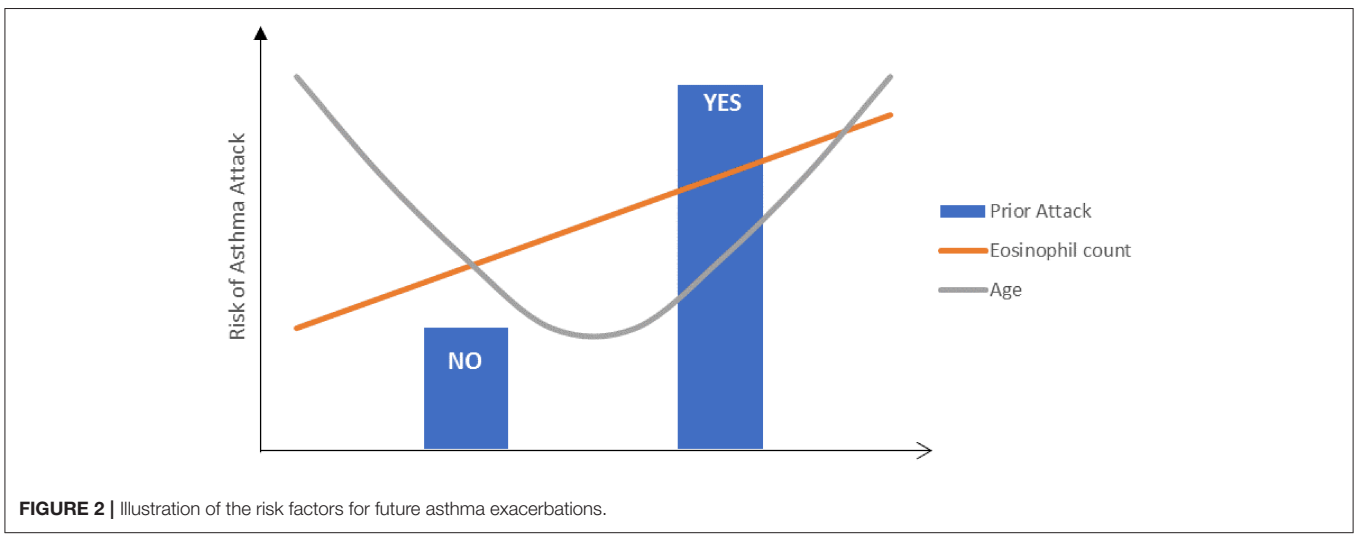

FIGURE 2 | Illustration of the risk factors for future asthma exacerbations.

FeNO level was associated with improved Asthma Control Questionnaire 7 items (ACQ7) score following ICS treatment (38). Therefore, FeNO measurement can be a non-invasive measure conducted in primary care practices to assist asthma diagnosis in preschool children and identifying patients who may benefit from ICS treatment.

Another available tool to assist primary care practitioners to predict whether the presenting wheezing symptoms in preschool children will develop into asthma by school age is the modified version (mAPI) (39) of the Asthma Predictive Index (API) created based on data from the Tucson cohort study (30, 40). The mAPI has been previously shown in an asthma birth cohort study to have high positive predictive capability for asthma at 6, 8, and 11 years based on mAPI score at the first 3 years of life (41).

Older age presents another diagnostic challenge distinct from that in younger patients (**Figure 3**). Symptoms of asthma in old age may be masked by aging-associated changes in pulmonary and other physiological functions (10, 42) and the presence of multiple co-morbid conditions (43). These factors lead to underdiagnosis of asthma within the elderly. The decreased respiratory capacity in the elderly may also make it difficult to conduct lung spirometry, as such the National Institute of Aging recommended alternative techniques which do not require inspiratory efforts such as imaging and forced oscillation (42) The GINA guideline recommends physical examination, such as electrocardiogram and chest x-ray, to aid in the diagnosis of elderly asthma in addition to the routine clinical history taking (10).

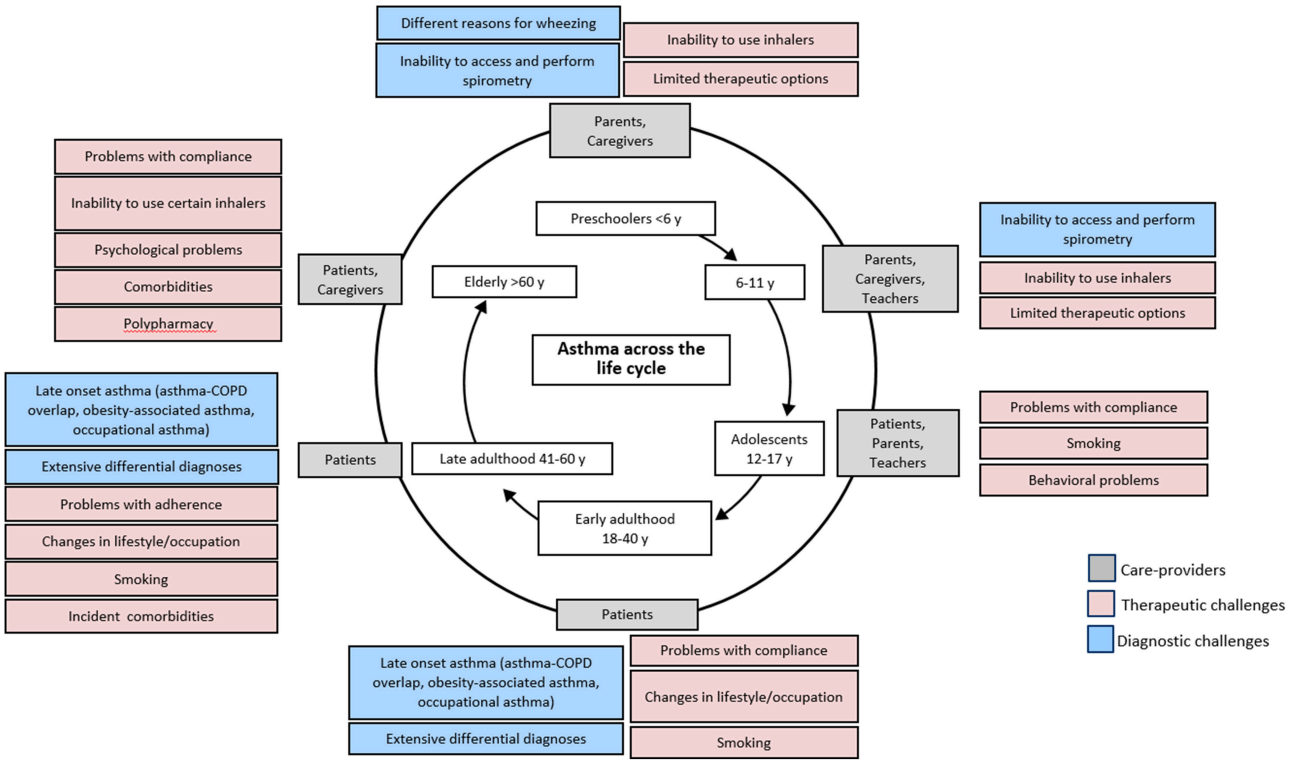

FIGURE 3 | Challenges related to asthma treatment across age. Adapted with permission from: Kaplan A, Covar R, Vanderwalker M. An update on treatment options for children and adults with asthma. Manuscript in Preparation.

Diagnosis of asthma is further complicated by differential diagnosis for symptoms which may mimic asthma. As mentioned above, wheezing and cough in children are likely to be infectious in nature. Non-infectious, non-pulmonary related causes of cough and wheeze, such as gastroesophageal reflux, airway obstruction due to foreign bodies, and congenital heart disease, should also be ruled out before the diagnosis of asthma in children (10). In old age, age-related problems such as heart disease and obesity are the major contributors to differential diagnosis. Chronic obstructive pulmonary disorder (COPD) is also a common cause of misdiagnosis in primary care due to overlapping symptoms with asthma (44). In addition, they may occur concurrently, in a term known as asthma-COPD overlap (ACO). Careful symptom history taking and post-bronchodilator spirometry to test for reversible airway obstruction are recommended to differentiate asthma from COPD and ACOS (10).

THERAPY ISSUES AT DIFFERENT AGES

Differences in Treatment Guidelines

The GINA guideline provides a step-wise management approach for treatment and management of asthma (10). The 2018 updated guideline still recommends as-needed short-acting β-agonists (SABA) for reliever treatment of asthma attacks and ICS as the initial controller medication for asthma, with addition of long-acting β-adrenoceptor agonists (LABA, as combination therapy with ICS), leukotriene receptor antagonists (LTRA) or stepping up of dosage as required for adolescent and adults patients above the age of 12 (10). Recommendations from other guidelines are similar (11, 16, 32–34): initial reliever with SABA, initial preventer treatment of ICS, and when needed, adding LABA in combination with ICS.

Initial treatment option for children 5–12 years follows that of older patients. However, LABA as the initial add-on is not recommended by the GINA (10) for this age group, in contrast to the BTS (16) recommendation. The CTS recommends LABA if stepping up ICS dosage fails to achieve control (34). Alternatively, tiotropium, a long-acting muscarinic antagonist (LAMA), administration by mist inhaler can be prescribed as an add-on in children ≥12 years and adults. LAMA is however not indicated for children <12 years by the GINA (10) and BTS (16) guidelines, though it is indicated for children ≥6 years in the US (45).

The GINA guideline dedicates a section outlining a step-by-step treatment guideline for children 5 years and younger, however, the current guideline is based on more limited evidence (10). Similar to older patients, (SABA) should be given as initial reliever upon presentation of wheezing. When necessary, i.e., symptoms suggestive of asthma or frequent wheezing episode, a

TABLE 3 | Objective tests recommendation in each age-groups and availability in primary care.

	Preschool (<5 years)*	Children (5–12 years)	Adolescent and adults (>12 years)	Availability in primary care
Peak flow variability	Not recommended by BTS	Recommended by GINA, CTS, and NICE; Not recommended by BTS	Recommended by GINA, BTS (in adults), CTS, GEMA and NICE.	Available
Spirometry	Not recommended by GINA† and BTS	Recommended by GINA, BTS, CTS, GEMA, AAH, and NICE	Recommended by GINA, BTS, CTS, GEMA, AAH, and NICE	Available
FeNO	Recommended by GINA, GEMA, and BTS (for 3–4years)	Not recommended by GINA; Recommended by NICE and BTS (for eosinophilic asthma)	Not recommended by GINA; Recommended by NICE, GEMA, and BTS (for eosinophilic asthma)	Not usually available
Bronchial provocation test	Not recommended by GINA	Recommended by GINA, BTS, AAH, and CTS	Recommended by GINA, BTS, CTS, AAH, and NICE (at >17 years)	Available in speciality clinics also
Allergen sensitization	Recommended by GINA and GEMA but not conclusive (doesn't exclude nonatopic asthma)	Recommended by GINA, GEMA, and BTS but not conclusive; Not considered essential by AAH. Not recommended by NICE	Recommended by GINA, GEMA, and BTS but not conclusive Not recommended by NICE	Available through speciality referral
Chest X-ray	Recommended by GINA, BTS, and CTS	Recommended by BTS	Recommended by BTS, and by GINA (in elderly).	Typically available

**NICE guideline does not recommend any objective tests to guide asthma diagnosis in children <5years †According to GINA, children 4–5 years may undergo spirometry with guidance. GINA, Global Initiatives for Asthma; BTS, British Thoracic Society; AAH, Australian Asthma Handbook; NICE, National Institute for Health and Care Excellence; CTS, Canadian Thoracic Society.*

low dose of ICS is recommended as the initial controller therapy. Similarly, GEMA (11) and Australian Asthma handbook (32) recommended initial SABA preventer with addition of low dose ICS when necessary. The BTS (16) guideline recommends SABA for reliever therapy together with low-dose ICS as the preventer, while the CTS guideline for preschool patients (31) recommends daily low-dose ICS as first-line therapy or SABA if symptoms were mild or infrequent. LTRA is recommended as an alternative to ICS by the GINA (10), GEMA (11), Australian Asthma Handbook (32), and BTS (16) but is not recommended for use by the CTS (31). If symptoms remain inadequately controlled with low-dose ICS, the GINA, GEMA and CTS guidelines recommend stepping-up to medium dose ICS, but this is not recommended by the BTS (16).

There is a lack of guideline on the treatment for asthma in elderly patients. Treatment of asthma in the elderly faces additional challenge due to poorer asthma control. However, more studies are required to determine whether this is due to decreased treatment response, difficulty with inhaler technique, or poorer adherence (43).

Challenges in Control

Adherence to inhaled corticosteroid (ICS) treatment is a key factor for reduction of exacerbation and achievement of asthma control. Yet, non-adherence toward ICS is constantly reported to be a very common occurrence, as high as 80% among asthma patients (46, 47). Various factors influencing adherence have been previously described, including educational level and confidence in the treatment (48).

One of the factors influencing adherence includes changes in attitude across ages. Younger children depend on parental intervention for medication, thus it is not surprising that parental concerns on medication to be influential toward adherence in pediatric asthma (49, 50). Improvement of adherence in pediatric patients should focus on parents and caregivers. Interestingly, pediatric asthma therapy adherence has been reported to be inversely correlated with children's age despite the supposedly increased understanding of their condition (50, 51). This could suggest the presence of teenage-related intentional non-adherence, which may be due to several factors such as teenage rebellion, or embarrassment of using prescribed inhaler therapy due to peer pressure (48).

In elderly patients, non-adherence may stem from the patients' struggle due to memory loss coupled with the complexity of the treatment regimen (42). This issue is further exacerbated by the multiple comorbidities in elderly asthma patients which may lead to an increased number of medications, also known as polypharmacy, which subsequently impacts asthma control (52).

Another factor which may negatively impact treatment success is improper inhalation technique, a problem repeatedly reported to commonly occur regardless of the ICS device type (53, 54). The extensive list of possible DPI and MDI device errors and their association with poor asthma outcomes were recently described in a study utilizing primary care records of 7 European countries and Australia (CRITIKAL study) (54). Among the errors reported to be associated with exacerbation is insufficient inspiratory effort for DPI device. This error is well-established to be a major challenge in preschool children and elderly patients (55). An MDI device (28) or soft mist inhaler (56) with properly designed valved holding chamber is more suitable for preschool children.

Smoking has been consistently reported to hinder response to ICS therapy (57, 58), and poor asthma control was associated with smoking status based on an interview of over 10,000 primary care patients aged 12 years and older (59). The BTS guideline recommends higher ICS dose in patients who are current or ex-smokers (16). Smoking remains a global health behavioral problem from teenage to adulthood, with a median reported global prevalence of 10.7% (range 1.7–35.0%) between 2012 and 2015 (60). A recent study on the impact of ICS adherence on asthma exacerbation and control within primary care reported one-third of their patients to be active smokers (47). Tobacco smoking thus represents another "wrench in the gears" in achieving asthma control.

Despite the recommendation for ICS, concerns remain regarding the associated side-effects, which have in turn been reported to negatively impact patient adherence toward ICS treatment (61). ICS is known to be associated with various local side effects such as oral thrush (candidiasis) and hoarseness (62, 63). A previous study reported 63.3% of children under 6 years of age to be affected (64). In addition to local side effects, ICS treatment may also result in growth retardation in children (65). It is therefore recommended to use the lowest ICS dosage for this age group and to monitor for reduced growth velocity (10). The Canadian Society of Allergy and Clinical Immunology (CSACI) also recommended monitoring for adrenal suppression for children and adolescents receiving high dose ICS (66). Another potential systemic side effects of ICS include osteoporosis (which leads to bone fractures), cataracts and diabetes, which pose additional concern on ICS use in older patients (65). Patients administered high dose ICS over a long period (more than 3 months) should thus be monitored for any potential side effect (10, 16).

Issues in Therapy Response

In addition to the challenges in diagnosis, old age poses additional challenges in the treatment of asthma due to decreased response to bronchodilator therapy (3, 67, 68). Knowledge and guidelines on elderly asthma are limited, and clinical trials tend to exclude elderly patients due to the presence of co-morbidities (43). Unlike in preschool children <5 years of age, there is still no dedicated section for elderly patients within the GINA guideline (10). It is also of relevance to understand whether the different phenotypes asthma: early onset atopic and late-onset asthma, would present with different responses to bronchodilator therapy in old age.

Issues Working With Multiple Guidelines

As discussed in the previous section, different guidelines provide different recommendations in terms of prescriptions across patient age groups. The GINA, BTS, NICE, GEMA, and CTS guidelines recommend SABA reliever and ICS preventer as initial treatment for asthma. However, there is less consensus on the subsequent add-on therapy for asthma which remains uncontrolled after the initial therapy in younger age-groups. In children (5–12 by BTS, 6–11 by GINA and CTS), LABA is recommended by the BTS and CTS guidelines as an add-on if symptom control is not achieved with ICS but is not recommended by GINA. Additionally, in the preschool age-group, there are conflicting recommendations regarding the use of LTRA as an alternative to ICS (recommended by GINA, NICE, GEMA, and BTS, but not CTS), and regarding stepping up ICS dosage to achieve control (recommended by GINA, GEMA, and CTS, but not BTS). The NICE guideline, on the other hand, recommended stepping up to a moderate dose of ICS for 8 weeks following initial SABA.

Working with multiple guidelines with different recommendations for asthma management in childhood patients may cause an additional challenge for primary care physicians as highlighted previously by the Primary Care Respiratory Society of UK (69).

Solutions

Despite the utility provided by subjective biomarker measures, they may be unavailable in primary care practices due to the barriers in implementation (70). Data sharing across practices which allow easier physician access to patients' clinical records, including records of past subjective measures, would provide a potential solution to circumvent this challenge. This may also enable a longer observation of patients' medical history to aid in differentiating between asthma, viral wheeze, and COPD in primary care.

To improve cross-sharing of patients' past medical records, there is a need to improve electronic medical records (EMR) systems which are often claims-based and lack uniformity between systems. A potential solution will be the creation of a uniform EMR template which brings together standardized past medical records while enabling patient self-reported information to be provided to primary care practitioners prior to consultation. Creation of a uniform EMR template can be done by utilizing research-based templates such as REDCap (71).

Moving forward, incorporation of clinical decision support systems (CDSS) to EMR systems may aid physicians in making informed clinical decisions despite conflicting treatment guidelines across age-groups (72) and guide the appropriate treatment while warning against the prescription of non-indicated drugs based on the patients' profile (73). Ultimately, a global EMR for primary care, which is capable of conducting machine-learning based on previous data to provide future recommendations, may serve to guide patient management in the lack of guidelines based on strong evidence.

CONCLUSION

Phenotyping studies have shown that depending on the age of onset, symptoms of asthma can represent distinct phenotypes from asthma with later onset. Together with the changing phenotypes across age are the changing challenges for diagnosis, treatment, and control of asthma.

Guidelines for asthma management in young children and the elderly are still based on weaker evidence, despite the

higher hurdles in management. Differentiating asthma from other diseases with similar presenting symptoms such as viral wheeze and COPD remains a challenge. Regardless, there are resources such as FeNO measurement and the mAPI (modified Asthma Predictive Index), and spirometry which can assist in the diagnosis of asthma for different age groups within the primary care setting. Future developments in electronic medical record systems to enable cross-sharing of clinical history and implementation of clinical decision support systems (CDSS) can potentially improve patient management across different age-groups.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Epidemiology of Asthma in Children and Adults

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Asthma is a globally significant non-communicable disease with major public health consequences for both children and adults, including high morbidity, and mortality in severe cases. We have summarized the evidence on asthma trends, environmental determinants, and long-term impacts while comparing these epidemiological features across childhood asthma and adult asthma. While asthma incidence and prevalence are higher in children, morbidity, and mortality are higher in adults. Childhood asthma is more common in boys while adult asthma is more common in women, and the reversal of this sex difference in prevalence occurs around puberty suggesting sex hormones may play a role in the etiology of asthma. The global epidemic of asthma that has been observed in both children and adults is still continuing, especially in low to middle income countries, although it has subsided in some developed countries. As a heterogeneous disease, distinct asthma phenotypes, and endotypes need to be adequately characterized to develop more accurate and meaningful definitions for use in research and clinical settings. This may be facilitated by new clustering techniques such as latent class analysis, and computational phenotyping methods are being developed to retrieve information from electronic health records using natural language processing (NLP) algorithms to assist in the early diagnosis of asthma. While some important environmental determinants that trigger asthma are well-established, more work is needed to define the role of environmental exposures in the development of asthma in both children and adults. There is increasing evidence that investigation into possible gene-by-environment and environment-by-environment interactions may help to better uncover the determinants of asthma. Therefore, there is an urgent need to further investigate the interrelationship between environmental and genetic determinants to identify high risk groups and key modifiable exposures. For children, asthma may impair airway development and reduce maximally attained lung function, and these lung function deficits may persist into adulthood without additional progressive loss. Adult asthma may accelerate lung function decline and increase the risk of fixed airflow obstruction, with the effect of early onset asthma being greater than late onset asthma. Therefore, in managing asthma, our focus going forward should be firmly on improving not only short-term symptoms, but also the long-term respiratory and other health outcomes.

Keywords: asthma epidemiology, incidence, prevalence, risk factors, lifecourse

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KEY POINTS

- Asthma is a major non-communicable disease affecting both children and adults, with high morbidity and relatively low mortality compared with other chronic diseases.
- The global epidemic of asthma that has been observed in both children and adults is still continuing especially in low to middle income countries, although some evidence suggests it has subsided in some high-income countries.
- Asthma is a heterogeneous disease and distinct asthma phenotypes and endotypes need to be adequately characterized. This may be facilitated by cluster and latent class analysis if clusters/classes are associated with clinically important asthma outcomes.
- Computational phenotyping methods to retrieve information from electronic health records using natural language processing (NLP) algorithms are innovative and may assist in the early diagnosis of asthma and in epidemiological research
- While some environmental triggers are well-established, investigation into possible gene-by-environment and environment-by-environment interactions may help to better uncover the determinants of asthma.
- Work-related asthma from occupational sensitizers (asthmagens) and/or irritants is common and is an important consideration for individuals who present with asthma symptoms during their productive working years
- For children, asthma may impair airway development and reduce maximally attained lung function, and these lung function deficits may track (or persist) into adulthood without additional progressive loss.
- Adult asthma may accelerate lung function decline and increase the risk of fixed airflow obstruction, especially for smokers with asthma
- People with asthma are more susceptible to infections and non-communicable chronic co-morbidities which are associated with worse asthma outcomes
- Defining asthma remains an ongoing challenge and innovative methods are needed to identify, diagnose, and accurately classify asthma at an early stage to most effectively implement optimal management and reduce the health burden attributable to asthma

INTRODUCTION

Asthma is one of the most common major non-communicable diseases and for many, has a substantial impact on quality of life. Globally, asthma is ranked 16th among the leading causes of years lived with disability and 28th among the leading causes of burden of disease, as measured by disability-adjusted life years. Around 300 million people have asthma worldwide, and it is likely that by 2025 a further 100 million may be affected (1). There is a large geographical variation in asthma prevalence, severity, and mortality. While asthma prevalence is higher in high income countries, most asthma-related mortality occurs in low-middle income countries (2). Despite the advances in asthma treatment in recent decades, there are still gains to be made in terms of improving patient education, employing new diagnostic approaches, and implementing personalized case management.

Patterns in asthma incidence and prevalence differ between children and adults. It is well-known that asthma often begins in childhood but can occur at any time throughout life, with some developing asthma for the first time as adults. While asthma incidence and prevalence are higher in children, asthma-related healthcare use, and mortality are higher in adults. Interestingly, incidence and prevalence of asthma differs by sex across the lifespan. Pre-pubertal boys have a higher asthma incidence, prevalence, and hospitalization rate than girls of the same age, but this trend reverses during adolescence (3). Females continue to have a higher burden of asthma than males well into the 5th decade of life. However, the female-male gap in asthma burden narrows around the 5th decade. Some even suggest that the sex differential in asthma incidence may reverse again, following a sharp increase in asthma incidence in males around the 4th decade of life (3). The sex reversal in asthma burden around major reproductive events suggests that sex hormones may play a role in the etiology of asthma.

The current evidence suggests that asthma is a complex multifactorial disorder and its etiology is increasingly attributed to interactions between genetic susceptibility, host factors, and environmental exposures. These include environmental factors (air pollution, pollens, mold and other aeroallergens, and weather), host factors (obesity, nutritional factors, infections, allergic sensitization), and genetic factors (asthma susceptibility loci on genes). Although underlying mechanisms of asthma are not yet fully understood, they may include airway inflammation, control of airway tone and reactivity (4). It is also now recognized that asthma may not be a single disease but a group of heterogeneous phenotypes with different etiologies and prognoses (5). While phenotyping individuals with asthma has been used to help guide clinical management, defining the entity of "asthma" has been a major challenge encountered in research, especially in epidemiological research, where in-depth data collection needs to be balanced with the large number of study participants necessary for adequate power.

This is not an exhaustive or systematic review on all the complexities of asthma epidemiology but aims to provide an epidemiological perspective by comparing and contrasting trends, and discussing the current debate on definitions, environmental risk factors, and long-term consequences of childhood and adult asthma. The roles of genetic factors and gene-environment interactions in the etiology of asthma are described in another article in this series and are therefore not addressed here. Similarly, an article published alongside this article will be covering asthma categories, phenotypes and endotypes, although these topics have been introduced in the present review.

GLOBAL EPIDEMIC OF ASTHMA PREVALENCE—SUBSIDING IN SOME PARTS OF THE WORLD

During the second half of the Twentieth century, notably since the 1960s, a sharp increase in asthma prevalence was observed in a number of developed countries. This observation was a result of repeated cross-sectional surveys of prevalence of asthma, mainly

in children but also in adults. As a result of this observation, in the 1990s, a series of epidemiological studies were established across the world to estimate global asthma prevalence and incidence, and identify risk factors associated with these outcomes. These include large multinational studies in children [such as the International Study of Asthma and Allergies in Childhood (ISAAC; http://isaac.auckland.ac.nz/) (6–8)] and in adults [such as the European Community Respiratory Health Survey (ECRHS; http://www.ecrhs.org/) (9)]. These studies confirmed that asthma is one of the most common chronic diseases across the globe in all age groups and there is substantial variation in asthma prevalence worldwide. It is now acknowledged that the prevalence of both childhood and adult asthma may have peaked in some areas, predominantly in high-income countries, whereas an increase may be continuing in low and mid-income countries (10). It is important to note that a reduction in the prevalence of current asthma is determined by improved asthma control and/or reduced asthma incidence at a population level. Thus, a reduction in prevalence of current asthma may well-reflect improved asthma control through increased medication use from more widespread prescribing habits and better compliance. Documenting reductions in asthma incidence is complicated as parallel cohort studies with specific age windows are needed to establish patterns with the comparison group ideally from the same geographical region. These challenges might in part explain why studies from Australia and UK have not consistently shown reductions in asthma prevalence and why temporal trends in European and Asian countries between the 1970s and mid-2000s have been conflicting (4).

Although greater awareness, recognition, and/or diagnostic shifts have been suggested as contributory factors to the steep rise in asthma prevalence observed over the last four decades of the Twentieth century, repeated cross-sectional surveys using objective measures, such as bronchial hyperreactivity, have confirmed that these factors are unlikely to fully explain this epidemic (4). Though the specific elements driving this rise in prevalence have not been established, it is now clear that the reasons almost certainly are linked to changing environmental factors, acting through gene-by-environmental interactions. Given the rapidity with which the prevalence has risen, this argues against alterations to the population's genetic makeup alone.

The increase in asthma prevalence has been paralleled by a similar increase in other allergies such allergic rhinitis and eczema (11). Multiple hypotheses have been proposed to explain this epidemic, and these have been investigated but are still debated in the field. In the late 1980s, it was thought that increased exposure to indoor allergens such as house dust mite, cat, and fungi due to modernization of housing with tighter insulation and the use of plush furniture and carpets may have contributed to increases in asthma and allergies. Also, in 1989, Strachan proposed the "hygiene hypothesis," suggesting that decreased exposure to unhygienic environments in early life may have led to the increased prevalence of these conditions (12). In 2003, Rook et al. proposed a lack of exposure to non-pathogenic microbes and commensal organisms as an alternative explanation for the increased prevalence of asthma and allergic diseases (13). This led to the "microbial diversity" hypothesis that suggests that environments rich in microbial diversity in the gut mucosa and respiratory tract are the key factors in priming and regulating the immune system.

Asthma mortality and hospitalization rates with acute severe asthma attacks also increased in all age groups during the period from 1960 to 1985, with the highest rates of increase in young pre-school children (14). Following this period, during the 1990s and early 2000s, a decreasing trend in severity has been observed. However, despite novel treatments and improved inhalers for the administration of topical therapies, no further improvements in either mortality or hospitalization rates have been observed in the last decade, either in children or in adults (15).

Given that some childhood asthma persists into adulthood, it is possible that the "asthma epidemic" in children during the 1980–90s has subsequently translated into an increased adult prevalence. However, establishing this trend is challenging due to increased trends also affecting adult asthma, variable asthma definitions, heterogeneity of asthma phenotypes, and limited sequential studies within distinct geographical regions.

EPIDEMIOLOGICAL DEFINITIONS OF ASTHMA—PART OF THE CHALLENGE

Definitions are key to our understanding of the epidemiology, pathophysiology and etiology of asthma, and ascertaining similarities or differences between childhood and adult asthma. Yet variation in asthma severity, age-of-asthma onset, allergic vs. non-allergic phenotypes and type of airway inflammation add complexity to the standard definitions used in large population-based studies (16).

Despite attempts to reach a consensus definition for epidemiological studies, as many as 60 different definitions of "childhood asthma" have been used across 122 published studies (17). Although some of these definitions may appear almost identical, the multiplicity in the way the primary outcome is defined can have a substantial impact on the estimated prevalence and risk factors. As an example, the above study has shown that the agreement between four seemingly very similar and commonly used definitions was overall relatively low (61%), and well-over a third of children in a study could move from being considered "asthma cases" to "controls" depending on the definition used (17). These differences need to be considered when interpreting results of meta-analyses of asthma epidemiology.

Some epidemiological definitions are more sensitive while others are more specific, with both scenarios leading to misclassification of asthma status. For example, current asthma defined by "wheezy breathing in the last 12 months in the absence of a cold" is a more sensitive definition than using "doctor-diagnosed asthma" as they do not rely on the individual to seek health advice (18), while the latter is a more specific definition. As such, survey definitions that adopt wheezy breathing effectively estimate a greater asthma prevalence than clinical definitions which may also incorporate objective measures such as the co-presence of bronchial hyperreactivity (19).

Furthermore, it is important to consider the age of the participants. Particularly for early childhood cohort studies, it can be difficult to distinguish between transient wheeze precipitated by viral infections and the onset of true asthma in young children, although in many cases, recurrent wheezing episodes during the first few years of life can represent the early stages of asthma. For adults, prospectively collected data on childhood asthma status can minimize the risk of recall bias, otherwise retrospective recall typically misclassifies relapsed childhood asthma as late-onset asthma and preferentially favors those who have more severe childhood disease (20). For older people at risk of co-morbidity, an asthma diagnosis may be difficult to differentiate from other diseases causing breathlessness, especially chronic obstructive pulmonary disease (COPD), and heart failure.

A consolidated definition of asthma may not be desirable given the emerging consensus in the research community that "asthma" is an umbrella term for several diseases with similar clinical manifestations but different underlying pathophysiological mechanisms (5), often referred to as "asthma endotypes" (21, 22). In this context, symptoms associated with asthma (such as wheeze or cough) and objective measures (such as lung function and biomarkers in blood, exhaled breath, sputum, and/or urine) should be viewed as observable traits (or "phenotypes") (23, 24). However, it is important to note that different mechanisms may give rise to similar or almost identical observable traits, while the same underlying mechanism may also result in distinct phenotypes in different patients (25).

To date, the framework of asthma endotypes remains a theoretical concept (23), but this framework may also help in developing accurate asthma definitions to facilitate further discovery of their underlying mechanisms (23). With increasing interest in endotypes, there have even been calls to abolish the term "asthma" altogether. However, the term "asthma" provides a practical and functional framework for clinicians to manage patients and for scientists to search for mechanisms; and before abolishing it, we first need to propose more useful and meaningful terminology, which will only come through a more thorough understanding of asthma endotypes.

To further this concept, asthma heterogeneity that features multiple different subtypes has major implications for future studies. However, phenotyping asthma from questionnaire data alone seems increasingly insufficient. While previous cluster analyses have been used to identify patient clusters based on asthma symptoms and airway eosinophilia (16), newer statistical techniques such as latent class analyses (LCA) also have the potential to effectively deal with asthma heterogeneity. Essentially, LCA methods are able to identify novel and statistically distinct classes among individuals in a relatively unbiased way, and are based on measured variables that relate to asthma symptoms (26) and/or biomarkers such as bronchial hyperresponsiveness and atopy (27, 28). A notable example that extended the knowledge of the observed wheezing phenotypes in childhood from the TAHS cohort (29) identified a new phenotype known as "intermediate onset wheezers" (30). This class was subsequently found to have persistent deficits in post-bronchodilator FEV_1 in adolescence (31). Thus, while LCA can readily document asthma heterogeneity, it is of most value if associations are shown between the LCA classifications and clinically important asthma outcomes. To assist in the early identification and diagnosis of asthma, there are currently available innovative computational phenotyping methods that leverage complex electronic health record data that have been validated in different practice settings (32, 33). Using natural language processing (NLP) algorithms, asthma is identified via automated chart review based on predetermined asthma criteria (PAC) via a two-step process: (1) finding asthma-related concepts in text that match specified criteria, then (2) assigning an asthma status classification to individual records (34). While this artificial intelligence algorithm is being developed to improve overall asthma care as a population management tool, it can potentially retrieve information for large-scale, multi-center population studies which has previously been an underutilized data source for asthma research.

SEVERE ASTHMA IN ADULTS AND CHILDREN

Severe asthma represents a small subgroup of individuals who have a disproportionately high health burden. The European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force defines severe asthma as "asthma which requires treatment with high dose of inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming "uncontrolled," or which remains "uncontrolled" despite this therapy" (35). This definition applies to both children and adults with asthma, and it is highly likely that the condition we refer to as "severe asthma" is the extreme end of the spectrum for several different asthma endotypes.

There is considerable variation in the prevalence estimates of severe asthma. For example, in has been reported that 4.2% of Swedish adult asthmatic patients in primary care settings have severe disease (36). Surveys in Denmark described a higher proportion of ∼8% of severe asthmatics (37), while some studies report that as high as 20% or even more than 30% of asthmatic patients have at least some features of severe disease (38, 39). The proportion of severe asthmatics appears lower in childhood asthma compared to adult asthma (40). For example, in a birth cohort in Sweden, only seven of 329 12-year old asthmatic children had severe asthma as defined by the World Health Organization (WHO) (41), suggesting a prevalence of 0.23% in the general population and 2.1% among children with asthma (42). Among 616 children in a Norwegian birth cohort, 67 had asthma, of whom only three were defined as having a severe disease, with an estimated population prevalence of severe asthma at age 10 years of 0.5, and 4.5% among asthmatic children (43). A study conducted within a birth cohort in Manchester (UK), identified a latent class of persistent troublesome wheezers, comprising children with high number of acute asthma attacks, hospital admissions, and unscheduled healthcare visits, which accounted for ∼10% of children with doctor-diagnosed asthma, and 3.2% of the general population (44). These children exhibited numerous features associated with severe asthma including diminished lung function, high FeNO and hyperreactive airways

(44), with a significant loss of lung function between preschool and mid-school age (45). However, when "severe asthma" was defined using ERS/ATS (35) or WHO (41) criteria, only a small number of children were classified as having severe asthma, suggesting that we need to look beyond the amount of medication and disease control when defining severe disease (46).

In the absence of linking data with national pharmaceutical schemes, capturing detailed information on medication use is challenging in epidemiological studies, although such information is critical when defining severe asthma. For example, in children the "maximum treatment" used to define severe asthma includes high doses of ICS or oral corticosteroids, often in combination with add-on therapy with long-acting β-2 agonists (LABA) and/or leukotriene-receptor antagonists (LTRA) (47–49). The limitation of the use of "maximum treatment" is that there may be different reasons for poor asthma control among patients on "maximum treatment," such as the wrong diagnosis (46), non-adherence with medication (50), or therapy-resistant disease (48).

To provide a more useful clinical and research framework for the investigation of severe childhood asthma, Bush et al. have proposed the term "Problematic severe asthma" (PSA) for children who require specialist referral because of the apparent poor response to maximum asthma treatment (48, 49). Once other potential causes of asthma-like symptoms are excluded and asthma diagnosis is confirmed, children with PSA can be broadly divided into three distinct (but occasionally overlapping) groups: Difficult-to-treat (or difficult) asthma (DA); Asthma with co-morbidities ("Asthma plus"); and Severe therapy-resistant asthma (STRA) (49). The main characteristics of DA are that principal factors which contribute to troublesome symptoms are potentially modifiable. These include poor adherence with medication (51), ongoing exposure to adverse environmental factors such as allergens (52–54), tobacco smoke (55), and air pollution (56–58), and psychosocial factors (59–61). If these modifiable factors are addressed, this should result in better asthma control, including improvement in symptoms, and reduction in severe asthma attacks (62, 63). Children with troublesome asthma and comorbid conditions such as food allergy (64), allergic rhinitis (65), and/or obesity (66) are considered to have "Asthma plus" (i.e., asthma + comorbidities). Treatment of these disorders co-occurring with asthma may improve asthma control (65), although there is a paucity of evidence to support this from well-designed randomized intervention trials (67). However, despite interventions and treatments aimed at addressing modifiable factors and comorbidities, some children with DA and Asthma plus may not improve [e.g., because of the continued poor adherence with medications (50, 68), or ongoing high exposure to allergens (69–71)], in which case they should be considered as having refractory DA or refractory Asthma plus (46, 72).

Although there is considerable within-group heterogeneity in each of the above categories, and strict differentiation may be challenging and on occasion not possible, the concepts which distinguish PSA, DA, and STRA are useful in both a research and clinical context (73), and can also be used in adult severe asthma (74).

A number of studies have described differences between childhood and adult severe asthma based on symptom patterns. Severe asthma is predominantly persistent in adults, but much more variable with rapidly evolving severe attacks in children, often remaining symptom-free between the attacks (75, 76). However, we would argue that these differences may have been over-emphasized. It is possible that severe asthmatics who are currently seen in adult clinics reflect the patterns seen in pediatric clinics 10–20 years ago, and that the pattern of severe disease currently seen in pediatric severe asthma clinics may be foreshadowing the severe adult asthma in years to come. It is possible that the differences observed in cross-sectional studies carried out contemporaneously in children and adults can in part be explained by a cohort effect.

Impaired innate anti-viral immunity with diminished interferon induction to rhinovirus has been reported in both children and adults with severe asthma (77–79). A recent study has identified different patterns of cytokine responses by blood mononuclear cells after stimulation with rhinovirus-16 between children with early-onset troublesome asthma compared to those with late-onset mild allergic asthma (80). The synergism between allergic sensitization, high allergen exposure, and viral infection (mostly rhinovirus) has been shown to increase the risk of hospitalization, both in children (52) and in adults (81) with asthma.

One factor strongly associated with severe asthma in children and adolescents is allergic sensitization (82–87). Several studies in recent years have suggested that there may be different classes of sensitization and that some of these sensitization subtypes are more pathologic than others (85, 88, 89). Further studies using component-resolved diagnostics rather than standard skin and blood tests to whole allergen extracts have identified different cross-sectional and longitudinal patterns of component-specific IgE responses associated with different risk of asthma presence, persistence and severity in children (90–93). If the above notion is correct, this may be an indicator of adult severe asthma research and practice in years to come.

ENVIRONMENTAL EXPOSURES ASSOCIATED WITH ASTHMA IN CHILDREN AND ADULTS

Childhood asthma and adult onset asthma are known to share many of the same causes and triggers. While there is stronger evidence on the role of environmental factors as triggers than causes, there is increasing evidence for interactions among and between environmental and other intrinsic factors, such as genetics and atopy, to potentially cause asthma. The vast majority of childhood onset asthma manifests as an allergic phenotype, while there is a predominance of the non-allergic phenotype in adult onset asthma. However, both allergic and non-allergic asthma can exhibit individual responses to both allergic and non-allergic airborne triggers such as animal hair and dander, pollen, and mold (fungal) spores, food allergens, tobacco smoke, or other pollutant exposures (**Table 1**). Other than this table that provides key references to the main environmental exposures associated

with asthma across the lifespan, the typical non-allergic, food and animal triggers of asthma are not described further in this chapter. Subsequent text has focused on the relationships between outdoor, indoor and workplace air pollutants and allergens and asthma, followed by a section on lifestyle factors such as obesity, diet, and breastfeeding.

Parental and Personal Smoking

In utero maternal smoking and parental smoking in early life has been shown to be temporally associated with increased asthma in young children (116). Recent evidence from multi-generational studies suggest that grandmaternal smoking while the mother is *in utero* and paternal smoking during his adolescence can independently increase the risk of subsequent offspring childhood asthma. These findings suggest that tobacco smoking may cause heritable modifications of the epigenome, which increase the risk of asthma in future generations (128).

Smoking also seems to interact with sex. Female smokers had a higher prevalence of asthma than female non-smokers, but this difference was less frequent for males, suggesting that females may be more susceptible. Many studies have found that personal smoking predisposes an individual to increased risk of incident or new-onset asthma, although smoking-onset in adolescence, or adulthood typically occurs after early-onset asthma (119). As non-atopic asthma becomes increasingly common compared with atopic asthma in adults, this is most likely because this phenotype frequently coincides with a substantial history of cigarette smoking and its potential to predispose to chronic airflow limitation (119, 120, 129). Smokers with asthma form a distinct group that are more likely to have suboptimal asthma control (119) and develop asthma-COPD overlap syndrome (ACOS) in later life, characterized by incompletely reversed airflow obstruction following an inhaled bronchodilator (130).

From an epidemiological viewpoint, smoking is common in people with asthma, with around one-quarter of adults from 70 countries receiving recent asthma treatment also reporting to be current smokers (2). Some evidence suggests that people with asthma may be more likely to smoke, and this was seen especially in adolescents who have more severe disease (130).

Outdoor Air Pollutants

Outdoor air pollution almost certainly has a major global impact on asthma for children and adults, especially in China and India (121). Worldwide, in 2015, 9–23 million and 5–10 million annual asthma emergency room visits have been attributed to the outdoor air pollutants ozone and particulate matter with an aerodynamic diameter $<2.5\,\mu m$ ($PM_{2.5}$), respectively.(Exposure to PM_1 has been found to increase the risk of asthma and asthma-related symptoms, especially among boys, and those with allergic predisposition (122). Residential markers of traffic-related air pollution, including nitrogen dioxide (NO_2) exposure and distance to major roads, have been associated with increased risk for new-onset asthma, persistence of asthma and current asthma in a middle-aged, asthma-enriched, population-based cohort (125). In a natural experiment of 60 young to middle-aged adults with mild-to-moderate asthma, when compared with walking in the less polluted Hyde Park in London, walking along Oxford Street was associated with reductions in lung function, neutrophilic inflammation and airway acidification (126). These changes were greater for individuals with moderate asthma compared with mild disease at baseline.

Outdoor Allergens

Exposure to ambient grass pollen is an important trigger for childhood asthma exacerbations requiring emergency department attendance and this has been recently confirmed by a systemic review (99). There is also scant evidence on the role of early life exposure to pollen in the development of childhood asthma (131). However, less evidence is available on the role of pollen in adult asthma (132), except in "Thunderstorm asthma" which is related to a combination of factors as described below.

In relation to other outdoor allergens, increasing evidence indicates that asthmatic children are susceptible to exacerbations that lead to hospitalization when exposed to outdoor fungal spores (104). Furthermore, high concentrations of outdoor fungal/mold exposure on peak days have been linked to asthma exacerbation and mortality in adults (103, 133, 134). IgE sensitization to fungal species is associated with increased asthma severity, neutrophilic inflammation, and reduced lung function consistent with ACOS (105).

Thunderstorm Asthma

Thunderstorm asthma is defined as epidemics that occur during or shortly after a thunderstorm, where individuals affected would experience asthma-related symptoms such as breathlessness, wheezing and coughing. "Thunderstorm asthma" (106, 107) is the outcome of a complex interaction between multiple factors but not necessarily any one of them individually. Under certain weather conditions such as a thunderstorm, pollen grains may swell and burst to form fine respirable particles that are sufficiently small to enter the lower respiratory tract and precipitate severe asthma in those susceptible. This can occur in sensitized individuals who may or may not have a prior history of asthma or asthma symptoms, but who often have a history of allergic rhinitis. Fungal spore allergens may also be involved (133, 134).

On the 21st of November 2016, Melbourne, Australia, experienced a thunderstorm asthma health emergency (106, 107) that exceeded all previously reported thunderstorm asthma events [mainly in the UK and Australia (135, 136)]. In addition to a 4.3-fold increase in emergency attendances for acute respiratory distress symptoms after adjustment for temporal trends (107), nine deaths over the subsequent 10-day period were attributed to asthma as the primary cause (137). This mortality statistic was 50% more than expected based on the average for the same period over the previous 3 years (137), with a total of 10 deaths (immediate and delayed) attributed to the specific epidemic.

Indoor Environment

Indoor pollutants such as products of combustion, including PM and NO_2, and airborne allergens have been the subject of intense scrutiny as determinants of asthma given that most of our time is spent indoors.

TABLE 1 | Environmental exposures associated with asthma spanning childhood to adulthood.

Environmental exposure	Feature	Children	Adolescents	Adults
ALLERGIC				
Airborne triggers - House dust mite (HDM) - Animal hair and dander - Pollen exposure - Mold (fungal) spores - Thunderstorm asthma	HDM aeroallergen is a perennial asthma trigger linked to asthma incidence in high-risk children	(94–96)	(94)	(94)
	Association between pet allergen exposure and asthma is conflicting and non-conclusive	(94, 97, 98)	(98)	(98)
	Grass pollen triggers asthma exacerbations requiring emergency department attendances	(99)	(99)	
	Indoor fungal spore exposure can worsen asthma control; decreased visible indoor mold reduces symptoms but not PEFM variability	(100, 101)	(100, 101)	(100, 101)
	High outdoor Alternaria exposure may contribute to severe asthma/ respiratory arrest (ages 11–25)	(102)	(103)	(103)
	Fungal spores, especially Cladosporium are associated with asthma hospitalization (ages 2–17)	(104)	(104)	
	IgE sensitization to mycoses linked to neutrophilic airway inflammation and lower lung function			(105)
	Thunderstorm asthma can be triggered by outdoor pollen, and possibly fungal, spores	(106, 107)	(106, 107)	(106, 107)
Food allergens ($n = 170$), e.g.,	In asthma, c/w non-atopy, odds for current asthma increased 3.8-fold if food allergy was likely	(108)	(108)	(108)
- Egg white - Peanut	Food allergy is an uncommon trigger in asthma, but may present as life-threatening asthma, especially to peanut and other tree nut allergens	(109, 110)		
- Tree nuts - Shellfish - Cows milk	Co-existing, poorly-controlled asthma is a risk factor for severe or fatal food-induced anaphylaxis	(110, 111)		
Occupational sensitizing agents (with latency)	Extensive lists of occupational asthmagens known to cause new-onset occupational asthma and/or exacerbate pre-existing asthma† - Sensitizing HMW agents (e.g., plant allergens like flour, flowers, latex; animal allergens by animal handlers and lab workers; biological enzymes; fungi-yeasts) - Sensitizing LMW agents (e.g., chemicals like isocyanates, reactive dyes, industrial cleaning/sterilizing agents; metals; pharmaceuticals like antibiotics, opiates; solder flux; wood dusts)		(112–115)	(112–115)
NON-ALLERGIC				
Non-allergic triggers - Respiratory viral infections - Cold air - Humidity - Exercise	Typically trigger variations in asthma symptoms and airflow limitation, and their presence increases the probability that the individual has asthma	(94)	(94)	(94)
Tobacco smoke exposure - Parental smoking	Parental smoking linked to increased incidence of childhood asthma and wheeze	(116)		
- Second-hand smoke exposure	Incident asthma from regular smoking from late childhood; may be greater for those non-allergic compared with allergic, and for those exposed to maternal smoking *in utero*	(117, 118)	(117, 118)	
- Personal smoking	Personal smoking may worsen asthma control/ exacerbations		(119)	(119)
	Personal smoking predisposes to post-BD airflow obstruction and asthma-COPD overlap			(120)
Traffic-related air pollution (TrAP)	Air pollutants (O_3, $PM_{2.5}$) linked to new asthma cases and increased ED admissions globally	(121)	(121)	(121)
- Car exhaust fumes	Long-term exposure to PM_1 may worsen asthma, especially for young males with childhood allergy	(122)	(122)	
	Pollution-related decline in FEV_1 growth was similar between those with and without asthma	(123, 124)	(123, 124)	
	Residential TrAP may contribute to new-onset and persistence of asthma in middle-aged adults			(125)
	Natural experiment of diesel exhaust exposure and adverse short-term changes in spirometry			(126)
Household air pollution (HAP)	Non-polluting home heating improved asthma symptoms, days off school, and healthcare utilization	(127)		
Occupational agents (no latency)	Airway irritants (e.g., chlorine, ammonia) - Irritant occupational asthma - Work exacerbated (pre-existing) asthma		(113, 114)	(113, 114)

BD, bronchodilator; COPD, chronic obstructive pulmonary disease; HMW, high molecular weight; FEV_1, forced expiratory volume in 1 second; LMW, low molecular weight; O_3, ozone; PM, particulate matter.

†*A web-based list of asthmagens can be found at www.occupationalasthma.com.*

There is substantial evidence to suggest that indoor allergens generated by house dust mite, mold and cat are triggers for both childhood and adult asthma, especially in those sensitized (100–102). However, their role in the etiology of asthma is not clear. On the other hand, primary prevention trials on reduction of allergen exposure in early life have failed to detect any benefits. Some observational studies have even reported exposure to allergens in infancy may help develop tolerance and reduce the risk of asthma. However, the evidence is not consistent. Interestingly, there is increasing evidence on this tolerance hypothesis in the etiology of food allergy in which a clinical trial has shown that early consumption of peanuts can reduce the development of peanut allergy (138, 139). These findings suggest that it may be worth exploring this notion of early exposure to allergens leading to development of tolerance, which in turn may reduce the risk of developing asthma.

Occupational Exposures

Occupational exposures to asthmagens or inciting sensitizing agents are common and often under-recognized causes of work-related asthma (WRA). WRA includes two distinct subtypes: work-aggravated/exacerbated asthma (WEA) occurring in individuals with pre-existing asthma, and occupational asthma (OA) occurring in individuals without previous asthma. OA is typically subclassified into immunoglobulin (Ig)-E-mediated or sensitizer-induced OA (90%) and irritant-induced occupational asthma (10%) (140). A diagnosis of WRA requires the objective diagnosis of asthma with symptoms temporally related to the individual's place of employment (141). Over 250 agents may potentially cause sensitization and possibly occupational asthma (OA), and comprehensive lists are available (**Table 1**) (112–115). Briefly, the two main classes of sensitizing agents, namely high molecular weight (HMW) and low molecular weight (LMW) agents can cause sensitizer-induced asthma which is usually after a latency period and this may contrast the frequent rapid action of irritant agent exposure. A web-based list of agents can be found at www.occupationalasthma.com.

Differentiating sensitizer-induced OA from WEA can be a major challenge for managing clinicians. The time-to-diagnosis of sensitizer-induced OA varies but is usually made between 2 and 4 years following the onset of work-related symptoms, and this timeframe is substantially shorter for the diagnosis of WEA as these individuals are usually medically managed for pre-existing asthma (142). Among compensation claims, confirmed OA diagnoses most have a causative sensitizing agent identified (143).

Despite challenges in estimating the true incidence of OA, around 10–20% of all adult-onset asthma is thought to be caused by respiratory sensitizers and/or irritants in the occupational setting. Of note, this figure can vary widely (from 4 to 58%) (144) and is largely derived from populations in high income countries (144–146). To contrast, work-related exacerbations can occur frequently in 20–25% of working adults who have pre-existing asthma (147), although objective evidence of poorer asthma control is often difficult to demonstrate (140). While past under-recognition and/or under-reporting of OA might have obscured changing trends over recent decades, the health care industry has successfully reduced the risk of latex-induced allergy and OA by substituting natural rubber latex (NRL) gloves for powder-free, protein-poor NRL gloves. This successful approach for exposure minimization highlights the benefit of identifying those at risk from occupationally-related asthma and minimizing potentially harmful exposures.

Lifestyle Factors

Although already mentioned as an "asthma-plus" co-morbidity, the prevalence of obesity in countries in which a Westernized diet predominates is now of epidemic proportions. These dietary patterns feature a high calorie intake which is high in saturated fat and refined sugars and associated with a high glycaemic index, as well as low nutritional value in terms of dietary fiber and vitamins. While this "obesogenic diet" may lack antioxidant and anti-inflammatory properties (148), a meta-analysis has found being overweight and obese to be associated with a dose-response increase in incident asthma in adults (149). While this review did not find significant sex-related differences, female obesity has been associated with a pauci-eosinophil and non-atopic asthma endotype that is symptom-predominant and less steroid-responsive in previous cluster and LCA (16, 28). For all individuals with otherwise poorly controlled asthma, the behavior of avoiding strenuous exercise might confuse severe disease with well-controlled asthma, and this in turn can lead to poorer fitness levels and a propensity to weight gain (94). This is of particular importance to children with asthma, at a time when lifestyle patterns are being especially shaped by external factors.

The role of infant breastfeeding in the prevention of asthma is debated, however this has been largely clarified by findings from the TAHS cohort. This longitudinal study of participants who were followed between childhood and middle-age showed that breast feeding reduced the risk of childhood asthma and conversely increased the risk of adult asthma, but for only those with a familial predisposition (150). In 2015, a systematic review summarized the overall estimate for a longer compared with shorter duration of breastfeeding to be modestly protective for asthma in later childhood-adolescence [odds ratio 0.90 (95%CI 0.84–0.97), $I^2 = 63\%$] (151). While the effect was stronger when restricted to studies from lower-to-middle income countries, no association was seen when restricting the meta-analysis to only cohort studies. The overall conclusion was that the evidence was of low quality. The authors primarily hypothesized that breastfeeding-related reductions in childhood wheeze might relate to the known beneficial immunological factors which could reduce childhood viral infections that predispose to asthma.

IMPACT OF CHILDHOOD AND ADULT ASTHMA ON LUNG FUNCTION TRAJECTORIES AND COPD

Childhood Asthma and Lung Function

Studies that have investigated the impact of childhood asthma on lung function from childhood to adolescence have found

that different asthma phenotypes differentially impact long-term lung function outcomes. This is particularly relevant to longitudinal asthma phenotypes, which earlier studies attempted to identify by manually classifying the change of symptoms, but more recent studies have identified distinct longitudinal phenotypes using advanced statistical techniques such as Latent Class Analysis (LCA) as mentioned above. Overall, the use of LCA has led to the identification of more asthma phenotypes and therefore has helped to better disentangle the long-term effects of childhood asthma. The majority of studies have shown that persistent wheeze is related to reduced lung function development throughout adolescence (31, 45, 152, 153), while some suggest the effects of persistent wheeze and relapsed wheeze on lung function are established from mid-childhood, without further decline in tracking of FEV_1 over time (154, 155). It has also been reported that childhood asthma associated with allergic comorbidities, such as eczema and allergic rhinitis, has persistent lung function impairment from birth to adolescence as compared to asthma without such comorbidities (156). These findings have led to the hypothesis that asthma with atopic dermatitis and allergic rhinitis may represent a specific phenotype originating *in utero* (156).

Several longitudinal studies have investigated the long-term impacts of childhood asthma on lung function decline and COPD. Childhood asthma has been associated with adult lung function deficits and increased risk of COPD (157–159). While a number of studies have reported that childhood asthma itself has no impact on adult lung function decline (154, 157, 158, 160), a study that collected childhood asthma status retrospectively has reported that it is associated with greater lung function decline, which may be related to recall bias (161). More recent findings suggest that childhood asthma is related to longitudinal lung function trajectories that are "below normal" within both the general population (162) and asthmatics (163).

Overall, current evidence suggests that many children with childhood asthma/wheeze, especially early persistent asthma/wheeze, may have reduced airway and lung development and not reach their peak lung function potential as influenced by pre-determined lung function trajectories. These lung function deficits may track (or persist) into adulthood without additional progressive loss. However, it is not clear whether childhood asthma can directly affect the rate of lung function decline unless it continues as adult asthma.

Adult Asthma and Lung Function

While asthma in adults is often the persistence or relapse of asthma from childhood, "true" adult onset asthma is a distinct phenotype most often related to environmental risk factors such as smoking (164). The impact of adult asthma on lung function outcomes appears to vary by phenotype including age-at-onset. It has been shown that both early and late onset adult current asthma were associated with a reduction in lung function and an increased risk of fixed airflow obstruction at 45 years, with the effect of early onset asthma being greater than late onset asthma (165–167). These findings differ from the above mentioned systematic review and meta-analysis which found greater levels of fixed airflow obstruction for those with late-onset adult asthma, which most likely relates to inaccurate retrospective recall of childhood asthma by adults (164).

Further evidence from longitudinal studies suggests that adults with asthma have greater lung function decline than those without asthma (168–170). While both early and late onset adult asthma seem to be associated with faster lung function decline, the decline associated with early onset adult asthma is greater than that with late onset adult asthma (167).

An important question is whether we can disentangle the components of lung function deficits in adults with asthma over the life course. Lung function deficits in those with early onset adult asthma may result from both the tracking of reduced lung function from childhood and additional loss from a greater rate of decline in adulthood (167, 171). It has been suggested that adults who developed new-onset asthma had reduced lung function at baseline (172, 173), but it is unknown whether lower lung function before early adulthood, in the absence of childhood asthma, predisposes to "true" adult onset asthma. However, asthma/wheeze status in early life is often forgotten by adults leading to misclassification of "true" adult-onset asthma (20). On the other hand, lung function deficits in adult-onset asthma after peak lung function has been attained are also likely to be due to faster lung function decline.

OTHER HEALTH IMPACTS OF CHILDHOOD AND ADULT ASTHMA

Another major impact of asthma is through its associated additional morbidities, including a predisposition to serious infections such as bacterial pneumonia from a higher nasopharyngeal carriage of *Streptococcus pneumoniae* (174). Although not well-understood, asthma-related chronic airway inflammation with damaged airway mucosa and immunomodulating treatments such as inhaled corticosteroids have been implicated, and lower antibody levels in response to the Pneumococcal vaccine have also been observed (174). In addition to a 2.4-fold increased risk for invasive pneumococcal disease (175), susceptibility to respiratory and non-respiratory infections (such as Herpes zoster and *E. coli* bacteraemia) in never smokers with asthma has been compared with the relative risk of diabetes (176). This susceptibility to infection supports the hypothesis of weaker T_H1 immune responses associated with T_H2-related disease. However, recommendations for Pneumococcal immunization are inconsistent (94) suggesting more evidence is needed to gain consensus of its benefits (177, 178).

Adult asthma is also associated with a number of chronic conditions. The associations between childhood asthma and allergies such as eczema and food allergy are very well-established. Adult asthma is known to be commonly associated with diabetes, osteoporosis, metabolic syndrome, cardiovascular diseases, and issues with mental illness such as anxiety and depression while there are a number of other morbidities that have been linked (179). When a chronic condition is present in people with asthma, that is known as asthma co-morbidity. Almost two-thirds (62.6%) of patients with asthma have at least

one comorbid condition with 16% having four co-morbidities (180). This prevalence of these morbidities in asthmatics is too high to be simply due to the chance development of chronic conditions while aging but these associations do not imply causality. The etiology of asthma co-morbidities may be linked to asthma itself, other morbidities, shared mechanisms, shared environmental, and/or shared genetic risk factors. Regardless of the etiology, it is well-known that asthma comorbidities are associated with worse outcomes for the patients and the healthcare systems (181), and managing asthma comorbidities has been associated with significant improvement in its prognosis. Revising guidelines on to handle comorbidities may lead to a more targeted treatment for comorbidities and more patient-centered asthma management, which in turn lead to better outcomes.

SUMMARY

The evidence on the trends and environmental determinants for childhood and adult asthma are similar, although the evidence is stronger for childhood asthma, which is partly related to the stronger attention that childhood asthma has received from the research community. The global epidemic of asthma is continuing, especially in low to middle income countries, although it has subsided in some high income countries. Epidemiological research has helped to uncover some important environmental determinants that trigger asthma, but the role of environmental factors in the etiology of asthma remains largely unknown. Research into interactions between potential determinants may help tease out the etiology. Therefore, there is an urgent need to further investigate the complex mechanisms driving the interrelationship between environmental and genetic determinants to identify high risk groups and key modifiable exposures. Given the long term impact of both childhood and adult asthma, we would argue that our focus going forward to reduce the health burden of asthma should be firmly on improving not only short-term symptoms, but also the long-term respiratory and other health outcomes (182).

AUTHOR CONTRIBUTIONS

The authors alone are responsible for the content and writing of the article. AC, SD, and JP wrote sections of the initial draft of the manuscript which was then critically revised for flow and important content areas by SD and JP. All authors approved the final version of the manuscript.

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REVIEW
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Asthma in Children and Adults—What Are the Differences and What Can They Tell us About Asthma?

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Asthma varies considerably across the life course. Childhood asthma is known for its overall high prevalence with a male predominance prior to puberty, common remission, and rare mortality. Adult asthma is known for its female predominance, uncommon remission, and unusual mortality. Both childhood and adult asthma have variable presentations, which are described herein. Childhood asthma severity is associated with duration of asthma symptoms, medication use, lung function, low socioeconomic status, racial/ethnic minorities, and a neutrophilic phenotype. Adult asthma severity is associated with increased IgE, elevated FeNO, eosinophilia, obesity, smoking, and low socioeconomic status. Adult onset disease is associated with more respiratory symptoms and asthma medication use despite higher prebronchodilator FEV1/FVC. There is less quiescent disease in adult onset asthma and it appears to be less stable than childhood-onset disease with more relapses and less remissions.

Keywords: asthma, pediatric, adult, childhood, airway

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CHILDHOOD ONSET ASTHMA

Introduction to Childhood Asthma

Childhood asthma is not a singular disease, but rather a uniquely diverse disorder with variable presentation throughout childhood. Asthma affects 8.3% of children in the United States and is the most common chronic disease of childhood (1, 2). Childhood asthma is responsible for 50 billion dollars in annual healthcare expenditures and is a major cause of emergency room visits, hospital admissions, school absences, and loss of parental workdays (1–3).

Asthma is characterized by inflammation leading to bronchoconstriction, edema, and increased mucous production in the airways. Interestingly, the disorder is more prevalent in boys in the first decade of life. However, after puberty and in the second decade of life, it appears that asthma is more prevalent in young women (4). Asthma disproportionately affects minority and low-income children with African American and Hispanic children having the highest prevalence rates, morbidity and mortality due to asthma (5, 6).

Asthma is considered a chronic disease of childhood however there are periods of time during which disease can go into remission or resolve altogether. Important risk factors for the development of childhood asthma have been identified. The phenotypes of childhood asthma and varied presentations are best defined through the periods of the pediatric life course and are described herein.

Childhood Asthma Risk Factors

The perinatal period has been implicated in the development of childhood asthma. Several cohort studies have unveiled risk factors for the development of asthma in offspring, with factors that span from genetic and environmental risk factors to features such as child's sex and presence of atopy.

Genetic Risk Factors

The genetics of asthma are an emerging and complicated topic. Multiple genes are thought to contribute to asthma and rapidly changing technology continues to build our current understanding of the genetic risk factors for asthma development. This is a complex topic that we will only briefly describe herein. Genome-wide Association Studies (GWAS) have dramatically improved our understanding of asthma susceptibility genes. Briefly, the following genes have been determined to have significant association with asthma susceptibility: the 17q21 locus with the *ORMDL3 and GSDML genes, the IL33 gene* on chromosome 9p24, the *HLA- DR/DQ gene* on chromosome 6p21, the *IL1RL1/IL18R1gene* on chromosome 2q12, the *WDR36/ TSLP gene* on chromosome 5q22 and the *IL13gene* on chromosome 5q31 (7). Interestingly, GWAS have shown evidence that loci may be specific to racial/ethnic populations, such PHYNN1 observed in African-Americans with asthma (8). However, as with other common diseases, for individuals, only a small degree of heritability of asthma can be explained by the genes observed in GWAS. Therefore, emerging and multi-genetic approaches are needed to further study the genetic susceptibility to asthma (7).

Environmental Risk Factors

Environmental perinatal risk factors are also important to consider for childhood asthma. Maternal tobacco smoking during pregnancy has been shown to increase the risk of childhood asthma (9). Maternal diet in pregnancy has also been implicated as an asthma risk factor with reports of maternal diets higher in vitamin E, zinc, and polyunsaturated fatty acids as protective against the development of childhood asthma (10–12). In contrast, high sugar intake in the maternal diet during pregnancy has been associated with increased risk of asthma in offspring (13). Other maternal dietary factors have been studied but with less conclusive results including the intake of vitamin D, vitamin C, and a Mediterranean diet. Other perinatal risk factors for childhood asthma that have been reported are neonatal jaundice, maternal preeclampsia, and cesarean section delivery, all which have been associated with higher risk of childhood asthma development (14–16).

Ultimately gene-environment interactions (the genetic-environmental axis) are critical for the development of asthma in a child (8).

Natal Risk Factors

Chronic lung disease of prematurity is known to increase the risk of asthma development in children (17). Specifically, extreme preterm birth (23–27 weeks gestation) is associated with an increased risk of asthma into young adulthood (18). Additionally, cesarean section delivery as mode of delivery (16, 19) and low birth weight have been associated with asthma diagnosis in mid-childhood with symptoms persisting into adult life (20).

Sex

Boys are more likely to develop childhood asthma, as compared with girls, at least until the point of puberty. This has been explained by smaller airway size in boys compared with girls under age 10 years, which predisposes to worsened airway reactivity, as compared with girls of the same age, height and weight (21).

Family History

Both maternal and paternal histories of asthma are associated with increased risk of asthma in offspring. Interestingly, maternal asthma history is more strongly associated with asthma development in the child (22).

Medical History

Presence of atopy (having IgE antibodies to specific allergens) is strongly associated with childhood asthma (23). Specifically the "atopic march" is a pattern that is described clinically in individuals with atopic disease. This "atopic march" begins as atopic dermatitis (or eczema) in infancy, develops on to allergic rhinitis (or hayfever) and then asthma later in childhood (24). Specific indoor allergen sensitization in early life have been of interest with regard to asthma development. Sensitization to house dust mite, alternaria mold, and cockroach allergens have been associated with increased risk of asthma (25, 26), whereas early life exposure to cat and dog allergens have been associated with both increased and decreased risk of asthma in different studies (27, 28).

Medication Exposure

Exposures to antibiotics (29) and antipyretics (30) in infancy have been described to be associated with increased risk of developing childhood asthma however the data has been conflicting and the study results have been concerning for uncontrolled confounding bias. Therefore, further studies are warranted before conclusions can be made about these associations.

Presentation of Asthma: Early Childhood (0–6 Years)

Studies of asthma's natural history have shown that almost 80% of cases begin during the first 6 years of life (31). The symptoms of pediatric asthma in this age group are varied and not specific to asthma making the diagnosis challenging. The primary symptoms of asthma in infancy and early childhood include cough, both dry and productive (albeit young children rarely expectorate), wheeze, shortness of breath, and work of breathing. Asthma symptoms are a result of airway inflammation, bronchospasm, airway edema, and airway mucous gland hypertrophy. Interestingly, these symptoms can also present with a multitude of other pediatric diseases including respiratory tract infections and congenital airway anomalies posing a diagnostic challenge. It is well-established that asthma in this age group is frequently under-diagnosed and undertreated (32, 33).

Often, clinicians including pediatric asthma specialists (pulmonologists and allergists) define asthma in this age group as symptoms of airway inflammation that reverse with bronchodilator therapy. However, given the diagnostic challenge in this age group, the Asthma Predictive Index (API) was developed to guide the diagnosis of childhood asthma in children under age 3 years (34). The API has limited sensitivity but reasonable specificity. The API major criteria were defined as physician-diagnosed eczema or parental asthma. The minor criteria were defined as physician-diagnosed allergic rhinitis, wheezing apart from colds, and serum eosinophilia >4%. Positive loose index were defined as parental report of wheezing on surveys at age 2 or 3 years and either 1 major or 2 minor criteria. Positive stringent index was defined as frequent wheezing on surveys at age 2 or 3 years and either 1 major or 2 minor criteria. Children with a positive loose index were found to be four times more likely to have active asthma on surveys at age 6, 8, 11, and 13 years (sensitivity 42%, specificity 85%). Children with a positive stringent index were seven times more likely to have asthma on a school-age survey (sensitivity 16%, specificity 97%). The API is most useful for its negative predictive value and thus, when negative, is an essential tool for determining who is not likely to go on to having later asthma. While not a perfect tool, a slightly modified API, with criteria of a higher score of frequent wheezing and replacing "physician-diagnosed allergic rhinitis" with skin prick testing, is endorsed by the US National Asthma Education and Prevention Program Expert Panel Report 3 for use in diagnosing asthma in this young age group (35).

Often in this age group, particularly over 0–3 years, symptoms are virally triggered rather than allergically triggered. Infants will often have very few symptoms until they experience an upper respiratory infection, which can trigger a significant and severe inflammatory cascade.

In children, the initial few years following asthma diagnosis are critical. For both physician visits and hospitalizations, the number of children having had a second asthma encounter peaked at 3 years after diagnosis and then stabilized (36). Overall, 75% of children had a second asthma episode within 3 years of diagnosis, suggesting that it takes ∼3 years to control and stabilize asthma episodes (36). The frequency of asthma episodes soon after diagnosis points to the need for attentive follow-up and aggressive management and education strategies in the early years (36). The mainstays of therapy in this age group are based on recurrence of wheezing symptoms or in severity. For those children with recurrent wheezing or significant morbidity with multiple emergent visits, oral steroid courses or hospital admissions, inhaled corticosteroids are the main therapy. There are a limited number of pathophysiological asthma studies in children under 5 years of age, which presents a challenge in the evidence base for the management of childhood asthma.

Presentation of Asthma: Late Childhood (7–11 Years)

By this age, children can more reliably perform spirometry, and reversible airway obstruction on spirometry can be a helpful diagnostic tool. However, it is important to note that in children with asthma, spirometry values can be normal despite significant disease and morbidity (37). Therefore, in children, spirometry is often used as a monitoring tool for asthma symptoms after the diagnosis has been established through other assessments (38).

Symptoms in this age group transition more from discrete episodes of wheezing in response to viral infections to allergic triggered exacerbations. In this age group, exercise-induced symptoms manifest more clearly which may be due to a true change in the clinical presentation of asthma in this age group or also due to sports and exercise becoming a more discreet activity for children of this age wherein caretakers are able to appreciate the symptoms of dyspnea or cough with exertion. In children who avoid or develop a loss of interest in exercise or physical activities, it is important to consider that asthma may be underlying.

Some children in this age group will have few day-to-day symptoms, but have severe asthma attacks in response to specific triggers such as cold weather, cigarette smoke, or seasonal allergies. Virally triggered asthma exacerbations occur in this age group but less often than in the 0–6 year age range and may contribute to the lower rates of healthcare utilization in this age group as compared with younger years of 0–4 years (2).

Presentation of Asthma: Adolescence (12–18 Years)

Puberty has an interesting impact on childhood asthma, specifically relating to sex. Prior to puberty, asthma risk is higher among male children. At the time of puberty, the risk of asthma is approximately equal between males and females, and after puberty, girls have a higher risk of asthma (39). Some of these differences could be explained by the differences in airway development between the sexes. The fetal lung is less developed in boys from 16 to 26 weeks, measured by mouth movements that reflect fetal breathing, a critical determinant of lung development. In the last 4 weeks of gestation, airway resistance is higher in males (21). Boys up to 10 years old appear to have smaller airways in relation to lung size as compared with girls of the same age, height, and weight (21). After puberty, smaller airway caliber is then observed in the female sex (39). The known sex differences in asthma may also be due to other factors such as hormonal effects, genetic susceptibility, immunologic response, and differences in consultation practices and health-seeking behaviors by sex (4, 40).

Asthma symptoms in this age group are most predominantly shortness of breath with exertion, wheezing in response to triggers, chest pain, chest tightness, and cough. In this age group, asthma symptoms can significantly impact sleep, school, sports, and social engagements. Children are more aware of symptoms in this age range and often feel more embarrassment or stigma around using an inhaler and in particular a spacer, often leading to under treatment of asthma symptoms (40).

Remission is common in adolescence, with remission rates reported at 16–60% (41). Factors that have been implicated in an increased probability of asthma remission include mild disease and minor airway inflammation before adolescence, male sex, and the absence of allergic sensitization (42, 43).

Wheezing and Asthma Phenotypes in Childhood

Childhood wheezing phenotypes have been explored given that nearly 50% of children experience wheezing before age 1, yet only 20% of those children progress to have continued wheezing later in childhood (44). While there are several longitudinal birth cohorts that have described wheezing phenotypes, we will describe the classifications according to the earliest of these studies: the Tucson Children's Respiratory Study and the most recent systematic comparison of the clinical and epidemiologic classifications (45).

WHEEZING PHENOTYPES (44, 45):

Never/Infrequent Wheeze

This Describes Children who do not Experience any Wheezing.

The Transient Wheeze

This describes children who have their first wheeze before the age of 3 years with resolved wheezing by age 6 years. Transient wheeze is not strongly related to atopy and genetic risk; there are only mild impairments in lung function in this phenotype, and medication use is very uncommon (45).

The Persistent Wheeze

This describes children who experience first wheezing before age 3 year, however go on to have continued wheezing at age 6 years. Persistent wheeze was strongly related to the asthma risk locus on chromosome 17, however this phenotype appears to be unrelated to environmental determinants. Interestingly, bronchodilator administration dramatically improved any compromises in lung function for children with this phenotype (45).

Intermediate Onset Wheeze

This describes children who experience rare (or no) wheezing before 18 months of age, but persistent wheeze thereafter. Intermediate-onset wheeze has associations with atopy, but only to pollen sensitization (45).

The Late Onset Wheeze

These children develop wheezing between age 3 and 6 years. Late-onset wheeze is strongly associated with fractional exhaled nitric oxide levels and sensitization to inhaled allergens at 6 years and at 4 years. There appears to be severe and irreversible reduction in lung function in this phenotype and asthma medication use is common (45).

CHILDHOOD ASTHMA CLINICAL PHENOTYPES

Asthma Diagnosis (45)

Physician's diagnosis of asthma at least once per lifetime or recurrent diagnoses of spastic, obstructive, or asthmatic bronchitis as reported by the parents at age 6 years.

Frequent Wheeze (45)

Wheeze on a monthly basis for at least 1 year between age 1 and 6 years.

Unremitting Wheeze (45)

Having symptoms between wheezing episodes or having wheeze without a cold at least once between age 1 and 6 years.

Recurrent Unremitting Wheeze (45)

Having *s*ymptoms between wheezing episodes or wheeze without a cold for 2 or more years between age 1 and 6 years.

Multi-Trigger Wheeze (45)

Having at least 2 common asthma triggers leading to wheeze between ages 3–6 years.

Episodic Wheeze (45)

Wheezing episodes associated only with viral upper respiratory infection between age 1 and 6 years.

Severe, Difficult to Control Asthma, Steroid-Resistant Asthma

Children that do not seem to respond to standard treatment are referred to as severe or difficult to control asthma, and these children experience substantial morbidity from asthma symptoms. To classify a child into this phenotype, the first step is to exclude an incorrect diagnosis, poor adherence to treatment, or incorrect technique with an inhaler and spacer (46, 47). Supervised asthma therapy programs can be extremely useful in managing asthma symptoms and reducing healthcare utilization for children with poor medication adherence and inhaler and spacer technique (48, 49). It is important to differentiate between severe therapy-resistant asthma and difficult-to-treat asthma due to comorbidities Difficult to treat asthma is a much more common reason for persistent symptoms and exacerbations and can be managed if comorbidities, such as allergic rhinitis and chronic exposure to asthma triggers, are directly targeted. Home visiting programs and assessment of the school environment are important features of the evaluation for children with concern for chronic exposure to asthma triggers (50–52). Children with persistent symptoms and exacerbations despite correct inhaler technique and good medical adherence to standard asthma therapy (steroid-resistant or therapy resistant asthma) should be referred to an asthma specialist to consider more potent biologic therapies such as anti-IgE, anti-IL-5, or anti-IL-13 therapies and further evaluation (47).

Eosinophilic Predominant

Eosinophilic inflammation is considered to be the main feature of allergic asthma in children (53). Sputum eosinophils and serum periostin are biomarkers that have been proposed for defining which children with asthma will respond to anti-IgE, anti-IL-5, or anti-IL-13 asthma treatment (54). However bronchoscopy is not routinely done in children with asthma, therefore serum eosinophils are often the least invasive and most common biomarker utilized to indicate the presence of eosinophilic predominant asthma and help predict responsiveness to inhaled corticosteroid therapy (55).

Neutrophilic Predominant

While initially most childhood asthma was thought to be eosinophilic in nature, a neutrophilic predominance has emerged as an important phenotype. In this phenotype, children generally have low IgE levels, low serum and sputum eosinophil counts with very little allergic symptoms. Neutrophil-predominant asthma is the most severe asthma phenotype with poor corticosteroid response (54) and may explain some of the children who have not respond well to standard asthma therapy.

OTHER CHILDHOOD ASTHMA CLINICAL PRESENTATIONS:

In clinical practice, there are different clinical presentations of symptoms that point to an underlying diagnosis of childhood asthma, and clinical improvement can occur in response to starting a child on preventive asthma therapy, such as a daily-inhaled corticosteroid and use of bronchodilator therapy for acute episodes.

Recurrent Croup

Croup, inflammation of the upper airway, which presents as barky cough and stridor, is a common isolated entity in infancy and early childhood. However, the presence of recurrent croup may indicate the presentation of underlying asthma in childhood. Recurrent croup has been shown to be a risk factor for childhood asthma and airway hyperreactivity (56) as well as strongly associated with bronchial asthma in children (57).

Middle Lobe Syndrome

Asthma in children is associated with significant atelectasis and specifically with middle lobe and lingula collapse, (58) and often infants and children who ultimately develop asthma, present as recurrent atelectasis, or mucous plugging in the right middle lobe and lingula. In contrast to adults, children are thought to have higher resistance to collateral airflow, possibly due to increasing number and size of collateral alveolar ventilation, through pores of Kohn and bronchoalveolar Lambert's channels, that develop from birth to adulthood (59). This theory is supported by the finding that pores of Kohn are absent in newborns, and develop around 4 years of age, with the greatest numbers of pores of Kohn found in the apical portions of upper and lower lobes, as well as in peribronchial, perivascular, and subpleural areas, (60, 61), leaving the right middle lobe and lingual vulnerable to atelectasis and mucous plugging, particularly in children with asthma.

Recurrent Pneumonia

In a child with recurrent multi-lobar pneumonia, with a normal immune function evaluation, asthma should be considered as an underlying cause of the recurrent chest infections. Many children referred to specialty care with recurrent chest infections will be found to have undiagnosed or undertreated asthma. Often the history reveals that most have recurrent episodes of cough, wheeze and breathlessness, with trigger factors of upper respiratory tract infections, exercise, cold air, emotional upset, or exposure to pets and other aero-allergens suggestive of asthma (62). In several studies, asthma was the main underlying cause for recurrent pneumonia in children (63).

Association Between Childhood Asthma and COPD

Children with asthma have an increased risk of developing chronic obstructive pulmonary disease (COPD) in adulthood. Specifically, it has been shown that children who smoke tobacco and also have asthma are at increased risk for developing low lung function and COPD as adults, when compared to smokers who did not have asthma in childhood (64).

Remission and Mortality in Childhood Asthma

Asthma remission occurs most commonly between the ages of 14–21 years (65). However, large longitudinal studies have also shown that, among children who wheezed before age 3 years, more than 50% had stopped wheezing either by 6 years of age (44) or by 12 years of age, (36, 66) depending on the study. Remission rates of childhood asthma have been reported between 16 and 60% by early adulthood, according to prior longitudinal studies (41, 65, 67). The wide variation in reported remission rates is likely due to diverse study designs, varying follow-up periods, and different study populations. In longitudinal studies, children with the following characteristics had higher remission rates: episodic asthma (rather than persistent asthma), milder initial asthma severity, less allergic sensitization, less allergic rhinitis, less atopic dermatitis, and male sex (36, 65).

While the morbidity of childhood asthma is significant, fortunately, mortality from childhood asthma is rare with an estimated 28 deaths per million children with asthma (2). As with childhood asthma morbidity, there are grave racial disparities in childhood asthma mortality, and black, and Hispanic children suffer disproportionately from the highest mortality rates (2).

ADULT-ONSET ASTHMA

Introduction to Adult-Onset Asthma

Asthma is increasingly recognized as an umbrella term for a heterogenous group of conditions that has been likened to the term "arthritis" in Rheumatology—not a specific diagnosis but a term that describes a diverse group of conditions clinically and biologically (68). Some have suggested discarding the term asthma altogether (69).

Asthma is a common condition amongst adults, estimated to affect 235 million people worldwide, and is estimated to cause more than 350,000 deaths per year (70). It carries a huge economic, morbidity and mortality burden in both developing and developed nations (70). The mortality in developed countries from asthma has remained static for more than a decade and it is clear that a better understanding and management of this diverse group of conditions is required (71).

Asthma is considered a childhood disease by many but this is erroneous as longitudinal studies have shown that approximately half of middle aged patients with asthma have had onset in adulthood rather than childhood (72–74). This proportion of adult onset asthma increases with age (73). The annual incidence

TABLE 1 | Comparison of childhood and adult asthma.

Feature	Childhood asthma	Adult asthma
Variable Phenotypes	Yes	Yes
Symptoms	Age 0–6 years: Cough, wheezing, acute episodes of dyspnea and increased work of breathing Age 6–11 years: cough, wheezing, dyspnea or cough with exertion Age 11–18 years: cough, wheezing, dyspnea, dyspnea on exertion, chest tightness, chest pain	Shortness of breath, wheeze, chest tightness and cough. *Allergic bronchopulmonary aspergillosis:* Above symptoms plus sputum production. *Aspirin exacerbated respiratory disease:* Above symptoms plus nasal polyps and sensitivity to aspirin.
Sex predominance	Males < 10 years	Females
Remission	Common	Rare
Factors associated with severity	Asthma duration, medication use, lung function, neutrophilic phenotype, low socioeconomic status, racial/ethnic minorities	IgE, FeNO, eosinophilia, obesity, smoking, low socioeconomic status
Mortality	Rare	Uncommon

of asthma amongst adults is estimated to be 0.5%, similar to the incidence in childhood and it remains unclear as to whether adult-onset asthma is a different disease to that occurring in childhood (75).

The area of asthma phenotyping amongst adults has been developing at a rapid rate. Initially clinical phenotypes were identified that help to categorize asthma in adults by clinical traits including that of early and late onset, obese vs. non-obese, and atopic vs. non-atopic (76, 77). More recently biologic phenotyping has been increasingly recognized and performed clinically, particularly with the availability of targeted biologic agents, and this phenotyping is currently based on presence of allergic or eosinophilic inflammation although this is a rapidly evolving field (68). This has led on to more complex molecular phenotyping which may well-inform future precision medicine in asthma (78).

The natural history of asthma occurring in adulthood is complex because it is such a heterogenous disease. Despite the complexities adult-onset asthma appears to run a different course to that of childhood-onset disease where the majority of the disease is mild and remission is common (79) (**Table 1**). In adults with asthma remission is uncommon and disease is often more severe and progressive (80).

Phenotypes

Although there has been significant development and research into asthma phenotypes in the past two decades the concept has developed slowly and to some remains controversial (68). In this context phenotype refers to subtypes of the disease that have recognizable properties produced by interactions of the genotype and the environment (81). From this concept has emerged the concept of asthma endotypes where a biologic pathway is identified that leads to the clinical phenotype (82). Phenotypes and endotypes are an attractive concept but unfortunately patients rarely fit into these classifications perfectly with many factors that muddy the waters including presence of comorbidities and confounders. For this reason a more pragmatic concept of treatable traits has gained momentum (83). Rather than attempting to categorize people with asthma, this approach seeks to describe traits associated with an individual's asthma including clinical aspects, biological characteristics, and comorbidities (83).

Phenotypes of asthma can be broadly categorized into *clinical*, *biological*, and *molecular* although there is considerable overlap between these and, ultimately, it is the combination of the three that is likely to form the asthma phenotypes of the future.

Clinical

The attempt to classify asthma is not a new concept with clinical phenotypes having been described since the 1940s (84, 85). One of the oldest approaches to clinical phenotyping was between allergic (extrinsic) and non-allergic (intrinsic) asthma that described two clinically distinct entities—that of early onset asthma associated with sensitization to allergens and other allergic diseases, and that of the poorly understood late onset asthma that was non-allergic (84). Because these phenotypes did not confer specific management there was little clinical utility in the distinction.

More recently different clinical phenotypes have been identified by unbiased cluster analysis of cohorts of asthma patients, with the most detailed analysis performed on the Severe Asthma Research Program cohort in the United States (76, 77). This analysis resulted in the development of five clinical groups, two with early onset, and three other groups. The two groups with early onset are those with normal lung function requiring minimal controller medications, and those with preserved lung function but requiring more medications and healthcare utilization (77). The first of the other three groups comprises obese women with late onset non-atopic asthma, moderately impaired lung function and frequent oral corticosteroid use for asthma exacerbations. The remaining two groups comprise those with severe airflow obstruction and bronchodilator responsiveness, and a less well-defined group with variable ability to attain normal lung function, age of onset, atopic status, and use of oral steroids.

These phenotypes have been further refined with the addition of biologic markers to five groups; early-onset allergic, late-onset eosinophilic, exercise-induced, obesity-related and neutrophilic (68). These will be discussed in more detail below.

The extension of the development of more detailed clinical phenotypes is whether these phenotypes represent distinct clinical entities with different treatment strategies. There is considerable work being done currently in this space.

There are, however, a number of clinical phenotypes amongst adults with asthma that are distinct, including those with occupational asthma, aspirin-associated asthma, and asthma associated with other conditions such as allergic bronchopulmonary aspergillosis and chronic obstructive airways disease (COPD) (86–88). Some of these subtypes have more

developed clinical characteristics associated with them, biological mechanisms, management, and natural history.

Biologic

As phenotyping of asthma has progressed there has been progressive attempts to describe the endotype, or biologic pathway, behind different clinical phenotypes.

The most developed of these is the distinction between the presence or absence of Type 2 inflammation (T2) in asthma (89). It has long been recognized that for many, but not all, patients with asthma there is upregulation of Type 2 inflammation. This is characterized by an stimulus at the level of the airway epithelium that results in production of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) that stimulate release of IL-4, IL-5, and IL-13 and, in turn eosinophils and antibodies that lead to the pathogenic airway changes characteristic of asthma (90). This upregulation of the Type 2 inflammatory response in asthma has important clinical implications because this inflammation tends to be responsive to corticosteroids.

Unlike in children, amongst adults there is a significant proportion of non-T2 high disease. This group of patients is less well-understood than their T2-high disease counterparts and accounts for a significant proportion of mild-moderate adult-onset asthma (91). Although these patients are poorly characterized there are significant implications for treatment as they tend to be less steroid responsive than those with T2-high disease and it is unclear what the best treatment strategy for these patients is (92).

Most asthma, even amongst adults, still appears to have T2-high etiology (76, 77). Even clinical subtypes such as exercise-induced asthma appears to be T2-mediated (93). With regard to the asthma phenotypes discussed above, different biologic mechanisms have been described. Early-onset allergic asthma is the predominate form in children, varies in severity, is associated with allergic symptoms and other allergic diseases and characterized by elevated specific IgE, T2 cytokines and is responsive to inhaled corticosteroids (68). A similar form does also occur in adults. Exercise-induced asthma can be diagnosed in children or adults and is characterized by relatively mild, intermittent symptoms. Biologically there is mast cell activation, T2 high and it tends to respond to leukotriene antagonists, beta agonists and IL-9 agonists (94).

Molecular

More recently molecular phenotyping has also been attempted. In one study on mild to moderate asthma patients upregulated genes were identified in epithelial brushings to molecularly classify those with T2-high and T2-low asthma (90). Those with T2-low asthma were found to have similar gene-expression patterns to the control group (90). Those with T2-high asthma on genetic profile were found to have increased IL-13, IL-5, eosinophils, and mast cells as well as more atopy (95).

Molecular phenotyping has potential implications for treatment with those with T2-high asthma based on genetic profile having a response to inhaled corticosteroids and those with T2-low disease having no response (90, 95).

Adult Phenotypes of Asthma

Late Onset Eosinophilic

Characterized by both clinical and biologic features of later onset, predominately female, and elevated sputum and serum eosinophils. Late-onset eosinophilic asthma is defined clinically by adult-onset, severe disease and is associated with sinusitis and less allergic sensitization compared to early onset disease. Biologically patients have increased IL-5 and IL-13 in the airways and elevated eosinophils in the sputum and serum (96–98). No cut off for sputum and serum eosinophils have been universally agreed upon however it is generally accepted that a sputum eosinophil count of >2% or a serum eosinophil count of >300 cells/uL (or in some cases >150 cells/uL) indicates eosinophilic asthma (99–101). Despite a high prevalence of positive skin prick tests this form of asthma appears to be less allergic but is often associated with sinusitis, nasal polyps, and aspirin exacerbated respiratory disease (96). A family history of asthma is seen less frequently than those with early onset asthma (96). This type of asthma can be relatively steroid resistant but biologic therapies targeting T2 pathways have been shown to be highly effective in this group of patients (102–105).

Obesity-Related Asthma

Obesity-related asthma is not well-understood. It is unclear whether it is a comorbidity common in asthma that confers greater likelihood of breathing pattern disorder, gastroesophageal reflux and deconditioning or whether it is the driver for a proinflammatory state that results in asthma (106–109). Higher body mass index (BMI) is associated with increased levels of TNFa, IL-6, and leptins and less eosinophils, FeNO and corticosteroid responsiveness (108, 109). Clinically there appears to be a group of older non-allergic, obese females who have significant symptoms but minimal healthcare utilization (76, 77). The interaction between BMI and eosinophils is more complex, with those who have early onset T2-high asthma having a correlation between duration of asthma and BMI, lower activity levels, and corticosteroid exposure that does not appear to exist in those with T2-low disease (110). Bariatric surgery has been shown to improve outcomes in asthma patients with late onset, non-allergic asthma but not in those with allergic disease (111).

Neutrophilic Asthma

Neutrophilic asthma is poorly defined and there is no consensus about the characterization of this entity. Adding to the confusion is the fact that corticosteroid treatment commonly suppresses eosinophils and causes neutrophilia making the assessment of corticosteroid-dependant patients difficult (112–114). The clinical phenotype remains controversial and inconsistent but has been suggested to be that of adult-onset, severely obstructed with only partial reversibility and a high healthcare utilization (77, 78). Smoking may also play a role. Furthermore, neutrophilic asthma can occur in those with elevated eosinophils conferring a particularly severe clinical phenotype (115). These patients tend to be less corticosteroid responsive and other treatment strategies have been tried including use of macrolide antibiotics (116). Although IL-17 has been suggested as a potential

therapeutic target in neutrophilic asthma a biologic targeted at this interleukin did not result in improvement in asthma control and so far this area remains disappointing (117, 118). The initial disappointment with targeted therapies such as the anti-IL-17 and anti-TNFa agents has been tempered by positive preliminary results with a newer biologic agent targeting TSLP that has showed promise in Phase 2 studies in a non-eosinophilic group (119, 120).

Aspirin-Associated Asthma

Aspirin-associated asthma, a subset of aspirin exacerbated respiratory disease (AERD) has been described for many years (85). It tends to occur in adulthood at an average age of 34 years and is more common amongst females (86). This is a subset of late-onset eosinophilic asthma and is associated with sinusitis, nasal polyps and sensitivity to cyclooxygenase-1 inhibitors including aspirin (86). Biologically it is characterized by upregulation of the cysteinyl leukotriene pathway and elevated eosinophils (96). Molecularly genes related to the leukotriene pathway have been implicated and periostin, a biomarker of IL-13 activity, has been found in nasal polyps present in patients with AERD (97, 121). These patients are often relatively corticosteroid resistant, requiring high doses for control, but can be responsive to leukotriene antagonists (122, 123). More recently biologic therapies that target T2 pathways including IL-4, IL-13, and IL-5 have been shown to be effective in patients with asthma and nasal polyps (124–126).

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) was first described in the 1950s and is caused by allergic sensitization to fungal colonization of the lower airways with *Aspergillus fumigatus* (127, 128). It occurs in 1–2% of asthma patients, although has been detected in up to 13% of the population in asthma clinics, predominately adults, and causes asthma exacerbations, deterioration of pulmonary function, mucous plugging, central bronchiectasis, and transient pulmonary infiltrates with characteristic biologic features including elevated total and Aspergillus-specific IgE as well as peripheral eosinophilia (88, 128, 129). The diagnosis is based on presence of asthma, proximal bronchiectasis, sensitization to Aspergillus, and an elevated total IgE (129). It is important to diagnose ABPA because of the progressive nature of the bronchiectasis in the absence of treatment (129). The mainstay of treatment for ABPA is systemic corticosteroids and, in some cases, antifungal agents (88).

Link Between Early Transient Wheeze and COPD

There is a link between childhood asthma and COPD (130). Both childhood asthma and childhood wheezy bronchitis have been associated with an increased risk of COPD in adults (131). Severe childhood asthma has been shown to confer a 32 times higher risk of COPD in adults despite the fact that just under half of those diagnosed with COPD in this cohort had never smoked (132). Early transient wheeze has been thought of as a benign condition but did significantly increase risk of the presence of COPD in adulthood with long term follow up (131).

Asthma-smoking associations have been described in both early and late onset asthma (133). Smoking remains a key risk factor for airflow obstruction in normal and asthmatic individuals, however the risk appears to be greatest in those with late onset disease (74).

Natural History

The natural history of asthma in adults is different to that of asthma in children with less remission of adult-onset asthma than that occurring in childhood.

Many adults with asthma have childhood-onset disease that has persisted and there have been many risk factors that predict the persistence of asthma into adulthood including the severity of childhood disease, the presence of bronchial hyperresponsiveness, atopy, exposure to allergens and a parental history of asthma (134–136). In longitudinal studies the amount of wheeze in early adolescence has been shown to predict the severity in later life. In an Australian-based cohort of second graders with wheezing of various severities followed up to age 50 there was remission of asthma in 64% of those with mild wheezy bronchitis or wheezy bronchitis, 47% of those with persistent asthma and only 15% of those with severe asthma (137). In this group risk factors for persistence of asthma at age 50 were severe childhood asthma, childhood allergic rhinitis, and female sex (137). In another longitudinal cohort 73% with few symptoms at 14 years had little or no asthma 14 years later whereas 68% of those with frequent wheeze at 14 years still had asthma 14 years later (138). Most who had frequent wheeze at 21 still had wheeze at 28 years and of those with infrequent wheeze at 21 years 44% had worsened at 28 years (138). These findings have been replicated in more recent studies—three quarters of children with childhood asthma will outgrow the disease by middle age although overall our understanding of the natural history of childhood asthma remains poorly understood (139).

Adult onset asthma has many different forms and the risk factors appear to be different to that of childhood-onset disease. Compared to childhood asthma, major associations with adult-onset disease are female sex, current smoking, and low socio-economic status but not atopy or a family history of asthma (74). Other risk factors include; clinical—historical symptoms of wheeze, rhinitis, chronic cough; physiological—lower lung function, bronchial hyperresponsiveness, lower height; comorbidities—higher BMI, nocturnal gastroesophageal reflux disease, habitual snoring, IgE reactivity to Timothy grass; and lifestyle—low physical activity amongst men (75, 107, 140–144). The evidence for smoking as a risk factor is mixed with two large cohort studies from Australia and Sweden showing that this is a risk factor for adult-onset asthma and other studies showing that it doesn't appear to be (74, 75, 141, 144).

In a large cohort with severe asthma with onset between 14 and 55 who were followed for 10 years 83% had less severe asthma at 10 years (145). Risk factors for the persistent presence of severe asthma was low socioeconomic status, high comorbidity burden

and high adherence to medications in the first year after diagnosis (145). In this cohort sex and other risk factors important in childhood asthma were not associated with continued presence of severe asthma (145).

The sex differences in asthma amongst different age groups are interesting. Amongst children males are more commonly affected by asthma than females and male sex is a risk factor for developing asthma (39). Around the time of puberty this risk becomes equal and after puberty the risk in females is greater than that amongst males, an observation partially but not fully explained by women's smaller airway caliber in adults (39). There is emerging evidence of the association between female hormonal changes and asthma that may partially explain the female predominance of asthma after puberty (146, 147).

Some factors that don't appear to be risk factors for adult onset asthma include level of education, atopy (either baseline or newly positive skin prick tests), occupational exposures or maternal asthma (141, 143, 144).

Despite the differences in risk factors for adult-onset asthma compared to childhood onset disease the prevalence of asthma amongst adults was shown to be increasing in the second half of the twentieth century similar to that of childhood asthma (73, 148).

Young Adults

In those who develop asthma as young adults the natural history appears to be more similar to that of childhood asthma with atopy an important a risk factor and more remissions (149). The 23 year follow up of one study in the US examined asthma incidence in participants 23 years after college, finding that the cumulative prevalence of asthma increases with age and that three-quarters of those who had asthma at the first visit were in remission or had improved symptoms at 40 years (149). Only a small number who had asthma at the baseline visit were worse (149).

Middle Age

Many patients are diagnosed with asthma in middle age and this disproportionately affects women. In fact for women most asthma occurring in middle age is adult-onset asthma and by 40 years more than half of asthma in women is adult onset (73). The proportion of adult onset asthma was even higher in women who were obese, non-atopic, ever smokers, white, and lower socio-economic status (73, 74). In contrast for men by 50 years only one third of asthma is adult-onset asthma (73). Therefore it is clear that adult-onset asthma is more common in women (73). Overall those with adult onset asthma are more likely to experience symptoms including wheeze, new rhinitis, snoring, and weight gain (143). Those with adult onset disease are also more likely to have a decline in lung function than those with childhood onset disease (143).

Older Adults

For those who first experience asthma in their senior year atopy does not appear to be a risk factor (149). Older adults who develop asthma have a similar incidence as younger people of ∼100 per 100,000 (150). However, disease severity is worse amongst older adults developing asthma compared to younger people and is also more progressive with poorer lung function and more fixed airflow obstruction (151). This poorer lung function and more fixed airflow obstruction is thought to be largely the result of the more common presence of comorbid lung diseases such as bronchiectasis, pulmonary fibrosis, and COPD (151). Older adults with asthma are less likely to experience remission than their younger counterparts (151).

Remissions

In adults with asthma remissions have been found to be uncommon after the second decade of life and particularly uncommon in those between 30 and 60 years old (79). In adult-onset, non-allergic asthma remission is especially unusual occurring in only 20% of patients (152). Risk factors for those not achieving remission were severe symptoms, impaired lung function, and a comorbid diagnosis of chronic bronchitis or emphysema (79). Amongst adults with asthma who do remit relapses have been found to be common and increase until the age of 70 years particularly if there was persistent symptoms despite remission (79, 153).

Lung Function

Lung function has been found to decline in some but not all adult-onset asthma patients (154–156). In those with persistent asthma there is generally a decline in lung function that eventually leads to a restrictive pattern of spirometry (157). Adult lung function is influenced by initial FEV1 and sex, with a larger decline observed amongst females, but not initial asthma severity or allergic sensitization (136). Lower lung function has also been found to be related to presence of bronchial hyperresponsiveness (136).

In aspirin-exacerbated asthma a steady progress in severity has been found (86). Rhinitis generally appears around the age of 30 years followed by asthma, aspirin sensitivity, then nasal polyps (158). Women generally have more severe disease with earlier onset, one third of patients are atopic and they tend to have an earlier onset, and lower FEV1 (159).

The natural history of ABPA is variable with five stages identified including acute, active; remission; recurrent; chronic; and severe, end-stage disease (160). Early diagnosis and treatment is associated with a reduced likelihood of progressive disease (146, 160). Serum IgE level is often used to track progress of disease and help to identify remission and relapse of ABPA (160). Overall those with ABPA have been observed to have a progressive decline in lung function although there are those who undergo complete remission (88).

Mortality

Thankfully mortality in asthma remain uncommon (71). However mortality rates are not declining and in fact have increased in some developed countries (71, 161). Asthma deaths are more common amongst adolescents and young adults, those of low socioeconomic status, black race, those with substance

TABLE 2 | Asthma presentations across the lifecourse.

Age	Presentation/Phenotype	Description
Child	Asthma diagnosis	Physician's diagnosis of asthma at least once per lifetime or recurrent diagnoses of spastic, obstructive, or asthmatic bronchitis as reported by the parents at age 6 years
	Frequent wheeze	Wheeze on a monthly basis for at least 1 year between age 1 and 6 years
	Unremitting wheeze	Having symptoms between wheezing episodes or having wheeze without a cold at least once between age 1 and 6 years
	Recurrent unremitting wheeze	Having symptoms between wheezing episodes or wheeze without a cold for 2 or more years between age 1 and 6 years
	Multi-Trigger wheeze	Having at least 2 common asthma triggers leading to wheeze between ages 3 and 6 years
	Episodic wheeze	Wheezing episodes associated only with viral upper respiratory infection between age 1 and 6 years.
	Severe asthma Difficult to control asthma Therapy resistant asthma	Asthma which is poorly controlled based on frequent symptoms and significant morbidity Often due to incorrect diagnosis, poor adherence to therapy, incorrect inhaler/spacer technique, uncontrolled comorbidities (allergic rhinitis) Poorly controlled asthma after ruling out "Difficult to control asthma"
	Eosinophilic predominant asthma	Allergic asthma
	Neutrophilic predominant asthma	Non-allergic asthma
	Recurrent croup	Repeated episodes of croup
	Middle lobe syndrome	Repeated episodes of middle lobe infiltrate or atelectasis
	Recurrent pneumonia	Repeated episodes of lung infection
Adult	Late onset eosinophilic asthma	Later onset, predominately female, and elevated sputum and serum eosinophils, associated with sinusitis
	Obesity related asthma	Associated with increased levels of TNFa, IL-6, leptins, less eosinophils, FeNO, and corticosteroid responsiveness
	Neutrophilic asthma	Difficult to characterize, often severely obstructed with only partial reversibility and a high healthcare utilization
	Aspirin- associated asthma	Subset of late-onset eosinophilic asthma, associated with sinusitis, nasal polyps, and sensitivity to cyclooxygenase-1 inhibitors
	Allergic bronchopulmonary aspergillosis	Lower airway allergic sensitization to *Aspergillus fumigatus* causing asthma exacerbations, pulmonary function deterioration, mucous plugging, central bronchiectasis, and transient pulmonary infiltrate

abuse, and are uncommon in young children and older adults (162). Other risk factors for death include previous near-fatal asthma, hospitalization or emergency department visit for asthma in the past year, current or recent oral corticosteroid use, non-adherence with inhaled corticosteroids, a history of psychiatric disease, lack of a written asthma action plan and the presence of comorbid food allergy (161). Overall the average life expectancy for those with asthma is not reduced compared to the general population (163). Elderly patients die more frequently from respiratory diseases and are more at risk of complications of medications (150).

Contrasts

It is difficult to accurately compare and contrast childhood and adult-onset asthma due to existing gaps in the literature and we acknowledge this limitation. Additionally because some findings are reported more in adults, this does not necessarily mean they are more prevalent, but rather a possible manifestation of publication bias. Nevertheless, we have provided a reflection of the similarities and differences based on the currently available literature (**Tables 1**, **2**). Adult onset disease differed from pediatric onset disease in regard to increased prevalence in women, non-atopic individuals, and obese patients (73). Adult onset disease is associated with more respiratory symptoms and asthma medication use despite higher prebronchodilator FEV1/FVC (73). There is less quiescent disease in adult onset asthma and it appears to be less stable than childhood-onset disease with more relapses and less remissions (73).

Severe asthma in children is distinct from severe asthma in adults and approaches to severe asthma in adults should not be extrapolated to children. In children the factors associated with severity have been found to be asthma duration, medication use and lung function rather than Type 2 inflammatory markers such as increased IgE and elevated FENO that are markers of severity in adult-onset disease (93).

AUTHOR CONTRIBUTIONS

MT and ED made substantial contributions to: The conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Provide approval for publication of the content; Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Transition for Adolescents and Young Adults With Asthma

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Asthma is a complex, heterogenous medical condition which is very common in children and adults. The transition process from pediatric to adult health care services can be a challenge for young people with chronic medical conditions. The significant changes in physical and mental health during this time, as well as the many unique developmental and psychosocial challenges that occur during adolescence can complicate and impede transition if not adequately addressed and managed. The transition period can also be a challenging time for health professionals to assess readiness for transition and manage some of the complications which are particularly common during this time, including poor adherence to therapy, smoking, drug use, and emerging mental health conditions. The natural history, presentation, symptoms, and management of asthma is often significantly different when comparing pediatric and adult practice. In addition, management in infants, toddlers, school aged children, and adolescents differs significantly, offering an additional challenge to pediatric physicians managing asthmatic children and young people. Despite these challenges, if the transition process for young people with asthma is planned and performed in a formalized manner, many of these issues can be addressed, allowing the transition to occur smoothly despite changes that may occur in medical and psychosocial domains.

Keywords: asthma, transition, transition process, asthma phenotype, asthma management, adolescent, young adult

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INTRODUCTION

Transition is "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered care to adult-oriented health care systems" (1). In 1993 the Society for Adolescent Medicine published standards of care for transition, the goals being to provide a transition process that was coordinated, uninterrupted, psychosocially sound, developmentally appropriate, and comprehensive (1). In 2011 the American Academy of Pediatrics (AAP) with endorsement of the American Academy of Family Physicians (AAFP) and American College of Physician (ACP) published a clinical report that described preparation for transition, the process of transition and tracking of transition as well as appropriate follow up post transition (2). This document was updated in 2018 (3, 4). The purpose of these documents was to highlight the importance of planning for transition and to provide a framework or model for transitioning adolescent and young adult patients from pediatric to adult care in a standardized and effective manner.

Asthma is the most common chronic medical condition in children, affecting over 7 billion children in the United States of America (5) and about 300 million people worldwide (6). Although

the underlying pathology (reversible obstruction of the small airways) is similar in asthma at any age, there can be marked differences in presentation, triggers, phenotype and treatment when considering asthma in children, adolescents and adults. The changes that occur in an individual during adolescence include physical, emotional, and psycho-social. The influence these changes exert upon pathophysiology, presentation, prognosis, and treatment of asthma must be carefully considered during the transition from pediatric to adult health care. For example, poor adherence to treatment is very common during adolescence as there is increasing independence and individuation, as a consequence more frequent asthma exacerbations may occur. Therefore, transitioning patients with asthma must be a carefully planned process, with consideration of the significant changes in all domains of a young person's life and the effects these changes exert upon their asthma.

NATURAL HISTORY OF ASTHMA

Patterns of wheezing are often quite variable in childhood in contrast to adults where there tends to be more stability in type, frequency and triggers of exacerbations. Viral induced wheeze is extremely common in the first year of life due to small airway caliber and the presence of multiple episodes of viral induced wheeze is not necessarily an indicator of future asthma (6). It is known that wheezing in the first year of life, even if episodes are severe, does not always predict persistence of wheezing at 10 years of age (7). Toddlers and pre-schoolers who wheeze tend to either have episodic viral induced wheeze or multiple trigger wheeze (commonly associated with personal and/or family history of atopy) (8). Viral induced wheeze (and asthma) tend to improve with age and increase in size of airway caliber, however young children who wheeze with atopy and/or a family history of asthma are at risk of persistent wheeze later in childhood (6, 9–11). The Tucson Children's Respiratory Study demonstrated that persistent wheezing in childhood is likely to persist at least to early adulthood (12). Despite asthma in children being strongly linked to atopy, the association between atopy and asthma extends beyond childhood, as atopic individuals without wheeze and/or airway hyperresponsiveness at 12 years of age can still develop asthma as adults (13).

Adolescence is a time where asthma may change significantly. Studies that have followed adolescents in a longitudinal fashion until adulthood have focused on asthma remission, persistence, relapse and new onset adult asthma (6). Although cross sectional studies have demonstrated that significant changes occur in the asthmatic population in adolescents, individual factors that influence prognosis have not been identified (14). Longitudinal studies of adolescents and young adults have demonstrated that bronchial hyperreactivity as a child is a strong predictor of persistence of asthma in adult life (15–18), however these studies have not allowed description of an accurate asthma "phenotype" in adolescents and young adults (14). Interestingly, the higher incidence of asthma in boys compared to girls tends to reverse after adolescence with asthma becoming more common in women than men (11, 14, 19, 20). This may be related to male sex being a risk factor for late onset atopy and female sex a risk factor for later onset bronchial hyperreactivity (14). However, as Xuan et al. (13) point out, this observation could be also caused by a higher rate of onset of asthma in puberty in females or a lower remission rate of asthma in females after puberty. It may also reflect better response to treatment in childhood in males with increased likelihood of resolution (6).

Remission of asthma can occur during adolescence (14, 21–23), with some reporting that "most" children have remission in adolescence and early adulthood (6, 24, 25). To the contrary, Xuan et al. (13) demonstrated in their longitudinal cohort of young adults recruited at ages 8–10 that onset of wheeze during follow up was more common than remission (12.4 vs. 5.6%) and the prevalence of wheeze increased by 6% in a 10 year follow-up period. Importantly, even if asthma truly remits, it is not known if remission of symptoms is the same as resolution of underlying airway pathology (6). The observations of a longitudinal Dutch cohort suggest that underlying airway pathology does not resolve despite remission of symptoms, as asymptomatic patients still had abnormal lung function and/or persisting airway hyperresponsiveness (26).

Between 3–5% of people who wheeze in childhood continue to wheeze as adults (6, 24). As demonstrated by the Tucson Children's Respiratory Study, persistent wheezing in childhood is likely to persist into early adulthood, with airway hyperresponsiveness at 6 years of age predicting the presence of asthma at 22 years (11). Other groups have demonstrated that persistent asthma in adulthood was associated with lower lung function in childhood, persistence of airway hyperresponsiveness, atopy by the age of 13 and early smoking as a young adult (27–29). In severe asthmatic adults, 69% reported asthma symptoms were present before the age of 20 years (8).

Asthma which has resolved in childhood may relapse later in life, even if asymptomatic as adolescents or young adults (6, 24, 27, 30). Relapse of symptoms in adulthood was associated with smoking (particularly in those who were not atopic), asymptomatic airway hyperresponsiveness at 13 years of age and atopy (24, 27).

Knowledge regarding asthma with the onset in adolescence or young adulthood is limited (13). Although new onset bronchial hyperresponsiveness is unusual in adolescence, the appearance of asthma in previous well adolescents and young adults is described (13). Adult onset asthma generally has a poorer prognosis and poorer response to treatment when compared to childhood onset asthma. In a longitudinal cohort study of young adults with asthma, of those who wheezed at any time, 7.8% had developed airway hyperresponsiveness after the age of 8–12 years (13). Atopy at ages 8–12 and parental history of asthma were also predictors of late onset wheeze and female sex a predictor of late onset airway hyperresponsiveness (13). However, it has been postulated that recall of childhood symptoms as an adult may be poor, and that adult onset asthma may actually represent a relapse rather than true adult onset of asthma (6). This is supported by the findings of the Tucson Children's Respiratory Study, where 63% of participants reporting "new" symptoms as

adults had already reported symptoms as children (11). The effect of cigarette smoking must also be taken into account for adults with the onset of asthma (6). In addition, new onset adult asthma may be a different phenotype as individuals are more likely to be female, obese, non-atopic and smokers (31–33).

PEDIATRIC, ADOLESCENT, AND ADULT ASTHMA—DIFFERENCES AND SIMILARITIES

Marked differences exist when comparing asthma in children, adolescents and adults. Even when considering children with asthma as a group, significant heterogeneity exists when comparing toddlers, school aged children and teenagers. To further complicate matters, asthma during the adolescent and young adult period has unique features and from an epidemiological perspective, the transition period from childhood asthma to young adult asthma is poorly understood (14). For these reasons, asthma is best thought of as a heterogenous, complex syndrome rather than a single disease (6, 34).

Phenotyping is not commonly applied to pediatric asthma as it does not tend to be particularly useful, in contrast to adult asthma (8, 35). Phenotypes can be defined in various ways, such as disease severity, presence of atopy or inflammation, temporal patterns of symptoms, response to treatments or triggers (6). When phenotypes are applied to children with wheeze and/or asthma, children frequent move between groups when they are young (34), making phenotypes less useful for prognostication. This is not surprising given the variability in the natural history, persistence and remission/relapse of asthma during childhood and adolescence. In addition, phenotyping in adults often relies on biomaterials sampled from the lower airways, which is often not available in children (6). Phenotyping by atopic status is not useful in preschool children as presence of atopy is often unclear, there is poor correlation between atopy and wheeze in this age group and atopy does not predict response to inhaled steroids (8). When considering severe asthma, older children with severe asthma tend to be male, highly atopic and are usually not completely steroid responsive which is in contrast to severe adult asthmatics who tend to be females, atopy is less common and neutrophilic inflammation is common (8).

It is known that asthma in early life is a risk factor for asthma and COPD in later life (27, 36–38). Although children who wheeze in early infancy often don't go on to develop asthma in childhood, they too have been shown to be at risk of developing COPD in adult life (6).

Therefore, it is difficult to say how similar pediatric and adult asthma are overall, given the complexities of early wheeze phenotypes, but the demonstration that many children with severe asthma continue to have severe asthma as adults (8, 11, 39) suggests that *severe asthma* may be similar in these different age groups. Prevalence of severe asthma in childhood ranges widely depending on location from 2.1% (40) of children in Sweden with asthma to 5% (41) in the U.S.A, 8.8% in Spain (42) and 36% in Canada (43). Therefore, given the heterogeneity in early viral induced wheeze and preschool wheeze, the authors estimate that approximately 10% of cases with adult asthma and childhood asthma have the same condition.

GENERAL CONSIDERATIONS FOR ADOLESCENT AND YOUNG ADULT HEALTH CARE

Some general considerations when seeing adolescent and young adult patients with medical conditions include seeing adolescents without their parents, increasing autonomy, confidentiality, consent, puberty/contraception/sexual health, poor adherence to medical treatment, mental health concerns, substance use and screening for risk taking behaviors (44). It is important to note that the following considerations not only apply in the pediatric health care system, but after transition to adult services. In addition, addressing these issues may prove very useful for adult physicians to help in building rapport, particularly during the first few appointments with a new patient who has just transitioned to adult services. Following the same principles of age and developmentally appropriate adolescent and young adult health care in adult services ensures continuity of care standards and demonstrates the commitment of the adult health professionals to providing individualized care that is tailored to age and maturity of the young adult.

As a pediatric patient enters adolescence, ideally at least some of the consultation should occur with the patient on their own (44). As adult patients will often be seen on their own, it is good to prepare young people to be able to provide relevant history and information for their appointment. This can be particularly challenging for pediatric physicians when they have known the patient since infancy, and are used to taking the majority of history from the parents (44). This concept can also prove very challenging to parents. Parents may worry their concerns won't be voiced by their child, that "secrets" may be withheld from them or that their child is unable to take responsibility for their own health care. Parents should be reassured that this is a normal, routine part of health care for all young people, and an excellent way to start preparing for future transition. Young people with cystic fibrosis have indicated that they wish to be seen at least partly on their own between the ages of 13–16 as they have private issues they wish to discuss with their doctor (45). Of concern, some young people indicated they were never offered the opportunity to be seen on their own (45). Gently introducing the idea of being seen alone for part of the consultation around the age of 12–13 is useful, with the parent present initially to provide any additional information about the medical concerns (while encouraging the adolescent to answer the questions), then some time with the adolescent alone to build rapport (44). After a rapport is built and confidentiality is discussed, screening for adolescent issues can occur at subsequent appointments. Explaining to the young person that seeing them alone is important as there may be health concerns they may not want to discuss with their parents present, and normalizing the process as part of becoming independent and assuming responsibility for their own health care (44). Discussing confidentiality is

imperative so that parents and patients are aware of this concept and exceptions to confidentiality (discussed below).

Confidentiality is of the utmost importance when seeing an adolescent or young adult patient alone, and it must be clear that they understand the exceptions to confidentiality (if someone is hurting them, they are in danger of hurting themselves or hurting someone else) (44). It is also helpful to explain that sometimes health information will need to be shared with other members of the medical team, but that this would only happen with permission from the adolescent. It is particularly important to discuss confidentiality prior to undertaking an adolescent health screen, as information may be disclosed which would require a breach of confidentiality (for example, disclosure of sexual abuse or suicidal ideation). The need to disclose this information and break confidentiality can be extremely damaging to the therapeutic relationship if the young person feels they have been betrayed or punished for disclosing this information. Clear discussion of the limits of confidentiality is therefore essential in maintaining the therapeutic relationship.

Providing consent for medical procedures will vary based on local laws. Under common law in Australia and the UK, adolescents under the age of 16 can provide informed consent without parental knowledge if they are deemed by the treating doctor to have sufficient understanding of the proposed treatment, consequences of accepting or rejecting treatment and alternative options (44). The gravity of the situation must be considered; as clearly there is a significant difference between a 14-year-old providing consent for antibiotics for a skin infection vs. providing consent for a chemotherapy. If there is any doubt seeking legal advice and advice from an ethics committee is advisable, particularly when there may be child protection concerns, questions about capacity of an adolescent to provide valid consent in the context of intellectual disability, mental health concerns, suicidal ideation or disagreement between the adolescent and their parents/legal guardian. In addition, clear documentation of conversations and decisions about providing consent, the adolescent's understanding of risks and benefits of treatment etc. must be recorded in the medical notes.

Adolescent health screening is not only an important part of providing age appropriate medical care but can assist in establishing a rapport with a young person. This is particularly important when an adult physician is meeting an adolescent patient for the first time, as it helps to establish who the young person is, their interests, their family and living situation and any health risk factors that may be present. Given the very personal nature of some of the questions, it is best to start with topics such as whom they live with before moving to topics such as drug use and sexuality. This may need to occur over a number of visits, particularly when meeting a young person for the first time. This process is often straightforward for pediatric physicians as they will usually know the adolescent quite well, but paradoxically it can complicate health screening as young people may be more reluctant to disclose risk taking behaviors to a doctor they know well for fear of disappointing their doctor or fear of their parents being informed. Often honest responses are obtained by normalizing the process ("we ask everyone your age these questions") and normalizing their situation ("lots of people your age drink alcohol, do your friends drink? What about you?"). A useful acronym to perform an adolescent health screen is HEARDDSS (home environment, education, activities they participate in, relationships with friends, family and opposite/same sex, drug use including smoking, alcohol and illicit drugs, depression, sexuality and suicide risk/risk taking behaviors) (44).

Generally by the time transition is occurring, adolescents will have completed growth and puberty but this is not always the case in chronic medical conditions. It is important to be sensitive as pubertal delay and short stature can be extremely distressing to young people, particularly if they look noticeably different and younger than their peers. Regular assessment of height and weight at each visit is essential and monitoring pubertal status with Tanner staging on a growth chart is most easily done by getting the adolescent to self-identify the picture that looks most like them. If significant pubertal delay and/or short stature are evident, assessment of bone age should be performed as well as screening for other medical causes of pubertal delay/short stature such as coeliac disease and thyroid dysfunction. Referral to an endocrinologist should be considered, particularly for those on high dose inhaled or oral steroids or complex medical conditions, as augmentation of puberty and/or Growth Hormone may be considered.

Following on from this, contraceptive needs should always be addressed, particularly when pregnancy may have an adverse effect on the underlying medical condition (for example cystic fibrosis and Type 1 Diabetes). Discussion about planning for future pregnancies, impact of pregnancy on the medical condition and potential side effects/contraindications of various methods of contraception should be discussed from early puberty. Consideration should be given to offering genetic counseling in inherited diseases when adolescents are in established puberty, and "safer sex" should always be encouraged to minimize risk of unwanted pregnancy and sexually transmitted diseases.

Adolescence is naturally a time of testing limits and boundaries, and often risk taking behavior such as experimentation with smoking and drug/alcohol use occurs (44). There is conflicting evidence regarding whether young people with chronic medical conditions are more or less likely than their peers to smoke or use drugs/alcohol (46, 47). Smoking can be particularly difficult to address, as adolescents will often want to experiment with their peers to fit in and minimize differences between themselves and their "well" peers. As adolescents often do not have the cognitive capacity to understand future consequences as a result of their current actions, explaining how smoking reduces lung function in the long term is unlikely to be successful in dissuading them not to smoke. Immediate consequences, particularly when related to appearance (such as yellow nails and teeth from smoking or missing out on a party as they require admission) may act as a deterrent to smoking (44).

Depression and anxiety can emerge or worsen in adolescence, particularly when there is a chronic medical condition. Mental health problems can have a negative effect on health outcomes, health related quality of life and adherence to treatment (44).

Depression is common in adolescents, with the incidence of major depression estimated between 3 and 5% (48, 49), unsurprisingly with a higher incidence (up to three times) in adolescents with a chronic medical condition (48–51). Chronic medical conditions are also known to increase the risk of suicide attempts, particularly in females (52, 53). It is important to screen for and refer on to appropriate services if there are concerns about emerging depression, anxiety or suicidal ideation, and recognize how these conditions can affect medical outcomes and adherence to treatment.

Adherence to medical treatment can be particularly challenging in the adolescent period for a number of reasons. Mean adherence rates for long term treatments in adolescents with a chronic medical condition are reported between 33 and 94% (44). Adherence is known to decrease in adolescence in those with chronic medical conditions (54, 55). Adolescents naturally test limits and boundaries and wish to become independent. Often part of developing autonomy includes adolescents not wishing to be "told" what to do, and this includes taking medications, doing airway clearance, physiotherapy and attending appointments. Barriers to adherence include a wish to rebel, lack of time, school commitments, not wanting to seem different to peers, forgetting, disagreement with the physician and feeling that treatments don't work. Non-adherence to treatment can impede transition, and occasionally a young person will purposefully stop taking their treatment to delay transition (unfortunately this may have the opposite effect and the pediatric team may transition out of sheer frustration) (44, 56). Pediatric physicians may also wish to delay transition as they do not feel confident the young person is adherent enough to manage their medical condition in the adult system. Non-adherence is best addressed with patience and over time, exploring in a sensitive and non-judgemental manner the barriers to adherence. Again, it can be helpful to normalize that non-adherence is common, trying to solve the problem together by offering choices, acknowledging the treatment burden and minimizing unnecessary or duplications of treatments. Focusing on the "most important" treatment can be helpful, as well as setting review dates for treatment and setting realistic goals. In some situations, the only way forward is to continue to reassure the young person that you will continue to see them and stick with them throughout the process regardless of whether they are adherent or not. Outlining issues with adherence with the adult team is crucial so that continuity of care after transition can be assured and that patients do not "fall through the gaps" if they fail to attend future appointments with adult services. This can become a particular problem as the pediatric health care system is often more accommodating when it comes to poor attendance, whereas adult services simply may not have the capacity to repeatedly book non-attenders.

MODELS OF TRANSITION

Although many different models for transition have been proposed, the Society for Adolescent Medicine position statement highlights the lack of published research comparing the different models of transition, in particular whether certain models performed better for specific medical conditions/illness severity or even if a formalized transition program actually improved health care outcomes (1). A review by Wright et al. (57) as well as the AAP report also highlighted the paucity of randomized control trials comparing different models of transition, as the majority of transition related research comprises interventional studies. Despite the existence of numerous models for transition, many share the core components of being well-prepared, starting transition early, familiarization with the adult health care system prior to transition and use of joint pediatric/adult clinics. Models draw on frameworks, concepts, and core components such as the AAP transition theory framework core principles of (3);

1. Importance of transition being youth focused
2. Emphasis on self-determination, self-management and family/caregiver engagement
3. Acknowledging individual difficulties and complexities
4. Recognizing vulnerabilities and the need for a population health approach
5. Importance of shared accountability and care co-ordination between pediatric and adult centers
6. Recognition of the influence of cultural beliefs, attitudes and socio-economic status
7. Emphasis on achieving health equality, eliminating disparities
8. Parents/caregivers to support young people to develop health knowledge and skills.

The Six Core Elements of Transition 2.0 are elements of a transition that must be present for it to be considered successful (4, 57, 58). These core elements are establishing a transition policy, tracking the transition process, administering transition readiness tools/checklists, planning for, transfer to and integration into adult care (58).

Combinations of these components appear in various forms in the majority of the proposed models for transition. Published models exist for transition in primary care/general pediatric care (for example the Medicaid Managed Care Plan and Health Practice Transformation Model) and for mental health care (European Union-Funded Transition Project) (57). Other models have been published for specific medical conditions, such as sickle cell anemia, renal transplant recipients and type 1 diabetes (57). Again, although the models are different, they all incorporate various aspects of the Six Core Elements of Transition 2.0 and include clinic based transition models, multi-disciplinary team models, transition co-ordinator models, patient developed transition curriculum and web based/mobile health interventions (57). Readers are directed to the excellent and comprehensive review by Wright et al. (57) for discussion and critical evaluation of the various models.

In 2016 a Cochrane review of intervention studies for transition models only included 4 small studies ($n = 261$ patients) and was unable to make conclusions regarding the effectiveness of various models in managing the chronic medical conditions during the transition process, healthcare outcomes or healthcare utilization (59). However, the review by Wright et al. (57) highlights the importance of a nominated individual to act as the

"transition co-ordinator" and facilitate the process as a common component of the models that were felt to be the most effective in their review. Although lack of provision of extra staffing and financial incentives for providing transition services has been identified as a barrier to implementing and sustaining transition programs, many of these effective models were able to perform effectively without extra staff or financial incentives (57).

In addition, the needs of a health care service (specifically education and resources) to provide an effective transition program need to be considered prior to choosing and implementing a transition model, based on the suitability of that particular model within the constraints of the health care system.

There are many considerations when choosing a model to use when implementing a transition program, and this highlights the importance of critical evaluation of transition models when determining effectiveness. The lack of published evidence comparing different models, particularly interventional studies, is a barrier to successful implementation of transition models and highlights the need for more research in this area.

GENERAL CONSIDERATIONS FOR TRANSITION

Table 1 for a summary of issues to be considered during transition. The general focus of pediatric health care can be very different to adult health care. Whereas, pediatric health care tends to be developmentally focused and family centered, development, growth, and family concerns are not commonly primary concerns for adult physicians (56). However, adult health care places an emphasis on autonomy, employment and reproductive health, which are often ignored in pediatric medicine, particularly as pediatricians may struggle with their patient's increased independence, autonomy and "adult" behaviors (56). This struggle of balancing the adolescent's need for increasing autonomy and individuation with the need for adherence to treatment is a struggle not only for pediatricians but parents. Transition can be complicated by a chronic illness as it can be difficult for parents to "let go" and allow the young person to assume primary responsibility for their medical treatment and develop their independence but at the same time ensure adherence to treatment remains optimal and medical management is continued. This struggle is often unconsciously reinforced by the pediatric health care system, which encourages family centered care and is at risk of "infantilising" the young adult (44). This can impede the transition process, particularly as it has been demonstrated that pediatric physicians are often reluctant to "let go" of their patients, and may consciously or unconsciously reinforce the idea that the adult health care system is a frightening environment (44). On the contrary, adult physicians may find it difficult to act in a manner they deem paternalistic when a young adult has not gained the necessary independence to demonstrate autonomy with their medical care, or feel frustrated with receiving patients whom they feel were "mollycoddled" or "treated as babies" by the pediatric system.

Barriers within the healthcare system to implementing a sustainable transition process include lack of infrastructure for co-ordination (particularly at adult healthcare sites), lack of financial reward with increased workload to implement programs and lack of electronic or shareable medical records (58). The difficult with multiple interfaces for entering and storing healthcare information can present a particular challenge, as it can significantly impede communication between pediatric and adult sites. It is useful to have a standard format for transition documents to be prepared by the pediatric service. If regular transitions are occurring to the same adult service, involving the adult physicians in designing a template for exactly which information they need and which formats will be compatible with their record system will reduce the risk of poor handover or loss of medical records.

Engagement of adult physicians in the transition process is essential to ensuring a successful transition, but can present a significant barrier (3). Adult physicians may require a significant amount of education regarding medical conditions that were traditionally considered "pediatric" diseases, with children not surviving to adolescence or adulthood, such as metabolic disorders, cystic fibrosis and congenital heart disease. Adult physicians may understandably feel overwhelmed at providing care to these very complex patients when they may not be familiar with their underlying medical condition, let alone the numerous challenges individuals with these conditions may face in young adulthood. Similarly, a unique challenge exists when there are no equivalent adult services for specific pediatric conditions, particularly those with inborn errors of metabolism, complex neuro-behavioral disorders, cerebral palsy and developmental disorders.

Although some adolescents wish to transition early as they find attending a pediatric center embarrassing, many find transition to be a distressing time due to loss of familiarity, particularly those who have been seen at the same center by the same team for many years. Preparation for transition to adult services should start early and young people and their families should be well-informed of the proposed timeline for the process. The age of transition varies between centers and should be individualized to the young person, however, generally will take place between the ages of 16–18, or when completing secondary education. This is a time of great change in all domains of a young person's life (44). Therefore, a transition checklist is very useful, ensuring all aspects of the transition have been covered (which may include a physical visit to the new site, ensuring the process for obtaining prescriptions is known, how to get to the new appointment and how to seek medical review or emergency review). Particularly for complex patients who require tertiary level care or a dedicated team, having prior appointments with the adult team or even joint appointments prior to transition can be extremely useful to familiarize the young person and their family with the new team and facilities. Young people have reported a tour of the adult facility, joint sessions and a familiar face from the pediatric team joining the first adult appointment are very reassuring (60).

Guidelines and standards for the transition process have been published for a wide range of medical conditions, including diabetes (61), congenital heart disease (62), and cystic fibrosis (63). The transition from being a dependent child to an

TABLE 1 | Considerations for transition.

Considerations for transition	Pediatric perspective	Adult perspective	Organizational perspective
Preparation for transition (young person and their family)	Start transition process early Normalize the transition process Joint clinics Regular assessment of readiness for transition See the young person on their own Encourage their independence and assuming responsibility for healthcare	Meet the young person prior to formal transition Normalize the transition process Joint clinics Adolescent health screen to build rapport Organize tour of adult site	Encourage joint clinics Consider formalized transition pathway/process Appoint a specific transition co-ordinator Facilitate visit to adult site
Poor adherence to treatment	Open and honest discussion about barriers to poor adherence Problem solving with the young adult Focus on immediate consequences, personal appearance Screening for depression	Open and honest discussion about barriers to poor adherence Problem solving with the young adult Focus on immediate consequences, personal appearance Screening for depression	Consider formalized transition pathway/process Appoint a specific transition co-ordinator
Avoiding being lost to follow-up	Ensure formal transition to adult team with letters and good communication Consider booking a final appointment/phone consult after seeing adult team to ensure everything is in place	Ensure clear communication with pediatric team as to when adult team will be taking over Ensure adult team knows contact details for young person and correct address to send appointment to Consider a written handout about arranging appointments or urgent review	Establish a "safety net"—transition co-ordinator or respiratory nurse to ensure follow-up has occurred
Clinical deterioration during transition process	Ensure follow-up with adult team occurs Address poor adherence as much as possible Delay transition if a major change in clinical status occurs Flag young people with complex issues to inform adult team May require several joint appointments Ensure verbal and written handover for all medical and allied health services Assess medical knowledge and understanding for the young person prior to transition	Close liaison with pediatric team to cover all outstanding issues Be prepared to attend more than one joint appointment	Have a "Transition Checklist" to ensure nothing is missed

independent adult is not always smooth, and becomes more complex when there is a chronic medical condition (44). The transition process must be well-planned and must not be rushed, and careful consideration of adolescent issues as well as medical issues must be addressed prior to handing over medical care to an adult physician (56, 64, 65). As well as managing general adolescent issues, transitioning a young person with asthma (particularly severe or poorly controlled asthma) offers some unique challenges. Specific considerations for transitioning the asthmatic patient with to adult heath care services is discussed in more detail below.

SPECIFIC CONSIDERATIONS FOR TRANSITIONING PATIENTS WITH ASTHMA

There is very little published literature specifically examining the transition process in adolescents and young adults with asthma (66). This is surprising given asthma is the most common chronic medical condition in children (5), and highlights the need for further research to determine optimal care for adolescents transition with asthma. For the majority of young people and adolescents with well-controlled asthma, transitioning to adult services is unlikely to be a difficult process. Indeed those already being managed very well in general practice/primary practice do not require transition at all as they can remain with their primary care provider, ensuring excellent continuity. If there is any concern about deterioration of asthma control in young adulthood, an opinion from an adult respiratory specialist could be sought, while the general practitioner maintains primary management with specialist reviews as required.

Those well-managed by general pediatricians are likely to be able to transition to ongoing care in general practice, and liaison with a suitable general practitioner should be encouraged early on to ensure they are comfortable with the transition plan. A study of the transition process for adolescents with asthma at a children's hospital asthma/allergy clinic found that young people with mild/moderate asthma were managed equally effectively regardless of whether they transitioned to primary or specialist care (66). All patients in this study with severe asthma were transitioned to specialist adult asthma services (66). It is important that adolescents with asthma do have ongoing follow-up, even if their asthma is mild, as childhood asthma is a risk factor for developing chronic obstructive pulmonary disease

(COPD) in later life (27, 36, 37). In addition, asthma can recur in adult life despite remission as a teenager (30).

Adolescents who require tertiary level care are more likely to have difficult to control or severe asthma and may have other considerations which complicate the transition process (particularly poor adherence to treatment, exposure to cigarette smoke, mental health concerns or additional medical conditions). These complicating factors are common in asthmatic adolescents. For example, in a study of adolescents with asthma, 25% were reported to be poorly adherent to treatment (66). Of particular concern is adolescents with asthma who smoke or are exposed to passive smoke from peers. A study of Swedish adolescents with asthma found that 8% reported being smokers and 28% were exposed to passive smoke at home or by their peers (66). The incidence of depression in individuals with asthma is higher than the general population and depression in asthmatics may be more common than in other chronic medical conditions (67). In addition, depression may increase morbidity and mortality associated with asthma (67). These concerns that may complicate transition should be identified and managed if possible prior to transition and handed over to the adult team for ongoing management.

The vast majority of adolescents requiring tertiary level care for their asthma would be expected to require tertiary level respiratory care as an adult, especially those requiring frequent hospital and/or intensive care admissions. This is reinforced in the study above, where all adolescents with severe asthma required transition to specialist adult respiratory services (66). If a tertiary adult respiratory service is not available, an adult respiratory physician with an interest in asthma could be considered to take over ongoing care. In more remote locations visiting respiratory services may be available, with a local doctor taking primary responsibility for ongoing care. Young people who are likely to require ongoing hospital admissions for exacerbations of asthma should be referred to a service that is able to manage emergency presentations, admissions and provide frequent review. In these cases, a suitable service with experience in managing difficult asthma should be identified early on and liaison should occur prior to transition, particularly if there is the possibility of a joint appointment or meeting the adult team prior to transition. Development of a specific center-based transition pathway for adolescents with difficult or severe asthma is encouraged to formalize the process and ensure nothing is missed.

Adolescent and young adult patients with frequent asthma exacerbations requiring presentation and management in emergency departments present additional challenges during the transition period. A review of care transition within the emergency department back to primary care identified that those who presented to ED often received improper management of exacerbations at home, and families required education and support to transition safely back to primary care (5). Although these findings are presented in the context of the emergency department, they highlight the need for excellent communication, care coordination and patient education to ensure a successful transition, regardless of the health care providers involved. It also highlights the need to specifically consider the high care needs of asthmatic patients who are frequent presenters at emergency services, and the value of involving the emergency department in planning for transition and ensuring access to adult emergency services as part of preparing for the transition process.

A common concern in chronic medical conditions is deterioration of stability during the transition process and loss to follow-up by adult services (44). This may delay the transition process, particularly if the pediatric service is not confident the young adult has acquired the skills to manage their medical condition or seek help appropriately if unwell. Bergstrom et al. (66) studied 150 adolescents with asthma during the transition process to identify risk factors for deterioration of asthma control during and after transition. They found that it was rare for pulmonary function to deteriorate during and up to 5 years post transition (66). In addition, the majority of those with reduced FEV1 at the time of transition had improved pulmonary function at follow-up (66) which is encouraging. Poor adherence to medical treatment and female gender predicted persisting bronchial hyper responsiveness and chronic symptoms (66), therefore this groups of patients may require more frequent monitoring during and post transition.

Untreated or poorly controlled asthma can be associated with pubertal delay (68–71), and the associated emotional distress secondary to pubertal delay can contribute to poorer asthma control and poor adherence to treatment (68). This is particularly the case as there is some evidence inhaled corticosteroids may contribute to pubertal delay (69) hence adolescent patients may be reluctant to use them. However, untreated or poorly treated asthma delays puberty on average by 1.3 years (71) and discussing this information may encourage adherence to treatment. Many young people with asthma are concerned about short stature and may attribute this to chronic use of inhaled corticosteroids, however in severe or poorly controlled asthma pubertal delay itself is more likely to explain the apparent growth failure rather than suppression from corticosteroids (71). Reassurance that treating asthma and better adherence to treatment may improve the pubertal delay and short stature may assist in encouraging adherence to treatment. Pubertal status and stature should be monitored closely in all adolescent patients with asthma, particularly those on high dose inhaled corticosteroids or oral steroids.

Prior to transition, contraception and sexual history should always be discussed. Although the majority of detailed discussion will be with female patients, sexual history should also be discussed with males and an open discussion about which form of contraception they use is encouraged. When choosing contraception to avoid unwanted pregnancy in asthmatic adolescents, a number of considerations are necessary. Firstly, barrier contraception is the only method offering any protection against sexually transmitted diseases, and barrier contraceptives should be used in combination with a more effective form of contraception for avoiding pregnancy. Second, if adherence to treatment is a challenge, a reliable form of contraception that doesn't rely on remembering to take medication should be chosen, such as a hormonal implant or intra-uterine device. In particular the Progesterone Only Pill should be avoided as

efficacy is dependent upon taking it regularly and at the same time each day. Thirdly, contraception should be encouraged, particularly in severe asthmatics, as asthma exacerbations during pregnancy have been shown to be associated with low birthweight babies (72) and oral contraception use in pregnancy has been shown to reduce the risk of asthma exacerbations (73). Although preconception and obstetric care of the asthmatic women is beyond the scope of this article, readers are directed to resources such as the Australian Asthma Handbook section on pregnancy and preconception considerations (74) (available from http://www.asthmahandbook.org.au). Although there appears to be a significant association between maternal ingestion of Paracetamol during pregnancy and subsequent risk of asthma in offspring (75), non-causal explanations have not been able to be excluded (76), and a significant number of confounders exist, particularly family history of asthma and atopy. The large Norwegian Mother and Child Cohort Study found that prenatal exposure to Paracetamol was associated with a small increase (13%) in the risk of developing asthma when accounting for confounders (77). Given infants of asthmatic mothers will already be at a higher risk of developing asthma given family history of asthma and/or atopy, it may be prudent to advise adolescent and young adult women of childbearing age to avoid Paracetamol while pregnant or planning a pregnancy.

Financial concerns after transition are more likely to be a concern for young adults, as adolescents will often live in the family home. Scal et al. (78) found that adolescents with asthma were more likely to have a usual care provider and private health insurance than young adults with asthma, with young adults facing increased financial barriers to accessing health care after transition. Of concern, these young adults reported more unmet health care needs and delays in receiving health care due to financial constraints (78). Other barriers to accessing appropriate health care for asthma in both adolescents undergoing transition and young adults post transition were difficulties with transportation, frustration at long wait times at physician offices, difficulties arranging appointments (especially by telephone) and inconvenient physician office hours (78). Addressing these concerns may require social work involvement and provision of financial assistance to ensure continued access to health care post transition.

Gibson-Scipio et al. (79) highlighted the additional challenges for young adults with asthma who are transitioning and are not Caucasian. For example, it is known that asthma morbidity and mortality rates are higher in those individuals who are not Caucasian (80). In addition, African American youth are less likely to discuss transition or engage in the transition process than Caucasian youth (81). In their study, Gibson-Scipio et al. (79) found that African American youth with asthma often did not use preventer medications and lacked understanding of the inflammatory nature of asthma that required preventer medication even when symptoms were well-controlled. Nearly half expressed that they didn't want to inform their peers of their medical condition as it was a sign of "weakness" and most felt routine visits for asthma were unnecessary (79). Although these concerns are unlikely to be limited to adolescents who are not Caucasian, it raises the importance of ensuring transition is well-planned and there is a good understanding of the medical condition, particularly in those groups with a higher risk of morbidity and poor ongoing engagement.

The importance of health education and assessing understanding of the underlying medical condition cannot be overstated, particularly when preparing for transition. Although this is important for all patients with asthma, it is particularly important in non-Caucasian adolescents who are at higher risk of poorer health outcomes and poor understanding of the their asthma and treatments (79, 82). Holley et al. (83) demonstrated that understanding of the medical condition and treatments was essential for allowing adolescents to develop self-management skills and improve adherence to treatment. Lack of knowledge about asthma was identified by adolescents as a significant barrier to adherence to treatment (83). Particularly important focuses for education were triggers, how to recognize symptoms indicating an exacerbation and the seriousness of asthma (83). Other groups describe the importance of educating about treatments, how they work and why to use them as key to encouraging self-management of asthma by adolescent patients (83–85). Correct inhaler technique is essential, particularly as few children use their inhalers in the correct way (86). Volerman et al. (86) highlight the need for careful assessment and direct observation of inhaler technique, given parents and children will over-estimate their skills in delivering inhaled medications effectively. If poor inhaler technique can be corrected prior to transition, it may contribute to better inhaler technique in adult patients, as up to 90% of adults with asthma and COPD do not use their inhalers correctly (87, 88). It is essential that people with asthma carry their inhalers at all times, and for young people there can be barriers to carrying their inhalers and using them at school (89), such poor knowledge of how to assemble the inhaler in an emergency (90). These results emphasize the importance of practical asthma education including careful assessment of inhaler technique, assembly of devices and discussing practical strategies for carrying devices at school to ensure rescue medications are used effectively. Other strategies for education written action plans for daily management (very common in pediatrics), formal asthma education with an asthma nurse and partnering with schools and housing authorities (82). Transition presents an opportunity for assessment of asthma knowledge, particularly treatments and identifying exacerbations, and encouraging the adolescent to be able to self-manage in preparation for transition. Importantly, it has been demonstrated that health education regarding asthma treatment can improve remove health literacy barriers, improving asthma self-management and treatment adherence (91). Therefore, the importance of regular asthma education with a focus on practical assessment prior to and after transition (and on an ongoing basis in adult health care) cannot be overstated.

A SUGGESTED APPROACH FOLLOWING TRANSITION TO ADULT SERVICES

For those young adults who do require transition to specialist adult asthma services, the transfer of their care provides an

opportunity for a detailed review of their asthma, starting with a careful reassessment of the diagnosis. For most patients a review of the pediatric case notes will identify objective evidence supporting the diagnosis, for example presence of variable airflow obstruction and/or airway hyper responsiveness, often along with markers of airway inflammation such as elevated FeNO, blood or airway eosinophilia. In the absence of this evidence, or where the pattern of symptoms or exacerbations has changed, it may be helpful to organize further investigations such as methacholine or histamine challenge testing, induced sputum, FeNO, and in selected cases to consider CT imaging or bronchoscopy. These investigations will not only help to confirm that asthma is still the primary condition driving their morbidity, but also help to characterize the underlying asthma phenotype and to determine which are the active treatable traits that require attention (11, 42, 43). Identification of an eosinophilic inflammation predominant phenotype, for example, may direct the clinician to consider targeted anti-eosinophil therapies such as anti-IL5 treatment (44, 45). As adolescent patients transfer to adult services and start to take more individual responsibility for their own healthcare, non-adherence to treatment is a particularly important issue (46). Transfer to adult services should prompt a full medication review including an assessment of the patients' beliefs and understanding of the rationale for treatment, their current and anticipated adherence pattern, use of rescue medication including any inappropriate reliance on short acting B2 agonists, inhaler technique and presence and understanding of a personalized asthma action plan for exacerbations. A review of inhaler device and treatment doses will often also be appropriate. Similarly it is important to remember that patients are often undergoing significant changes in their psychosocial circumstances such moving away to university or starting full time employment and it will be important to consider the impact that these lifestyle changes will have on the patient's asthma. With appropriate initial support from the multidisciplinary asthma team most patients can accept increasing responsibility for managing their own asthma following transition. For some young adults, particularly those with the most severe asthma who have had a history of frequent hospital admissions, more time will be needed to lessen the need for the input of parents and other carers, but wherever possible the goal should be independent asthma self-management with support from the specialist asthma team.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Severe Asthma—Perspectives From Adult and Pediatric Pulmonology

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Both adults and children with severe asthma represent a small proportion of the asthma population; however, they consume disproportionate resources. For both groups it is important to confirm the diagnosis of severe asthma and ensure that modifiable factors such as adherence have, as far as possible, been addressed. Most children can be controlled on inhaled corticosteroids and long term oral corticosteroid use is rare, in contrast to adults where steroid related morbidity accounts for a large proportion of the costs of severe asthma. Atopic sensitization is very common in children with severe asthma as are other atopic conditions such as allergic rhinitis and hay fever which can impact on asthma control. In adults, the role of allergic driven disease, even in those with co-existent evidence of sensitization, is unclear. There is currently an exciting pipeline of novel biologicals, particularly directed at Type 2 inflammation, which afford the possibility of improved asthma control and reduced treatment side effects for people with asthma. However, not all drugs will work for all patients and accurate phenotyping is essential. In adults the terms T2 high and T2 low asthma have been coined to describe groups of patients based on the presence/absence of eosinophilic inflammation and T-helper 2 (TH_2) cytokines. Bronchoscopic studies in children with severe asthma have demonstrated that these children are predominantly eosinophilic but the cytokine patterns do not fit the T2 high paradigm suggesting other steroid resistant pathways are driving the eosinophilic inflammation. It remains to be seen whether treatments developed for adult severe asthma will be effective in children and which biomarkers will predict response.

Keywords: asthma, children, adults, adherance, type 2 inflammation, biological therapies

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INTRODUCTION

Most children and adults diagnosed with asthma can achieve good symptom control on a low dose of correctly administered inhaled steroids with or without additional controller medication. However, there remains a small but significant proportion with ongoing symptoms and/or frequent attacks despite high intensity treatment. This group consume a high proportion of healthcare resources in terms of treatment costs and hospital admissions, as well as the wider societal costs of time of work and school. Direct healthcare costs are mostly due to prescribed medication for asthma

and corticosteroid induced morbidity, particularly in adults (1, 2). In both adults and children, it is essential to firstly confirm the diagnosis of severe asthma in order to implement appropriate management. This article will outline the definition of severe asthma, before exploring the similarities and differences between adults and children in terms of demographics, pathophysiology and management.

DEFINITION OF SEVERE ASTHMA

Many terms, including difficult; problematic; therapy resistant and refractory asthma have been used interchangeably with severe asthma. Over the past 20 years national and international organizations have sought to clarify these differences and refine the definitions and nomenclature. The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines 2016 (3) set out a framework for the diagnosis of severe asthma in adults and children and more recently the Global Initiative for Asthma (GINA) has produced a useful guide for the diagnosis and management of "Difficult-to-treat" and Severe Asthma in adolescents and adults (4). Only those with a confirmed diagnosis of asthma, prescribed high dose treatment, who have ongoing poor control (or who require a high level of treatment to maintain control) once modifiable factors have been addressed are classified as severe asthma. The diagnosis of asthma is covered elsewhere in this supplement and will not be dealt with further here but identification and addressing poor medication adherence, comorbidities and psychosocial issues is a critical aspect of determining if severe asthma is present and will be discussed below. High intensity standard treatment is generally defined for both adults and children as high dose inhaled corticosteroids (ICS) plus at least one additional controller medication (long acting beta agonist (LABA), theophylline or leukotriene receptor antagonist (LRTA) (5, 6). The definition of high dose ICS is usually stratified by age: children under 5 (or 6) years; between 5 (or 6) to 12 years; and over 12 years. Children and young people (CYP) over 12 years are often included in the adult classification. The rationale for such an approach is likely based on drug licensing studies. Most Phase 3/4 adult studies include adolescent patients but these data are rarely reported separately (or indeed include sufficient adolescents for meaningful subgroup analysis). The definition of "high dose" varies between guidelines. The ERS/ATS and British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines use cut offs of $\geq$1,000 mcg/day fluticasone propionate (FP) or equivalent for adults and $\geq$500 mcg/day FP equivalent for children whereas GINA uses lower cut points of >500 mcg FP/day for 12 years and older and >400 mcg for children aged 6–11 years (3, 5, 6). Given the flat dose response curve of ICS, there is little additional benefit from stepping up to very high doses in most patients (7) and therefore the GINA thresholds are probably more appropriate. Furthermore, adolescence is an important time of growth and development and most pediatricians are judicious in their use of very high (i.e., adult) doses of ICS in teenagers, preferring to stick with the pediatric thresholds.

PREVALENCE OF SEVERE ASTHMA

Estimates of the prevalence of severe asthma vary depending on the definition used. It is widely quoted that 5–10% of the asthmatic population have severe asthma, but this will include a significant number of patients with ongoing poor adherence, untreated co-morbidities or mis-diagnosis. In a Dutch study, 17.4% of the adult asthma population had "difficult to control" asthma (poor asthma control despite prescription of high intensity treatment) but after excluding non-adherence and poor inhaler technique, only 3.6% had severe refractory asthma (8). In adults referred with severe asthma, when evaluated systematically with a multi-disciplinary team, high rates of mis-diagnosis and comorbid disease are identified (9, 10). In children the numbers are likely even lower. A study which defined severity on the basis on symptoms, exacerbation frequency and spirometry found that 13% of children with asthma were classified as "severe persistent asthma" (11). However, "difficult to control asthma" would have been a more appropriate label for this group. Of children with difficult to control asthma referred to a specialist severe asthma clinic less than half were assessed as having severe asthma (12). Improvements in assessment of those children, particularly adherence monitoring has seen that figure fall to around 20% (13), suggesting that <2.5% of children with asthma have severe refractory asthma. Severity in pre-school children is even harder to estimate, particularly given the challenges of asthma diagnosis. In the Manchester Asthma and Allergy birth cohort approximately 6% of children with a history of wheeze were classified as severe (14).

DIFFERENTIATING SEVERE REFRACTORY ASTHMA FROM MILDER ASTHMA

The umbrella term problematic severe asthma or difficult to treat asthma covers all those with ongoing poor control despite high intensity treatment (5, 15, 16). A significant proportion of this group will have improved control once modifiable factors such as adherence, allergen exposure and psychosocial issues are addressed, and co-morbidities identified and managed appropriately (9, 12, 17). Those with ongoing poor control despite attention to these basics of asthma management are considered to have severe asthma, although it is accepted there is overlap between these groups (18).

POOR ADHERENCE TO MEDICATION

Poor adherence to ICS, for both adults and children is the most common reason for treatment failure and poor asthma control (19, 20). In adults, 65% of patients with "difficult to control" asthma and prone to exacerbation and referred for specialist assessment in the UK, collected <80% of their inhaled preventive medication (21, 22). Medication issues including poor adherence (from prescription records), poor technique and inappropriate device were assessed as contributing to poor asthma control in half of children with seemingly severe asthma referred to a tertiary center (12). Identification of

poor adherence to inhaled treatment as the primary clinical problem can be difficult. Physician assessment and patient self-report overestimate adherence when compared with objective or surrogate measures such as prescription records (21, 23). Whilst prescription or dispensing records are helpful, these still overestimate adherence as patients may pick up their inhalers and not use them or use them incorrectly. In children, there is a reliance on parents to request and collect prescriptions; and the child must actually take the medication. A US study which sought to determine if azithromycin or montelukast was an inhaled steroid sparing treatment (MARS trial), was abandoned as most of the children were adequately controlled when adherence was addressed under close medical supervision (24). Objective measures for monitoring inhaled medication are available but have been slow to be implemented in routine clinical care. In both adults and children monitoring adherence to inhaled corticosteroids, aligned with biological response—including suppression of fractional exhaled nitric oxide (FeNO) with monitored treatment—can be used to identify patients with poor prior adherence to inhaled corticosteroids who are likely to achieve substantial benefit from optimized inhaled treatment (13, 23, 25, 26). In addition, this approach can identify those subjects who are unlikely to suppress markers of type-2 biology (FeNO and blood eosinophils) with optimized inhaled treatment alone, and would potentially be candidates for biologic (27, 28). Collectively, these studies have shown that at least 50% of adult and 80% of pediatric patients who would qualify for novel biologic therapies based on their exacerbation history and inflammatory biomarkers are simply not taking regular inhaled anti-inflammatory treatment.

However, having identified that adherence is the primary problem, we still need to define the best intervention to change non-adherent behavior in the medium to long-term and there is unlikely to be a "one size fits all" solution. In adults and children there are a number of factors that can influence adherence, both intentional and unintentional (29): The device must be age appropriate and use demonstrated by an appropriately trained team member (30). Unfortunately, even among healthcare professionals, inhaler technique skills are poor (31). A metered dose inhaler (MDI) should always be used with a spacer in children, and all but the youngest children should be able to use a spacer with mouth piece. In children, an additional complexity is the need to engage parents and caregivers in their child's asthma management. The use of remote directly observed therapy using a Smartphone and associated App has demonstrated that children's inhaler technique is generally inadequate, even when use has recently been demonstrated by a specialist children's asthma nurse (32). Ongoing and continued education is needed, particularly as parents often over estimate their child's technique (33). Furthermore, supervision by parents is often poor; 20% of children aged 7 years are not supervised and by 11 years this figure rises to over 50% (34). Interestingly rates of adherence are equally poor among preschool children; younger school aged children and adolescents (13, 35).

Mobile text messaging in chronic disease management improves adherence rates and simple reminder systems have also been shown to improve inhaled maintenance treatment in asthma, suggesting the gains are potentially large in this population (36–38).

Multiple pharmaceutical companies are now involved with digital technologies and "smart inhalers." Monitoring of inhaled treatment may potentially become available across a number of inhaler platforms for asthma patients.

CO-MORBIDITIES

In both adults and children, co-morbidities and psychosocial factors, such as atopy, obesity, gastroesophageal reflux (GER), rhinitis, anxiety disorders, depression, and dysfunctional breathing can negatively impact on asthma control, medication adherence, mimic the symptoms of asthma and contribute to the complexity of asthma management in those with both severe and difficult to treat asthma (10, 18, 39). These should be regarded as "treatable traits" which can be identified and targeted as part of a comprehensive disease management approach (40–44). **Table 1** [adapted from Porsbjerg and Menzies-Gow (39)] summarizes these extrapulmonary traits and potential management strategies. The prevalence and importance of many of these comorbidities is much better described in adults than children with asthma (39, 53). Identifying and addressing these multiple factors is critically important because factors such as psychological dysfunction can be a major driver of recurrent exacerbation in this population (60).

The majority of children (>80%) with asthma are sensitized to at least one aeroallergen, and those with severe asthma are likely to have multiple sensitisations (46, 61). In adults, atopy defined by positivity to skin prick testing or specific IgE measurement in severe asthma cohorts is between 60 and 80% (45, 57, 62), with higher prevalence noted in research cohorts. However, atopy with sensitization to aeroallergens is common in non-asthmatic subjects and in many adults with severe asthma, the role of allergic driven disease even in those with co-existent evidence of sensitization, is unclear. Other atopic conditions such as allergic rhinitis and hay fever are common in children (46) and have been shown to impact on asthma control (63). Chronic rhinosinusitis and nasal polyposis is common in adults, although not children and indeed the presence of nasal polyps in children should be a red flag for an alternative diagnosis such as cystic fibrosis or primary ciliary dyskinesia (9, 45).

Gastro-esophageal reflux (GER) and asthma frequently co-exist in children and adults with asthma (64); however, there is inconsistent evidence of a "cause and effect" relationship between the two GER is associated with asthma symptoms and poor control (65) however, a study of lansoprazole in children with proven GER showed no impact on asthma control (66). A Cochrane review concluded that treatment of GER did not result in an improvement in asthma symptoms in adults or children (67). However, it is possible that non-acid reflux may be important and explain the relationship between symptoms and lack of treatment effect (68).

TABLE 1 | Comorbidities in children and adults with severe asthma.

Clinical Trait	Adults	Children	Management
Obesity	Patients with severe asthma have a higher BMI than healthy controls and up to 40% are obese (45)	Children with severe asthma have a higher BMI although few children with severe asthma are clinically obese (46)	Weight loss programme; bariatric surgery
Depression and anxiety	Anxiety and depression found up to 27% of patients with difficult asthma (9, 47)	High levels of anxiety in both children with severe asthma and their caregivers	Psychological support
Breathing pattern disorder (BPD); including vocal cord dysfunction (VCD)	BPD common in difficult asthma, 19–52% (39, 48); VCD reported in up to 50% (49, 50)	One study in children found only 6% of children with severe asthma had BPD; this is likely an underestimate (51), prevalence of VCD unknown	Physiotherapy for BPD and EILO; speech and language therapy for VCD; surgery for supraglottic EILO in selected cases
Chronic rhinosinusitis and nasal polyps	Approximately 50% of severe asthma patients have chronic rhinosinusitis; and over 30% nasal polyps (45, 52)	Rare in children; nasal polyps suggest an alternative diagnosis such as cystic fibrosis or primary ciliary dyskinesia	Sinus rinses, nasal steroids, surgery
Allergic rhinitis	Allergic sensitization common in severe asthma (approximately 70–80%; and up to 60% report symptoms of allergic rhinitis (although this is similar in milder asthma) Ref Shaw UBIO	Allergic sensitization and allergic rhinitis common in children (up to 80%) (53)	Anti-histamines, nasal steroids
Obstructive sleep apnoea (OSA)	Common in severe asthma, up to 92% in one cohort (54), 31% in SARP (55)	Reported prevalence of 63% in poorly controlled asthma secondary to adeno-tonsillar hypertrophy (56)	CPAP, weight loss, adenotonsillectomy (children)
Gastro-esophageal reflux	Common in severe asthma, 17–74% (45, 57, 58)	Diagnosed in 20% of children with severe asthma, although unrelated to any measures of asthma severity (46, 59)	Proton pump inhibitors; little evidence to suggest an impact on asthma symptoms

Obesity is a growing global health problem and can impact on asthma diagnosis, control and exacerbation severity in both adults and children (69, 70). In children the strength of this relationship appears less strong than in adults, although this may in part be because it has been less well-studied (71). There are a number of plausible mechanisms for this relationship: deconditioning leading to breathlessness may mimic asthma symptoms leading to an erroneous asthma diagnosis or assessment of control; lung mechanics are altered in obesity with pulmonary restriction and lower functional residual capacity and ventilatory reserve which can have secondary effects on airway smooth muscle shortening during bronchoconstriction; dysynaptic lung growth (increased in lung volume and airway length but not caliber has been shown to be more common on obese children and associated with worse disease severity and poor response to steroids (72–74). Obesity is also associated with systemic inflammation and IL-6 may be a potential mediator of T2 low asthma (and hence steroid resistance) in some obese patients (75). Furthermore, an adult-onset obese female phenotype has been identified with a link to non-eosinophilic airway inflammation (76). Data from small randomized controlled trials show that weight loss improves asthma control, quality of life and lung function but the overall level of evidence of benefit is low (77, 78) and bariatric surgery has been shown to have a positive effect on asthma outcomes (79–81). The relationship between asthma severity and obesity is further confounded by the fact that steroids lead to weight gain. Thus, it can be difficult to untangle whether obesity is driving asthma symptoms (via the mechanisms described above) or whether persistent symptoms and attacks lead to increased steroid use, causing obesity. Furthermore, weight loss is hindered by steroid use.

Anxiety and depression are both associated with increased exacerbation frequency, poorer asthma control and quality of life (60, 82, 83). A negative life event can increase the risk of an asthma attack within a short time of that event and the effect is magnified if there is a background of chronic stress (84, 85). The precise mechanisms underlying the relationship between stress and severity are not known, however an increased T-helper 2 (TH_2) cytokine response has been associated with higher chronic stress and perceived threat in children (86). It may also be that psychological factors such as anxiety and depression along with other mental health conditions may affect a patient's ability to self-manage their asthma and impact on other behaviors such as smoking and poor adherence.

Dysfunctional breathing (DB) is common in adult patients with severe asthma with a reported prevalence of 19–52% (39, 48). There is good evidence that breathing retraining can improve asthma control and quality of life (87, 88). Much less is known about DB in children. A single study assessing dysfunctional breathing in a pediatric severe asthma clinic found that only 5.4% were found to have a breathing pattern disorder (51). It is likely that DB in under-recognized in children and in the broader population of children with difficult to treat to asthma the prevalence is likely much higher. A more comprehensive review of this topic can be found elsewhere in this supplement.

SMOKING

Although active cigarette smoking does not appear to be related to the development of adult onset asthma, it is associated

with asthma severity, frequent exacerbations and lung function decline (89, 90). Active smoking has been shown to reduce expression of histone deacetylase (HDAC2) via phosoinositide-3-kinase activation, leading to reduced glucocorticoid sensitivity (91). The same has also been found in children with severe asthma exposed to second hand smoke (92).

THE PATHOBIOLOGY OF SEVERE ASTHMA AND ASTHMA PHENOTYPES

Both pediatric and adult severe asthma are characterized by heterogeneity in clinical expression and underlying pathobiological features (**Table 2**).

In contrast to adults, where a female preponderance is very consistently seen, there is a male preponderance in childhood (47, 97). The increasing proportion of women with severe asthma through the life course is particularly seen in adolescence and around the time of the menopause suggesting a link with female sex hormones (98).

T2 HIGH AND T2 LOW ASTHMA

In 1958, Dr. Harry Morrow Brown published a seminal paper in the Lancet, which demonstrated that the clinical response to corticosteroids in adults with chronic persistent asthma was associated with the presence of eosinophils in sputum (99). This study was performed after the United Kingdom Medical Research Council subcommittee on clinical trials in asthma reported no advantage of cortisone acetate in the treatment of chronic asthma, which was a result which many, including Dr. Morrow Brown, found surprising (99). This outcome may have been due in part to the study design and reported outcomes but also in part to the inclusion of a heterogeneous patient population with a clinical diagnosis of asthma. Many years later, a study in adults using sputum samples induced with hypertonic saline also demonstrated that patients with asthma and a sputum eosinophil count $\geq$3% had a greater response to inhaled corticosteroids (ICS) compared to those with an eosinophil count <3% (100). Woodruff et al. (101) subsequently demonstrated that an IL-13 derived epithelial gene signature (periostin, serpin B2, and CCLA1) was associated with airway eosinophilia and upregulation of T-helper 2 (TH_2) cytokines IL-5 and IL-13 but importantly this was only seen in 50% of asthmatics who had withdrawn ICS. Further, reintroduction of ICS was again associated with an improvement in lung function in subjects with evidence of eosinophilia and upregulation of type-2 cytokines, but which importantly was not seen in those subjects without evidence of airway type-2 inflammation/eosinophilia. The authors coined the terms TH_2-high and TH_2_low asthma and reinvigorated the debate about non-eosinophilic asthma and importantly asthma, which is not responsive to ICS. The classical paradigm was that this process was predominantly driven by TH_2 cells however it is now recognized that there are other cellular sources of these cytokines and innate lymphoid cells and mast cells are potential sources of these pro-inflammatory cytokines (102, 103).

Asthma in children is predominantly an atopic disorder. Children with severe asthma are characterized by multiple aeroallergen sensitization, food allergy, high exhaled nitric oxide and progressive loss of lung function throughout childhood (47, 97, 104). Childhood severe asthma is predominantly eosinophilic with increased luminal (bronchoalveolar lavage) and tissue eosinophils (105). However, inflammatory phenotypes based on sputum are not stable in children (106). Furthermore, bronchoscopic studies have demonstrated an absence of TH_2 cytokines (105, 107) suggesting that airway eosinoplhia in children is mediated by relatively steroid resistance pathways. IL-33 remains elevated despite maximal steroid therapy (108, 109) and increased levels of innate lymphoid cells (ILCs) in children with severe asthma suggests a possible therapeutic target (110). Few studies in children have targeted eosinophils. The only study in children that based management on sputum eosinophils did not show a significant reduction in exacerbations (111), in contrast to benefit demonstrated in adult studies as described above (112).

Bronchoscopic studies in adults have provided rich evidence for underlying pathobiology of adult severe asthma and potential endotypes. Mechanistic studies in children are hampered by ethical constraints: samples from healthy controls have to be opportunistically collected from those having bronchoscopy for upper airway problems or a general anesthetic for an unrelated procedure and it is not possible to repeat bronchoscopies to assess the airway response to an intervention or challenge.

Recent data suggests that steroid resistant type-2 biology in adults is associated with older patients. There is likely to be a degree of overlap but our understanding of inhaled steroid resistant disease has been hampered by our prior failure to measure effective drug delivery in mechanistic studies (25, 113).

NON-T2 MECHANISMS IN SEVERE ASTHMA

A study using data form the National Asthma Research Programme in the United States demonstrated that subjects with mild to moderate asthma and no evidence of sputum eosinophilia (defined as sputum eosinophil count <2%) had no improvement in lung function with ICS but showed evidence of a bronchodilator response consistent with asthma (114). This study also identified that in ICS naive subjects 47% have no evidence of sputum eosinophilia in serial samples taken at various points over a 1-year period but this proportion increased to 72% in subjects currently taking ICS treatment. Taken together, these data suggests that substantial groups of patients with mild and moderate asthma have little evidence of type-2 cytokine driven airway eosinophilia (T2-low asthma) and by extension are likely to have little response to either initiation or escalation ICS treatment. Unfortunately, many patients who are unresponsive to inhaled steroids have their doses relentlessly increased, with no clinical benefit but substantial risk of harm.

McGrath et al. (114) also reported that the patients with non-eosinophilic mild asthma had less bronchial hyperresponsiveness than those with airways eosinophilia and Arron et al. (115) also

TABLE 2 | Comparison of phenotypes in adults and children with severe asthma.

Phenotype	Description	Adults	Pediatrics	Therapy
T2 high	High levels TH_2 cytokines (IL4, IL5, and IL13); biomarkers include airway and blood eosinophils, FENO, and periostin	More severe disease with higher risk of asthma attacks	Children with severe asthma are predominantly eosinophilic, although TH_2 cytokines may not be elevated	Steroid sensitive, anti IgE or anti IL4, IL5, or IL13
T2 low	Low levels of eosinophils, often associated with airway neutrophilia	Patients tend to be older; associated with low FEV_1 and air trapping, poor steroid response	Little evidence for T_2 low asthma in children; airway neutrophils may be protective; airway neutrophilia associated with infection	Macrolide antibiotics may have some benefit
Persistent airflow limitation	Low FEV_1 or FEV_1/FVC post bronchodilator, post steroid trial	40–60% with severe asthma, older age, longer asthma duration, smoking (93)	25% of children with severe asthma have PAL; associated with increase in airway smooth muscle (94–96)	Optimize long acting bronchodilators, down titrate steroids to lowest dose to control symptoms
Atopic	Sensitisation to aeroallergens and elevated IgE	Associated with early onset asthma persisting into adulthood	Most children are atopic and have co-morbid atopic diseases	Steroid responsive; T_2 targeted therapies as above

demonstrated an inverse relationship between an IL13-high gene signature (T2-high asthma) and bronchial hyperresponsiveness suggesting that T2-low/non-eosinophilic disease is associated with less physiological abnormalities. This is supported by data which suggest that non-eosinophilic asthma is associated with lower risk of asthma exacerbation and there is strong evidence that surrogate biomarkers of type-2 airways inflammation (blood eosinophil count, FeNO, serum ECP, and serum periostin) are all prognostic biomarkers for exacerbation (116–118). In addition, elevated blood eosinophil count and FeNO have consistently been associated with a higher exacerbation rate in the placebo arms of clinical trials in patients with severe asthma unselected on the basis of a pre-stipulated biomarker threshold (119–121) This would suggest that within severe asthma populations, defined using usual diagnostic and treatment criteria, there are subjects with little evidence of active T2-driven disease (type-2 biomarker low), who are persistently symptomatic and defined as uncontrolled asthma, but who have a comparatively low exacerbation risk. However, it is important to comment that severe asthma exacerbations still occur in these symptom high type-2 biomarker low patients albeit at a much lower rate.

It is recognized that ICS will down-regulate type-2 inflammation and related biomarkers (122, 123) and is thus an important confounder in subjects with more severe asthma on ICS treatment raising two important issues—firstly, whether true T2-low asthma exists in more severe asthma, when corticosteroids are down titrated and secondly, what is the mechanism of persistent symptoms in subjects with asthma when type-2 corticosteroid responsive asthma is not present. As discussed above, "true" T2-low asthma appears to be relatively common in mild asthmatic subjects but is generally associated with mild symptoms, less bronchial hyperresponsiveness and a lower risk of asthma exacerbation compared to subjects with T2-high disease. Intuitively, it seems improbable that this group of patients would be progressed to high dose ICS treatment, however if symptoms are persistent and not ICS responsive as appears to be the case, it is possible that some of these patients may be escalated to high intensity treatment to try and improve their symptoms. The issue of whether true T2-low asthma exists in severe asthma is currently being explored in the RASP-UK programme, where patients are having corticosteroids "down titrated" if their biomarkers of T2-driven disease are low (124).

The neutrophilic phenotype is not seen consistently in children (106) and there is evidence to suggest that airway neutrophils may be protective (125) and very little is known about T2 low asthma in children (if it exists at all).

Non-atopic clinical phenotypes described in adults including those associated with sensitivity to non-steroidal anti-inflammatories and nasal polyposis are rare in childhood.

AIRWAY REMODELING

Airway remodeling starts early in childhood asthma. Although no differences in reticular basement membrane (RBM) thickness were seen in infants with respiratory symptoms with or without evidence of reversible airflow obstruction at a median 1 year of age (126) by a median of 3 years there were significant differences between those with troublesome wheeze and healthy controls (127) and by school age the changes were consistent with those seen in adult severe asthma (128). Interestingly, only increased airway smooth muscle in pre-schoolers predicted the persistence of asthma at school age (129). Almost a quarter of children with severe asthma have persistent airflow limitation (PAL), defined as post systemic post-bronchodilator z score ≤ -1.96 for FEV_1 (94, 97). In adults this rises to almost 50% and is associated with older age, longer duration of asthma symptoms and airway eosinophilia (93). In children there appears to be no association between PAL and eosinophilic inflammation although there is evidence of an increase in airway smooth muscle surface area and mass in those with PAL (95, 96).

MANAGEMENT

As previously discussed, the first stage of management is the confirmation of the diagnosis of severe asthma and the comprehensive assessment and modification of co-morbidities and factors driving persistent symptoms and asthma attacks. For who remain poorly controlled following this assessment and remain on high intensity conventional treatment (high dose ICS as defined above, plus additional add on treatments including LABA, LRTA or theophylline or maintenance OCS) there is an exciting pipeline of targeted treatments which predominantly target the type-2 cytokine axis including IL-4, IL-5, and IL-13 causing IgE production and eosinophilic inflammation (130, 131).

Omalizumab, the monoclonal antibody to IgE, was the first biologic licensed in the United Sates (US) in 2003 in adults and children (>12 years) and by 2009 it was approved in the US and Europe for all patients with asthma from the age of 6 years. The last 3 years have seen an acceleration in the number of Phase 2 and 3 studies and the licensing of new drugs. The choice of biologic depends on the patient's age, weight, IgE evaluation (both total and specific), degree of eosinophilia and route of administration. The Global initiative for Asthma (GINA) has recently produced a pocket guide to aid the physician in determining the most appropriate treatment for the individual (4).

OMALIZUMAB

Omalizumab is a recombinant antibody to IgE that diminishes free IgE levels and prevents IgE binding to mast cells and basophils, thus inhibiting degranulation and release of proinflammatory mediators. Studies in adults and children have demonstrated benefit, particularly in terms of reduction in exacerbations (132). The dose is based on IgE level and weight. Approximately 25% of children have an IgE level outside the licensed range and for those at the upper end of the range it may entail 2 weekly injections (97) and additionally adults may not qualify without sensitization to an aeroallergen. The frequency of these scheduled visits must be balanced against a reduction in attacks and hence unscheduled time off school and work. In children omalizumab has also been used seasonally to attenuate the September peak in asthma attacks (133) and this approach showed greatest utility in children on the higher treatment steps. In a randomized withdrawal study, after long-term treatment with omalizumab, patients on omalizumab did better than those randomized to placebo suggesting continuation of omalizumab results in continued benefit and does not support a disease modifying effect of this treatment (134).

DRUGS TARGETING IL-5—MEPOLIZUMAB, RESLIZUMAB, AND BENRALIZUMAB

Mepolizumab is a humanized monoclonal antibody to IL-5 that inhibits eosinophilic maturation and activation. The DREAM and MENSA studies recruited patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of inhaled glucocorticoids and demonstrated a reduction in asthma attacks in those randomized to mepolizumab (135, 136). In subjects with increased blood eosinophil levels, greater efficacy was seen with additional improvements in lung function and symptoms. Although adolescents were recruited for the licensing studies the data were not reported separately and there are no specific pediatric randomized controlled trials. The results of an open label pharmacokinetics and pharmacodynamics study in children aged 6–12 years are awaited (137). Despite this, mepolizumab has recently been licensed by the European Medicines Agency (EMA) for use in patients with severe asthma from 6 years of age. Two further drugs targeting the IL-5 axis have recently been licensed by the EMA for adults: reslizumab and benralizumab. Reslizumab has a similar mode of action to mepolizumab. It binds to IL-5 thus reducing IL-5 mediated maturation and trafficking of eosinophils from the bone marrow as well as inhibiting mediator release and eosinophil apoptosis. It is given by 4 weekly intravenous infusion and demonstrated a significant reduction in exacerbations in the reslizumab arm compared to placebo (138). It is licensed by the Food and Drug Administration (FDA) and EMA for use in adults only and notably studies using a fixed sub-cutaneous dose of 110 mg were negative (139, 140). Benralizumab binds to the IL-5 receptor and in addition to inhibiting growth and activation of eosinophils benralizumab also binds to the Fc receptor on natural killer cells and induces antibody dependent cell mediated cytotoxicity leading to apoptosis of eosinophils. In clinical trials benralizumab led to decreased exacerbations, improved lung function and enhanced quality of life (141, 142). It is theoretically more effective than other IL-5 blockers which allow IL-5 independent migration of eosinophils into the tissue, although superior efficacy was not evident in clinical trials to date and the results of targeting the IL-5 axis seem broadly consistent with reduced exacerbation rates (rescue OCS $\geq$ 3 days) by approximately 50% and more modest improvements in symptoms and asthma-related quality of life measured and lung function (143). Benralizumab and mepolizumab have also been shown to reduce oral corticosteroid dose compared to placebo with a parallel reduction in exacerbation rate in adult subjects with severe asthma on maintenance oral corticosteroids (144, 145). It also has the advantage of being given every 8 weeks after the initial three, four weekly injections. The FDA have licensed benralizumab for use as an add on treatment for patients with eosinophilic asthma aged 12 years and above. In Europe it has been licensed by the EMA for use in adults only.

DUPILUMAB

Dupilumab binds to the IL-4 receptor-α blocking signaling of IL-4 and IL-13, thus reducing IgE production and eosinophil recruitment. Phase 3 studies have demonstrated a significant reduction in severe exacerbations (47.7% reduction for 200 mg dupilumab compared to placebo, $p < 0.001$) and additionally

demonstrated lung function improvement which was evident early after treatment initiation (at week 12, FEV_1 increased 0.14 liters compared to placebo, $p < 0.001$) (120). Dupilumab treatment also resulted in a significant reduction in OCS in adult subjects with severe asthma on maintenance OCS treatment (70.1% with dupilumab vs. 41.9% in the placebo group ($p < 0.001$) with a 59% lower exacerbation rate than placebo and mean increase in FEV1 of mean 0.22 liters more than placebo (146). It was licensed in October 2018 by the FDA and in May 2019 by the EMA for use in patients with severe eosinophilic asthma from 12 years of age. It also has a license for treatment of severe atopic eczema and will clearly be a useful treatment in patients with both conditions.

It is disappointing that no data from pediatric specific randomized controlled trials have been presented for mepolizumab, reslizumab, benralizumab or dupilumab and there has been no separate analysis of the adolescents recruited for these studies (likely because of insufficient numbers for meaningful subgroup analysis). Given the challenges recruiting to the MARS trial as discussed above (24), and the inference that there are relatively small number of children who have uncontrolled asthma when adherent with standard of care inhaled treatment, it is acknowledged that the feasibility of any such study is challenging and the need for international collaboration essential (147, 148). None-the-less the majority of these drugs have been licensed by the FDA and EMA for 12 years and older and in the case of mepolizumab by the EMA for use from the age of 6 years. In view of the limited add on choices for children with severe asthma, the addition of an increasing number of biologics is to be welcomed. It will be important to use "real-world" outcome data to identify if similar efficacy is seen in pediatric cohorts and to identify markers of response (149). In addition, it has become clear that there is substantial overlap in the populations for these new biologic therapies and randomized pragmatic head to head comparisons between the various biologics will potentially identify which patients should be treated with each drug (149, 150).

SUMMARY

There is heterogeneity both within and between pediatric and adult severe asthma. Although there is overlap between the two there are a number of differences in clinical expression and disease mechanisms in children and adults. The impact of the growing lung and developing immune system is likely to account for some of the observable differences however, much remains poorly understood, including the natural history of asthma; adult onset vs. childhood onset disease; and the impact of early life influences (including in utero). Studies such as the Unbiased Biomarkers for the PREDiction of respiratory outcomes (U-BIOPRED) marks a step change in asthma research. Cohorts of preschool, school aged and adults with severe asthma (45, 46) were recruited to this multi-omics study which aims to define phenotypes and endotypes of severe adult and pediatric asthma and preschool wheeze and compare these groups across the life course. In the meantime, there remain a number of unmet needs in the management of severe asthma. Expensive biologics are available to only the minority of patients with severe asthma globally; there is an ongoing disease burden both in terms of asthma related morbidity and mortality and corticosteroids, the mainstay of treatment for many, have an unacceptable side effect profile. Finally, there is the absence to date of any disease modifying treatments. The window of opportunity for such an intervention is likely to lie in very early childhood and therefore to improve the care of all patients with severe disease, there needs to be investment and a focus on research in young children.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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REVIEW
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Genetics and Gene-Environment Interactions in Childhood and Adult Onset Asthma

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Asthma is a heterogeneous disease that results from the complex interaction between genetic factors and environmental exposures that occur at critical periods throughout life. It seems plausible to regard childhood-onset and adult-onset asthma as different entities, each with a different pathophysiology, trajectory, and outcome. This review provides an overview about the role of genetics and gene-environment interactions in these two conditions. Looking at the genetic overlap between childhood and adult onset disease gives one window into whether there is a correlation, as well as to mechanism. A second window is offered by the genetics of the relationship between each type of asthma and other phenotypes e.g., obesity, chronic obstructive pulmonary disease (COPD), atopy, vitamin D levels, and inflammatory and immune status; and third, the genetic-specific responses to the many environmental exposures that influence risk throughout life, and particularly those that occur during early-life development. These represent a large number of possible combinations of genetic and environmental factors, at least 150 known genetic loci *vs.* tobacco smoke, outdoor air pollutants, indoor exposures, farming environment, and microbial exposures. Considering time of asthma onset extends the two-dimensional problem of gene-environment interactions to a three-dimensional problem, since identified gene-environment interactions seldom replicate for childhood and adult asthma, which suggests that asthma susceptibility to environmental exposures may biologically differ from early life to adulthood as a result of different pathways and mechanisms of the disease.

Keywords: asthma, genetics, environmental exposures, gene environment interactions, childhood, adulthood

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INTRODUCTION

Asthma is characterized by a significant heterogeneity in relation to age of onset, clinical manifestations, genetics, environmental risk factors, response to treatments, and prognosis. Asthma affects as many as 339 million people worldwide (1), of whom 33% are under the age of 14, 27% are adults who first experienced symptoms in childhood (2), and 40% adult-onset cases. What proportion of this last group has the same underlying disease processes acting as in the first two groups? Is the "Dutch" hypothesis of a continuum from asthma to chronic obstructive pulmonary disease (COPD) a better description? (3). Similarly, there is much current interest in the relationship between childhood asthma and obesity. It has been suggested that obesity might affect childhood and adult-onset asthma by separate pathways (4), but evidence for this is still

patchy. Allergy plays a key role in childhood-onset asthma, and these subjects more frequently have atopic dermatitis, hay fever and a family history of atopy in comparison to those who develop asthma in adulthood (5). Adult-onset asthma is characterized by reduced lung function and poor prognosis (6). So what proportion of adult-onset asthma has an atopic contribution? Our current understanding is that we need to comprehend both genetic factors, environmental exposures and their interactions.

Asthma runs strongly in families and estimates of its heritability range from 35 to 70%, showing higher estimates among boys and early-onset cases (7, 8). The study of asthma genetics has offered the possibility of understanding the causes and biological mechanisms of the disease as well as the identification of potential targets for treatment, although identified multiple loci only explain a limited proportion of asthma heritability (9).

Differences in rates of asthma between countries and its increasing prevalence in the past few decades clearly suggest that environmental exposures have an important role on asthma occurrence. Environmental risk factors of asthma include exposure to tobacco smoke, farm animals and related products, domestics cats, respiratory viral infections, microbial exposures, dietary factors, breastfeeding, medication, occupational exposures, indoor and outdoor air pollution, and diverse allergens (10). Environmental exposures, including those beginning in early life, play a pivotal role and the exact timing of exposure at critical windows of development influences genetic specific responses and individual risk trajectories that ultimately lead to the development of asthma (11, 12). Gene-environment interaction studies aim to explain how the strength and direction of associations between certain genetic variants and asthma may depend on given environmental exposures, and *vice versa*, and might explain in part the hidden heritability of asthma.

In the light of clinical and epidemiological importance of asthma and the potential benefits of further research into its etiology, this review will provide an overview on current understanding of genetics and gene-environment interactions in childhood and adult onset of the disease.

GENETICS OF CHILDHOOD AND ADULT ONSET ASTHMA

We first examine evidence from: (a) multivariate family based studies, where two traits e.g., childhood-onset asthma and adult-onset asthma are measured in the same family and the correlations between family members (who might be twins) across traits are interpreted; (b) the counting of overlapping genome-wide significant simple nucleotide polymorphism (SNPs) regression results from genome-wide association studies (GWAS) of each trait; (c) the accuracy of a genetic risk score generated from a GWAS of one trait in predicting the second trait in a second GWAS; (d) methods combining all SNPs from two GWAS to estimate the genetic correlation between traits; and (e) Mendelian Randomization (MR) studies of asthma risk factors, where genetic variants affecting the risk factor are tested for an association for asthma, thus increasing evidence of causation between the risk factor and asthma.

Childhood-onset asthma is most commonly accompanied by atopy. We know from a myriad of family-based studies, and now from large genotyping studies of unrelated individuals, that the diseases of the atopic triad are strongly heritable, and genetically correlated. Heritability is a measure of what proportion of trait differences between individuals in a given population are due to causative genetic differences between those individuals (13). Being a proportion, interpretation must be fastidious. For example, in developed countries asthma incidence has increased several-fold over the last 100 years, which must be due to changing environmental exposures. However, heritability estimates have remained roughly constant (14), which implies that average difference between individuals in environmental exposures has not greatly changed (else the genetic proportion of difference would be diluted), and that these exposures affect all genotypes equally at the first approximation. This puts an upper limit on the importance of gene-environment interactions at the population level, but the niceties would take too long to explain. A genetic correlation is also a proportion, comparing the genetic contribution (in the sense above) shared by two traits to those that are unshared. The correlation may well be via a mechanistically uninteresting causative chain e.g., the genetic correlation ($r_g = +0.21$, SE $= 0.03$) (15) between asthma and depression in the UK Biobank population might be mediated by atopy genes predisposing to chronic asthma, which is depressing for some individuals due to limiting effects on lifestyle. The latter might be suggested by the fact that the genetic correlations for Type 2 diabetes and depression, BMI and depression, myocardial infarction and depression, and schizophrenia and depression are all of a similar magnitude.

The concepts of heritability and genetic correlation come from the theory of inheritance for quantitative traits which are assumed to be (roughly) normally distributed. The extension to binary traits such as asthma requires modification of this model for use in a logistic or probit regression framework.

These methods deal easily with the usual case for complex diseases of very many contributing genes and can be calculated via trait correlations in pedigrees (including monozygotic—MZ, and dizygotic—DZ twins), as well as by measuring genotype-trait association directly (i.e., genome-wide association studies). They have a straightforward mathematical relationship to other measures such as the MZ twin recurrence risk ratio—the expected risk of disease of individuals genetically the same as asthma cases vs. whole population baseline risk (**Figure 1**).

Recently, we have seen the development of statistical methods to estimate heritability and genetic correlations in genome-wide association studies (GWAS) of multiple traits within the same study population, and even by combining separate univariate analyses of different populations using just summary data. These include the GCTA-COJO (16), LDAK Sumher (17), HESS (18) and LD score regression approaches (19). These approaches model contributions of loci of small effect that will not reach genome-wide statistical significance ($P < 5 \times 10^{-8}$) when tested one SNP at a time. Family-based methods will better estimate contributions of rare alleles, or alleles that are not well-measured

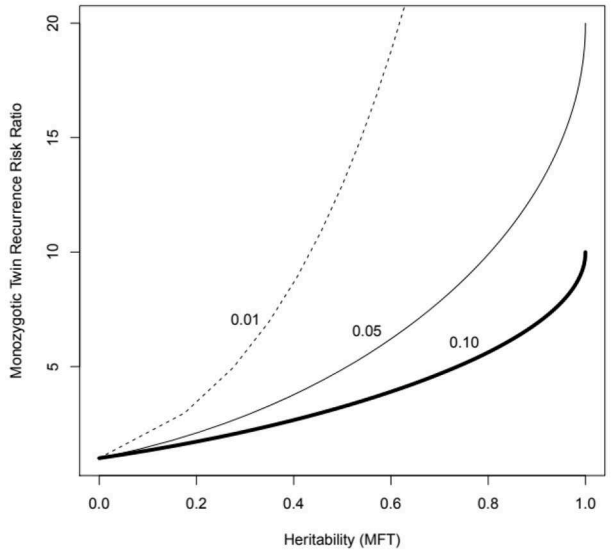

FIGURE 1 | MZ twin recurrence risk ratio vs. heritability under the multifactorial threshold model (probit-normal mixed model, MFT) for three levels of population prevalence (1 to 10%), which might represent asthma of different levels of severity. Note that the recurrence risk ratio is bounded by the trait prevalence (e.g., cannot exceed 10 if the prevalence is 10%). The recurrence risk to an ordinary sibling will correspond to the value for half the heritability (the kinship coefficient for sibs is 0.5).

by a particular set of genetic markers e.g., on a given SNP array, but sample sizes will usually be smaller when compared to genotyping studies of unrelated individuals.

In the case of Mendelian Randomization (MR) and related methods, the pattern of correlations between two traits and a measured SNP is interpreted knowing that genotype is both fixed at birth and largely unaffected by external confounders (ethnic confounding can be controlled for). MR analyses can involve one SNP at a time, a set of known associated SNPs from other studies, or whole genome; they can be bidirectional; and one of the traits can be gene transcript or expressed protein levels, simultaneously confirming the SNP to have biological effects on an intermediate trait and pointing to biological mechanisms for the trait-SNP correlation.

Family Based Studies

A variety of recent studies generally confirm that the heritability of childhood-onset asthma is high, and that this tends to be higher than that of later-onset asthma (**Table 1**). The classical twin studies of children, where the family members being utilized are exactly the same age and birth cohort, tend to give the highest estimates. It should be noted that studies do not find an increased prevalence of asthma in twins, particularly MZ twins, especially after adjusting for covariates such as birth weight (20). Thomsen et al. (21) were able to break down that twin sample by age at onset of asthma, and found the heritability for onset after age 20 to be 60%, compared to 80% in younger twins. And data reported by Paaso et al. (5) can be reanalyzed to estimate the genetic correlations between parental allergy and adult-onset and childhood-onset offspring asthma (first two entries of

TABLE 1 | Heritabilities of asthma from different studies using different designs and statistical methods.

Trait	Heritability	References	Study type
Asthma (<12 y.o.)	0.82 (0.79–0.85)	(20)	Twin study (12635 pairs)
Asthma (<20 y.o.)	0.78 (0.72–0.84)	(21)	Twin study (9051 pairs)
Asthma (>20 y.o.)	0.58 (0.58–0.82)	(8)	Twin study (11147 pairs)
Asthma (<13 y.o.)	0.46 (0.4–0.5)	(5)	Family study (1623 families?)
Asthma	0.42 (0.41–0.43)	(22)	Family study (128989 families, 481657 individuals).
Asthma	0.47 (0.23–0.72)	(23)	GWAS Bayesian mixture linear mixed model
Asthma (UKBB)	0.38 (0.35–0.41)	(24)	GWAS linear mixed model (GCTA)
Asthma (UKBB)	0.34 (0.32–0.36)	(25)	GWAS moment-matching LMM
Asthma (UKBB)	0.07 (0.05–0.08)	(26)	GWAS LD regression
Childhood-onset Asthma (UKBB)	0.004 (0.001–0.007)	Neale, 2018[a]	GWAS LD regression
Asthma onset (UKBB)	0.0 (−0.009 – 0)	Neale, 2018[a]	GWAS LD regression

[a] *http://www.nealelab.is/uk-biobank/.*

Table 2). These give a consistent pattern, where the allergy early-asthma correlation is higher, but there is still a significant genetic correlation between atopy and later-onset asthma.

The heritability estimates based on GWAS (**Table 1**) tend to be lower, given they only represent the contributions of common measured SNPs ("array," "chip," or "SNP" heritability). Even so, the estimates from LD regression seem to be lower again.

Overlap of Identified Causative Loci

The Trans-national Asthma Genetic Consortium (30) compared SNP allele frequencies in 24,000 asthma cases and 119,000 controls to detect 22 asthma associated loci. The locus of greatest effect was that on chromosome 17q21 in the region of *GSDMB* and *ORMDL3* genes. It has been known since 2008 (31) that this locus is associated with childhood onset asthma. Despite the association with early onset disease, these SNPs are not associated with atopy, and the asthma-increasing alleles probably reduce risk of other immunological conditions such as inflammatory bowel disease and Type 1 diabetes. If we take one of the functional 17q21 SNPs rs12936231 (actually within ZPBP2), in the UK BioBank the C allele increases "all" asthma OR = 1.1 ($P = 1 \times 10^{-59}$) and self-reported "emphysema/chronic bronchitis" OR = 1.07 ($P = 1 \times 10^{-8}$, but not doctor-diagnosed emphysema, $P = 0.5$), as well as neutrophil count ($P = 7 \times 10^{-142}$), but less strongly with eosinophil count ($P = 3 \times 10^{-5}$) (32). The effect sizes of these alleles are not large,

TABLE 2 | Genetic correlations between asthma and related traits.

Trait 1	Trait 2	Genetic correlation	References	
Allergy (Espoo)	Childhood Asthma (Espoo)	∼0.75	(5)	Family study
Allergy (Espoo)	Later Asthma (Espoo) >13 y.o.	∼0.5	(5)	Family study
All Adult Asthma (UKBB)	Asthma (GABRIEL)	0.66	(26)	GWAS based LD regression
All Adult Asthma (UKBB)	Allergic Diseases (UKBB)	0.75	(26)	GWAS based LD regression
Asthma (GABRIEL)	Allergic Rhinitis	0.60	(27)	GWAS based LD regression
All Adult Asthma (UKBB)	Eosinophil count (UKBB)	0.45	(15)	GWAS based LD regression
All Adult Asthma (UKBB)	BMI (UKBB)	0.21	(15)	GWAS based LD regression
Childhood Asthma (GABRIEL)	BMI (GIANT Consortium)	0.19	(28)	GWAS based MoM method
All Adult Asthma (UKBB)	FEV_1/FVC (UKBB)	−0.30	(15)	GWAS based LD regression
Adult Asthma	COPD	0.38	(29)	GWAS based LD regression

so general inferences about childhood vs. adult asthma must be based on aggregated effects of multiple loci.

Demenais et al. (30) also confirmed the association of rs9272346 and rs9273349 in the region of HLA-DQ with asthma. These SNPs were reported more strongly correlated with adult-onset than childhood-onset disease (9, 33), but still exhibiting detectable association in early-onset cases. Like the 17q21 locus, are unrelated (or only weakly associated) to atopy. In the UKBB (32), the rs9272346*A allele increases incidence of asthma, coeliac disease, Type 1 diabetes, hypothyroidism, rheumatoid arthritis, and diminishes risk of multiple sclerosis and ulcerative colitis. It has no association with self-reported COPD. Pividori et al. (34), see below, classify it as shared by childhood and adult onset asthma in UKBB.

Ferreira et al. (35) carried out a GWAS meta-analysis (13 studies, total $N = 360838$) to detect 99 loci (136 peak SNPs) for atopic disease, defined as any of asthma, hayfever or atopic dermatitis. Of these, 49 were novel. Several loci were disease-specific, such as Filaggrin (FLG) for atopic dermatitis, or a SNP near IL18R1, where the effect allele was increased in asthma and hayfever, but not atopic dermatitis. Several variants were associated earlier onset of asthma (7445 asthma-only cases)—the strongest being rs921650 in GSDMB (17q21 region).

Pividori et al. (34) and Ferreira et al. (36) have recently reported on childhood and adult onset asthma within the UK Biobank (UKBB) sample. Pividori et al. were able to detect 61 independent asthma loci comparing 9433 childhood-onset cases, 21564 adult-onset cases, and 318237 controls. Of these, "23 were childhood onset specific, one was adult onset specific, and 37 were shared." Ferreira and coworkers supplemented the UKBB data with data from 23andMe (further 32,000 childhood-onset cases and 215,000 controls) and reported 123 childhood-onset (age <20 years) asthma loci, of which 98 were reproducible in the second dataset. Five of these loci did not affect risk of adult-onset asthma. For adult-onset asthma, they found 34 replicable loci, of which 3 were significantly weaker as predictors of childhood disease. They estimated the genetic correlation between adult and childhood-onset asthma as 0.67. They further tested for loci specifically for age at diagnosis within their childhood-onset sample (defined as < 20 years old) and concluded that such effects were relatively small (5% of variance, $P = 0.02$; but N was only 14,000, so power was low). There were 25 novel childhood-onset asthma loci detected, in or near biologically important genes such as *NOD2*, *IL4R*, *IL2RA*, and *IRF4*. Because the UKBB dataset is generally available, we can contrast these findings to those published by Zhu et al. (26) who reported a total of 38 loci for "doctor diagnosed" asthma detectable using an earlier available version of the dataset containing 7908 cases and 76768 controls, and Johansson et al. (24) who reported 52 loci defined via 41934 cases and 239773 controls (**Figure 2**). The "pure" adult-onset SNP reported by Pividori et al. was rs12617922 on chromosome 2 near *TEX41,* which decreased risk of tobacco smoking ($P = 5 \times 10^{-24}$), as commented on by Ferreira et al. (36). **Figure 3** shows that such a strong negative association is not seen for any of the other asthma loci from Zhu et al. (26). A SNP in the same region near *TEX41*, rs10193706, was previously highlighted as associated with tobacco use in the subset of UKBB used for the BiLEVE study of COPD (37). In European populations, it is in moderate linkage disequilibrium with rs12617922 ($r^2 = 0.37$), but not associated with self-reported asthma in the full UKBB sample.

An even more intriguing observation is that the peak SNP for this region in terms of "any" asthma and smoking (and suggestively with caffeine intake as well) is rs10427255, previously flagged as a locus for the photic sneeze reflex ($P = 1 \times 10^{-11}$) by Eriksson et al. (38) in the 23andMe dataset (see **Table 3**). These SNPs (rs12617922, rs10427255) are not associated with serum eosinophil level or atopy. Of the 32 SNPs known to be associated with photic sneeze reflex, only these near *TEX41* predict asthma, so there is no general relationship between these two phenotypes.

Hobbs et al. (29) examined COPD in 25000 cases and 58000 controls. There were 22 associated loci (13 novel), none overlapping with asthma loci from the GABRIEL study or the NCBI GWAS catalog. Examining the UK BioBank via the GeneAtlas web site (32), one does find that five of their top COPD SNPs are associated with self-reported asthma at $P < 1 \times 10^{-5}$. The strongest association of these five is for rs2070600 (a protein coding change Gly82Ser in AGER on chromosome 6, $P = 4 \times 10^{-29}$), where the T (Serine) allele (European frequency 5–10%) increases asthma (OR = 1.15). The Hobbs et al. (29) result for COPD is OR = 1.21 ($P = 6 \times 10^{-10}$) for the C (Glycine) allele, so (if replicable) this would lead to a negative genetic correlation between asthma and COPD due to this locus. The Ser82 allele reduces sRAGE levels and increases FEV1 (39).

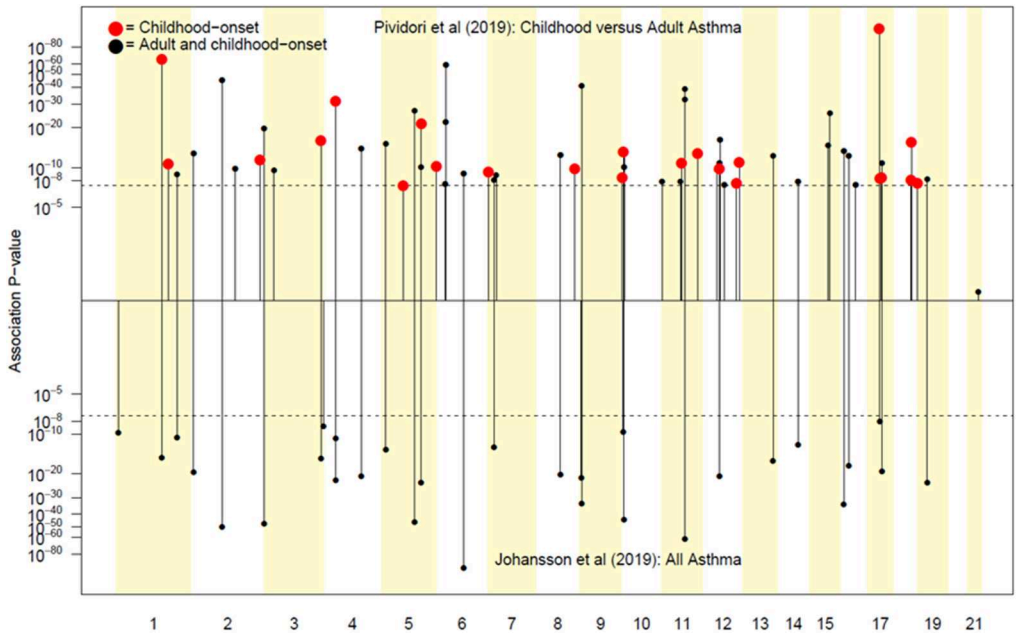

FIGURE 2 | Top association peaks from Pividori et al. (34) and Johansson et al. (24).

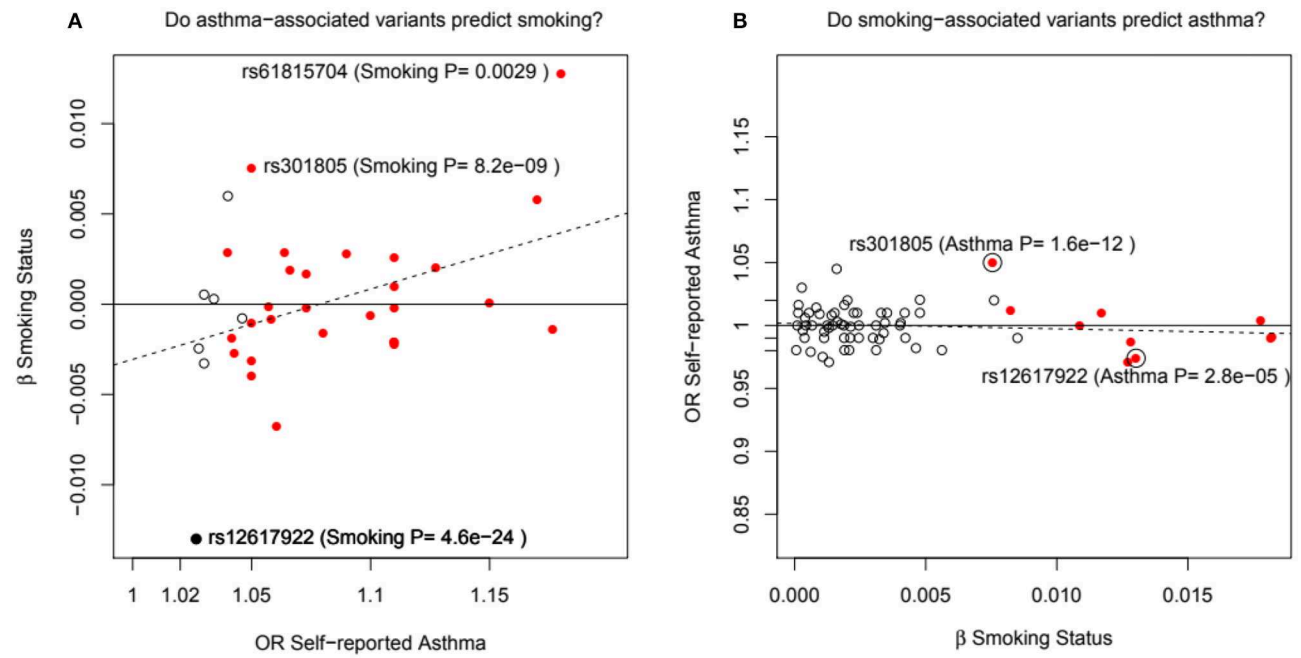

FIGURE 3 | In **(A)**, the adult asthma SNP, rs12617922, from Pividori et al. (34), and all top asthma SNPs from Zhu et al. (26) vs. their relationship to smoking status in the UK Bio Bank analysis of Canela-Xandri et al. (32). Red color denotes an asthma association *P*-value in Canela-Xandri et al. (32) $<5 \times 10^{-8}$. For smoking status, only the *P*-values for rs12617922 and rs301805 are $<5 \times 10^{-8}$. The rs301805 SNP also shows a strong association with eosinophil count, and was flagged by Ferreira et al. (35) as an allergy locus. In **(B)**, smoking-associated SNPs [GWAS Catalog 2018] are tested—red color now denotes a smoking association *P*-value in Canela-Xandri et al. (32) $< 5 \times 10^{-8}$.

Hayden et al. (40) describe the COPDGene study of 10200 current and former adult smokers. The GWAS analysis found known childhood asthma risk SNPs were associated with asthma, and childhood asthma (7% of the sample) increased the risk of later COPD 3.4-fold, and also reduced lung function.

TABLE 3 | Association between SNPs on chromosome 2q22.3 with self-reported asthma, tobacco use and coffee intake in the UK Biobank (32).

SNP	Build 37 position	Allele	LD in Europeans (r^2)			Smoking status		Current smoking		Coffee drinking		Self-reported asthma	
						Beta	*P*-value	Beta	*P*	Beta	*P*	OR	*P*
rs1533426	146119018	G	1			−0.013	1.0e-22	−0.0050	4.9e-06	−0.015	3.9e-05	1.03	8.4e-06
rs10427255	146125523	T	0.74	1		−0.013	9.5e-23	−0.0051	4.0e-06	−0.018	4.0e-05	1.03	6.9e-06
rs12617922	146156679	A	0.55	0.48	1	−0.013	4.6e-24	−0.0053	1.5e-06	−0.019	3.2e-06	1.03	2.8e-05
rs10193706	146316319	C	0.32	0.18	0.37	1	−0.013	8.9e-24	−0.0056	3.6e-07	−0.025	1.6e-09	1.02	0.01

Both rs1533426 and rs10427255 (38) are associated with the photic sneeze reflex and rs10193706 was previously associated to heavy cigarette smoking (37).

TABLE 4 | Application of SNP-based Risk Scores derived for one trait to predict a second trait from http://mrcieu.mrsoftware.org/PRS_atlas/ (41).

PRS trait	Second trait	N SNPs	Beta	*P*-value
Cigarettes/d	Asthma	44	0.004	0.43
Asthma	Cigarettes/d	42	−0.001	0.82
BMI	Asthma	251	0.025	4.1×10^{-6}
Asthma	BMI	42	0.002	0.23
Asthma	"Chronic bronchitis/ emphysema"	42	0.050	2.6×10^{-4}
Major depression	Asthma	37	−0.005	0.37
Asthma	Depression	42	0.004	0.62

The P-values test significance of the regression of the PRS on the second trait.

Genetic Risk Scores

The components of the polygenic risk score (PRS) approach have already been presented (e.g., **Figure 3**), in that the PRS for a trait is merely the weighted sum of the regression coefficients for a number of significantly associated SNPs. Richardson et al. (41) have made available a web site presenting results of such cross-trait analyses (162 PRS, 551 outcomes) using the UK Biobank dataset (see **Table 4**). For example, while the BMI PRS predicts asthma, the asthma PRS does not predict BMI, a finding we can interpret as implying BMI is causative of asthma risk.

A table of results for COPD PRS (spirometric phenotypes including FEV1/FVC were used to define COPD) has been presented by Shrine et al. (42) in yet another preprint. This score (294 SNPs) is a significantly predictor of self-reported asthma ($P = 10^{-41}$). Examining the individual SNPs, we can see that 20 are significant ($P < 1 \times 10^{-5}$) independent predictors of UKBB self-reported asthma, and three are associated with hayfever/rhinitis (in *IL1RL1, SUOX* and *LRP1*).

GWAS Genome-Wide Estimates of Genetic Correlations

The most widely used approach for this is the LD score regression method, and results from this are listed in **Table 2**. Speed and Balding (17) suggest that magnitude of estimates of genetic correlations tend to relatively similar across different methods, which is less true of heritability estimates, as seen above. We see that "any" asthma is more strongly correlated with atopic diseases such as allergic rhinitis (r_g 0.6–0.7) than it is with COPD (r_g 0.4).

Mendelian Randomization Studies

Chen et al. (43) carried out a bidirectional MR analysis of the direction of causation between obesity and childhood asthma in Taiwan. While the obesity genetic risk score was a significant predictor of asthma, the asthma genetic risk score did not predict obesity. Granell et al. (44) similarly estimated the causal relative risk for the effect of BMI on asthma at 1.55 per kg/m^2, slightly more strongly for non-atopic childhood asthma. In 162124 adults from European studies (45), the causal OR for BMI on asthma was 1.07 (−9 ml FEV1, 16 ml FVC). There was no causal effect on allergic sensitization or serum IgE level—despite a positive phenotypic correlation between IgE and overweight in their study

population. After all the above, however, Contreras et al. (46) found in a traditional longitudinal study that asthma diagnosis by age 4 was associated with obesity at age 8, which would seem consistent with the idea that asthma causes obesity, or at the very least that genes causative of asthma also cause obesity via a different pathway (acting at a different age) than that by which they cause asthma. Does this give an insight into adult-onset asthma? Multiple longitudinal studies in adults have found that overweight precedes and predisposes to asthma. Burgess et al. (47) showed BMI at age 7 years predicted development of asthma with an onset after age 21 years. So, in this case a causal pathway from overweight to asthma would be supported by both genetic and non-genetic studies.

Finally, the relationship between vitamin D deficiency and childhood and adult asthma is still unclear, with both cross-sectional epidemiological and animal model evidence making this plausible but results from supplementation studies unsupportive (48). MR studies (49, 50) have showed no relationship between vitamin D level SNPs and asthma or atopy.

GENE-ENVIRONMENT INTERACTIONS IN CHILDHOOD AND ADULT ONSET ASTHMA

The most frequently evaluated genetic-environment interactions on asthma include early-life and lifelong exposure to tobacco smoking, outdoor air pollutants, indoor exposures, a farming environment, and microbial exposures. The vast majority of the studies have applied a candidate gene approach and generally examined genes involved in antioxidant defenses, detoxification, inflammation, innate immunity, lung development, and epithelial function. Some investigations are based on family studies and few hypothesis-free studies, also called genome-wide interaction studies (GWISs), are available yet (**Table 5**).

Tobacco Smoking Exposure

This is the most well-studied environmental exposure with respect to genetic interactions in asthma in humans. Family studies have shown regions of linkage to asthma phenotypes to differ by environmental tobacco smoke (ETS) exposure in childhood (51–54). A study in 144 US families suggested that genes in chromosomal regions 1p, 5q, and 17p might interact with ETS to confer asthma risk in the exposed groups (51). The evidence for linkage for asthma and bronchial hyperresponsiveness (BHR) for chromosome 5q in the passive smoke-exposed groups during childhood was subsequently replicated in 200 Dutch families (52). A French study conducted in 295 families reported four regions, 1q43-q44, 4q34, 5p15, and 17p11, potentially involved in genetic susceptibility to BHR interacting with ETS in early life (53); however, none of these regions had been reported by previous genomes scans on gene-ETS interaction, except for the region in the 1q43-q44. Moreover, an interaction has been described between 17q21 variants and early-life exposure to ETS in early-onset asthma (54). The interaction between *ORMDL3* variants and early-life exposure to ETS in childhood-onset asthma was later replicated (94, 95).

Most candidate gene studies have focused on examining variants in genes coding for antioxidant defenses and xenobiotic-metabolizing enzymes and childhood-onset asthma susceptibility to tobacco smoking, especially the glutathione-S transferase (GST) family of antioxidant enzymes. Childhood-onset asthma risk has been shown to differ by *GSTM1* genotype in relation to both maternal smoking in pregnancy (55, 56) and childhood ETS exposure (57), with effects largely restricted to children with *GSTM1* null genotype. Results from other studies have suggested an interaction between *GSTP1* rs1695 A (Ile105) is a risk allele for childhood wheeze illness in relation to maternal smoking in early life, with an effect most clearly seen in children who are exposed to maternal smoking (59, 60). Most of the studies looking at interactions with *GSTM1* and *GSTP1* genetic variants have shown a positive finding, but not always in the same direction for *GSTP1* (58).

Given the importance of inflammation in asthma, genes related to inflammation responses and innate immunity have also been examined. Genetic variation in tumor necrosis factor (*TNF-α*) may contribute to childhood asthma and that associations may be modified by parental smoking (60, 61). Ramadas et al. (62) showed interaction of the interleukin-1 receptor antagonist (*IL1RN*) gene polymorphism rs2234678 and maternal smoking during pregnancy increased the risk for childhood asthma. Salam et al. (63) found that children with the transforming growth factor beta-1 (*TGFB1*)−509TT genotype are at increased risk of asthma when they are exposed to maternal smoking *in utero*; however, no interaction was found for parental tobacco smoke exposure in childhood (96). Household ETS and interleukin-13 gene (*IL-13*) variants may have interactive effects on childhood asthma phenotypes (64). Interactions between the human intercellular adhesion molecule 1 (*ICAM1*) polymorphisms and ETS have also been associated with risk of childhood-onset asthma (65). In adults, Miyake et al. revealed that the combination of ever smoking with interleukin 3 (*IL-3*) genetic variants was significantly positively associated with adult asthma in Japanese women (66).

Several studies have focused on genes related to epithelial function. Reijmerink et al. (67) first reported gene–environment interaction of *ADAM33* genotypes, the first identified asthma gene by positional cloning, and *in utero* tobacco smoke exposure with respect to childhood-onset asthma risk; however, no interaction was detected with postnatal ETS exposure (97). Moreover, Wang et al. (68) reported joint effects of ETS exposure and E-cadherin *CDH1* genotypes associated with the development of childhood asthma.

To date, two GWIS on tobacco smoke exposure and asthma are available. Scholtens et al. (69) conducted the first GWIS specifically aiming to identify genetic polymorphisms that interact with two well-known environmental risk factors for childhood-onset asthma: *in utero* and childhood tobacco smoke exposure. The authors found that genes reported previously to interact with tobacco smoke exposure with respect to asthma development (i.e., *GSTP1, TNF* and *ADAM33*) were not among the most significant hits and showed suggestive interactions between rs8094633 near erythrocyte membrane protein band 4.1 like 3 (*EPB41L3*) and exposure to *in utero* tobacco smoke,

TABLE 5 | Summary of the most relevant examples of gene-by-environment interaction identified in asthma in epidemiological studies.

Exposure	Study design	Gene/region (variant)	Gene/region functionality	Asthma onset	References
Tobacco smoking					
Childhood ETS	Family study	Chr. 1p, 5q, and 17p	—	Childhood/adult	(51)
Childhood ETS	Family study	Chr. 5q	—	Childhood/adult	(52)
Childhood ETS	Family study	Chr. 1q43-q44, 4q34, 5p15, and 17p11	—	Childhood/adult	(53)
Childhood ETS	Family study	Chr. 17q21	Transcriptional activity of ZPBP2, GSDML and ORMDL3 genes	Childhood	(54)
Maternal smoking *in utero*	Candidate gene	*GSTM1 (deletion)*	Antioxidant defenses/detoxification	Childhood	(55) (56)
Childhood ETS	Candidate gene	*GSTM1 (deletion)*	Antioxidant defenses/detoxification	Childhood	(57)
Household ETS	Candidate gene	*GSTP1(Ile105Val)*	Antioxidant defenses/detoxification	Childhood	(58)
Maternal smoking during childhood	Candidate gene	*GSTP1 (Ile105Val)*	Antioxidant defenses/detoxification	Childhood	(59)
Maternal *in utero* smoking or first 2 months of age	Candidate gene	*GSTP1(Ile105Val)* *TNF-α(−857)*	Antioxidant defenses/detoxification Inflammation	Childhood	(60)
Parental smoking	Candidate gene	*TNF-α (−208, −308)*	Inflammation	Childhood	(61)
Maternal smoking *in utero*	Candidate gene	*IL1RN (rs2234678)*	Inflammation	Childhood	(62)
In utero ETS	Candidate gene	*TGFB1 (−509)*	Airway inflammation and remodeling	Childhood	(63)
Household ETS	Candidate gene	*IL-13*	Inflammation	Childhood	(64)
Childhood ETS	Candidate gene	*ICAM1 (rs5491, rs5498)*	Inflammation	Childhood	(65)
Ever smoking	Candidate gene	*IL-3 (rs40401)*	Leukotrienes, IL-4 and TNF-α release	Adult	(66)
In utero ETS	Candidate gene	*ADAM33*	Lung development Endothelial celldifferentiation	Childhood	(67)
Childhood ETS	Candidate gene	*CDH1 (−160)*	Epithelial function	Childhood	(68)
In utero ETS ChildhoodETS	GWIS	Chr. 18 near *EPB4IL3 (rs8094633)* *PACRG(rs1575472)*	Cell-cell junctions and lung development Motile cilia function andmorphogenesis	Childhood	(69)
Active tobacco smoking	GWIS	Intergenic regions on Chr. 9 and 12	Gene expression regulation in lungs	Adult	(70)
Outdoor air pollutants					
NOx and SO_2	Candidate gene	*GSTP1 (Ile105Val)*	Antioxidant defenses/detoxification	Childhood	(71)
Ozone	Candidate gene	*GSTP1 (Ile105Val)* *GSTM1(deletion)*	Antioxidant defenses/detoxification	Childhood	(72)
Ozone and PM2.5	Candidate gene	*GSTP1 (Ile105Val)*	Antioxidant defenses/detoxification	Childhood	(73)
PM10	Candidate gene	*GSTP1 (Ile105Val)*	Antioxidant defenses/detoxification	Childhood	(74)
NO_2	Candidate gene	*GSTP1 (Ile105Val, rs1138272)*	Antioxidant defenses/detoxification	Childhood	(75)
Major road length in 100-m buffer	Candidate gene	*GSTM1 (deletion)* *GSTT1(deletion)*	Antioxidant defenses/detoxification	Childhood	(76)
Living <200 m from a major road	Candidate gene	*GSTT1 (deletion)*	Antioxidant defenses/detoxification	Adult	(77)
NO2	Candidate gene	*NQO1 (rs2917666)*	Antioxidant defense	Adult	(78)
Ozone	Candidate gene	*TNF-α (−308)*	Inflammation	Childhood	(79)
PM2.5	Candidate gene	*TLR2 (rs4696480)* *TLR4 (rs2770150, rs10759931, rs6478317,rs1927911)*	Innate immunity	Childhood	(80)

(Continued)

TABLE 5 | Continued

Exposure	Study design	Gene/region (variant)	Gene/region functionality	Asthma onset	References
NO_2	GWIS	*BMGALT5* *ADCY2* *DLG2*	Glycosphingolipids synthesis Lung function Epithelialstructure	Childhood	(81)
Indoor exposures					
Mold/dampness	Candidate gene	*IL-4*	Humoral and adaptative immunity	Childhood	(82)
Gas cooking	Candidate gene	*GSTM1 (deletion)*	Antioxidant defenses/detoxification	Adult	(83)
Household carpet use	Candidate gene	*IL-13 (h1011 haplotype)*	Airway inflammation	Childhood	(84)
Farming-related exposures					
Farm milk consumption	Candidate gene	*CD14 (−1721)*	Innate immunity	Childhood	(85)
Living on farm	Candidate gene	*TLR2 (−16934)*	Innate immunity	Childhood	(86)
Farm environment	Candidate gene	*TLR6 (rs1039559, rs5743810)*	Innate immunity	Childhood	(87)
Farming exposures	GWIS	*GRM1*	Immunologic synapsis Th1 cytokineproduction	Childhood	(88)
Microbial exposure					
Early respiratory infections	Candidate gene	Chr. *17q21*	Transcriptional activity of ZPBP2, GSDML and ORMDL3	Childhood	(89)
Endotoxins	Candidate gene	*TLR4 (−299, −399)*	Innate immunity	Adult	(90)
Dust endotoxins	Candidate gene	*CD14 (−260)*	Innate immunity	Childhood/adult	(91)
Endotoxins	Candidate gene	*CD14 (−260)* *MD2(rs10808798)*	Innate immunity	Adult	(92)
Endotoxins	Candidate gene	*CD14 (−260)*	Innate immunity	Childhood	(93)

and between rs1575472 in parkin coregulated gene (*PACRG*) and childhood ETS. Interestingly, these two SNPS had not been identified previously in GWAS on childhood asthma. Subsequently, Vonk et al. conducted the first hypothesis-free genome-wide study to identify SNPs that interact with active tobacco smoking with respect to adult-onset asthma using data of the GABRIEL consortium, showing suggestive evidence for an interaction with two intergenic markers (rs9969775 on chromosome 9 and rs5011804 on chromosome 12) with potential regulatory functions linked to gene expression regulation in lung tissue (70).

Overall, existing literature has shown that prenatal and postnatal exposure to maternal/paternal smoking interacts with genetic variants to increase the risk of childhood-onset asthma; interestingly these genes are related to regions of linkage to asthma phenotypes and coding for antioxidant defenses and xenobiotic-metabolizing enzymes, inflammation responses and innate immunity and epithelial function. However, GWIS approaches have failed to replicate those findings revealing additional loci.

Outdoor Air Pollutants

Interactions between outdoor air pollution and genetic variants have been focused on candidate genes related to antioxidative stress and detoxification systems, inflammation, and innate immunity as pathogenic pathways for asthma. Interactive effects of variants in genes belonging to the GST family (*GSTP1* Ile105Val, *GSTM1* deletion) with levels of different outdoor air pollutants (e.g., NO_2, ozone, and particulate matter PM_{10} and $PM_{2.5}$) have been described for childhood asthma (71–75) and traffic-related air pollution (76). Bowatte et al. (76) first reported significant effect modification of *GSTT1* polymorphisms for the association of traffic-related air pollution exposure and childhood-onset asthma, in contrast to previous studies that found no evidence of interaction (73, 74). In addition, Bowatte et al. also first demonstrated effect modification by *GSTT1* genetic variation, but not by *GSTM1* or *GSTP1* polymorphisms, on the association between traffic-related exposure and asthma in adults (77), in contrast to the study by Castro-Giner et al. that only detected an interaction with common polymorphisms in the *NQO1* gene (78).

Genetic variation in few genes related to inflammation and innate immunity have also been investigated as effect modifiers between outdoor air pollution and asthma. In the study of Li et al., the common TNF-α−308 GG genotype was found to interact with annual average levels of ozone in childhood onset asthma (79); although results were not replicated (75). Polymorphisms in toll-like receptor genes (*TLR2* and *TLR4*) have also been identified as potential effect modifiers of the association between outdoor PM2.5 levels and childhood asthma (80).

Recently, a GWIS of air pollution exposure and childhood asthma showed supportive evidence for interaction with outdoor NO_2 levels for the novel loci *B4GALT5* and the previously lung disease associated loci *ADCY2* and *DLG2* (81).

In summary, results on interactions between exposure to outdoor air pollution and genetic variants on genes related to antioxidative stress, detoxification system, inflammation, and innate immunity on childhood and adult onset asthma are inconsistent across studies.

Indoor Exposures

Several studies have investigated interaction between candidate genes and diverse indoor exposures. Gene-environment interactions between the IL-4 promoter and an indoor mold may play an important role in childhood asthma (82). Increased BHR in adults was associated with gas cooking (a major indoor source of NO2), but only among subjects with the *GSTM1* null genotype (83). IL-13 variants were found to interact with household carpet use on the risk of asthma in Taiwanese children (84).

Farming-Related Exposures

The number of gene interactions with a farming environment remains very limited, focusing primarily genes related to innate immunity. Bieli et al. reported an interaction between early farm milk consumption and a polymorphism in the *CD14* gene (CD14/-1721) on the risk of childhood asthma (85). Effect modification by farm exposure in childhood on the association between polymorphism in *TLR* genes and asthma have been shown. Being exposed to a farm environment in childhood was protective against childhood-onset asthma for those with *TLR2*/-16934 T-allele (86), *TLR6*-rs1039559 T-allele and *TLR6*-rs5743810 C-allele (87). The most comprehensive GWIS in 1708 children from 4 rural regions of Central Europe for childhood asthma in relation to farm-related exposures did not reveal any significant interaction with common SNPs (88); however, strong interactions were found for rarer variants in 15 genes, particularly of the glutamate receptor, metabotropic 1 gene (*GRM1)*.

Microbial Exposures

Respiratory viral infections in the first few years of life increase risk of childhood asthma; however, not all children develop the disease, suggesting an interaction with the host genetic factors (98). Smit et al. (89) found that 17q21 genetic variants enhance the association between early respiratory infections and childhood-onset asthma. The presence of two common polymorphisms in the extracellular domain of the *TLR4* has been found to modify the effect of endotoxins on asthma in adults (90). Moreover, multiple studies have characterized a similar interaction between asthma, *CD14* variants and environmental endotoxin exposure, a marker of microbial exposure capable of inducing severe airway inflammation. Zambelli-Weiner et al. found CD14/260 polymorphism to interact with dust endotoxin on the risk of childhood-onset asthma (91). Similarly, in adults, Smit et al. showed occupational endotoxin exposure and wheeze in agricultural workers to be significantly modified by genetic variants in *CD14* and *MD2* (92). A recent systematic-review has highlighted the apparent modification of the effect of early life endotoxin exposure on risk of asthma in childhood, but not in adults, by the CD14/260 polymorphism (93).

Literature on inhaled exposures such as indoor air pollution and farming-related is scarce and mostly focused on genetic interactions with genes related to innate immunity and childhood onset asthma. Host innate immunity genetic variation might play a key role in childhood and adult onset asthma susceptibility in relation to microbial exposures including endotoxins.

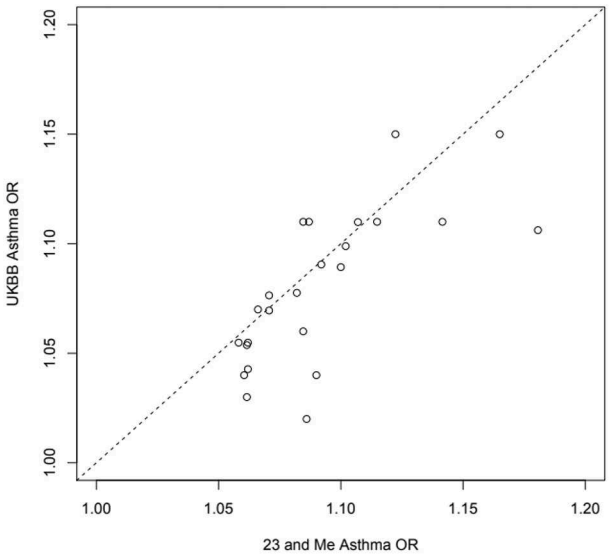

FIGURE 4 | Estimated odds ratios for 24 independent top self-reported "any" asthma associated SNPs from 23 and Me (99) and the UK Biobank (32) samples: exact same SNP in or near *RORA*, *ZBTB10*, *ZPBP2*, *GATA3*, *ID2*, *IL33*, *CD247*, *TSLP*, *RAD50*, *HLAC*, *STAT6*, *D2HGDH*, *RAD51B*, *ADAMTS4*, *SMAD3*, *TLR1*, *BACH2*, *PEX14*, *ADORA1*, *TNFSF4, CDHR3*, *CLEC16A*, *LPP*, *LRRC32*.

CONCLUSIONS

There are relatively few large genetic studies examining adult-onset asthma. Studies often rely on relatively simple questionnaire based diagnostic criteria which are validated by the consistency of genetic associations detected (that is, diagnostic looseness is trumped by statistical power, see **Figure 4**), but might be less useful when trying to make fine distinctions about disease onset and persistence. In the present review we have attempted to triangulate via large studies of disorders that will overlap to greater and lesser extents with this condition. Specifically, this has been via the known fact that atopy is more strongly genetically correlated with childhood onset, and the likely fact that COPD overlap will be stronger for adult-onset asthma. In some cases, we can fix pathways of causation by using other types of study, such as traditional longitudinal studies, thus testing and constraining possible interpretations of the genetic evidence. Roughly, it seems that genetic causes of adult-onset asthma tend to affect childhood asthma to the same extent, which in hindsight seems very plausible. Childhood asthma has a larger contribution from atopy loci, while non-atopic immune-related genetic variants seem to be shared by adult-onset and childhood asthma. There are a few loci that might be specific to adult-onset disease, which may overlap with COPD e.g., AGER, but childhood asthma does seem to be a risk factor for adult COPD. Some constitutional risk

factors such as increased BMI affect childhood-onset and adult-onset disease equally, and others such as vitamin D level do not show any genetic correlation with asthma.

Most of available studies on gene-environment interaction are focused on childhood-onset asthma, and few studies are based on adult subjects. Gene-environment interactions have revealed novel genes that have previously not been implicated in the pathogenesis of asthma; however, inconsistencies between studies and differences in direction of effects with specific genetic variants have been reported. These issues may likely be due to chance, insufficient power, different populations or ethnic origins, variation in study design and characterization of both exposures and disease phenotypes. Available GWISs have not replicated gene by environment interactions previously reported between common genetic variants and tobacco smoking, outdoor air pollutants, and farming-related exposures. Considering time of asthma onset extends the two-dimensional problem of gene-environment interactions to a three-dimensional problem, since identified gene-environment interactions seldom reproduce for childhood and adult asthma (e.g., endotoxin exposure and CD14/260 genotype). Therefore, evidence suggests that susceptibility of asthma to environmental exposures may biologically differ from early life to adulthood resulting in different pathways and mechanisms of the disease.

FUTURE DIRECTIONS AND RECOMMENDATIONS

- Genetic contributions are higher for childhood-onset asthma.
- The genetic overlap between childhood and adult onset asthma is large.
- The usually small size of the contribution of a single locus to heritability in the population does not preclude a large effect of a drug targeting that pathway. This is the justification given for these larger and larger studies that can detect smaller and smaller effects.
- Mendelian Randomization is a useful tool to investigate pathogenesis—if variation in a gene altering a putative intermediate variable is associated with risk, then environmental exposures affecting that same pathway are supported as truly causative.
- Lacking gene-environmental studies on important risk factors for asthma phenotypes such as diet, medication, microbiota, emerging pollutants, climate change and extreme weather conditions merit consideration.
- Despite methodological challenges, GWIS studies through collaboration hold promise for identifying unexpected gene environment interactions and improving our understanding of asthma phenotypes during a lifetime, beyond candidate studies based on our knowledge of biological processes and/or pathways.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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