Chapter 2
Special Considerations in Preschool Age

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Prevalence of Severe Asthma and Wheezing Disorders in Preschool Children

Prevalence of Asthma

There has been a significant increase of global preschool asthma prevalence since the early twentieth century, paralleled with reported increases in the prevalence of allergies. This increase may have leveled off in some areas, while in others the rise seems to continue [1]. Specifically, the prevalence of asthma seems to have reached a plateau in high-income countries, whereas in low- and middle-income countries, the prevalence is ever increasing. Factors affecting this increase in prevalence in preschool children have been actively studied but are yet to be fully understood, as both genetics and environmental exposures affect several aspects of disease risk and severity. There is a male predominance in prevalence of asthma and wheezing disorders before puberty and a "sex-shift" toward females after puberty [2]. Relating to environmental exposures, it has been hypothesized that the transition to a more urban environment may have driven the development of asthma in general and wheezing disorders in preschool children [3, 4]. Whether the prevalence of severe asthma in preschool children has changed in the last decades is largely unknown.

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Prevalence of Wheezing Disorders

Population studies from the USA and Europe report that half of all children at age 6 have experienced wheezing during their lifetimes [5] and that one in three children has at least one episode of wheezing before their third birthday [6]. Approximately 40% of preschoolers who wheeze show respiratory symptoms later in their childhood, although there is variation from 22% to 55% [7–9]. Despite the high incidence and prevalence, there are knowledge gaps regarding the mechanisms of disease pathogenesis and the optimal treatment of wheezing disorders in preschool children. There is substantial heterogeneity in the spectrum of symptom development, duration, frequency, severity, and response to treatment, as well as the pathophysiology and risk factors behind preschool wheezing [10]. This hinders general preventive efforts and may also result in inadequate treatment. A special consideration with preschool wheezing compared to that of later age-groups is that wheezing is predominantly triggered by viral infections, whereas later in childhood reasons such as allergens or exercise dominate. Approximately one half of all preschoolers wheeze at some point in time, and one third of this group will have asthma later in their life [11]. Fortunately, most infants with wheezing disorders have a good prognosis and remain free from subsequent wheezing episodes later in life.

Definition

Wheezing is defined as a high-pitched whistling sound produced in the chest during expiration, as a result of obstruction or narrowing of the air passages. Asthma and severe wheezing are common conditions in emergency departments at children's hospitals. In addition to wheezing, children typically present with symptoms such as tachycardia, tachypnea, dyspnea, cough, and reduced blood saturation of oxygen. Older children may use their accessory muscles to aid their breathing, whereas in younger children chest wall recession (severe retractions) is observed. Older children with an acute asthma attack often have a history with asthma causing their symptoms; however, children in preschool age do not necessarily have known asthma or bronchospasm as the cardinal reasons behind their wheezing. In addition, lower respiratory tract infections or foreign body aspiration may manifest with similar symptoms. Details of the differential diagnoses of wheezing disorders are discussed in other chapters. In epidemiology studies, the prevalence of wheezing is often derived from questionnaires answered by parents using questions like "Has your child had wheezing or whistling in the chest in the last 12 months?" [12].

Asthma is challenging to diagnose in preschool children due to a wide spectrum of disease symptoms, lack of objective markers, and the fact that several asthma-related phenotypes may give rise to the same symptom (e.g., wheezing). In general, asthma is diagnosed based on presence of, or history of, symptoms like wheezing,

coughing, chest tightness, and trouble breathing. In addition, information on symptom triggers, effect of asthma medications, family history, and atopic status may be used as basis for the diagnosis. It is important to keep in mind that many large epidemiological studies use questionnaire-based parental report of asthma symptoms or outcomes in order to define disease status and severity. Parental report may be subject to over- or underreporting, and even validated questionnaires are not fully free of the risk of bias. In older children objective tools such as spirometry, bronchodilator response, and methacholine challenges may be helpful; however, in the preschool years, such tools are difficult to administer.

Characterization of Wheezing Disorders

Preschool wheezing may be divided into two groups based on temporal patterns and causal factors: episodic (or viral wheezing) and multiple-trigger wheezing [13]. The clinical phenotype and temporal patterns depend on characteristics such as prematurity or age of onset as well as congenital or previously acquired factors such as abnormal airway function, atopy, and tobacco smoke exposure. Although the two definitions can be clinically useful to differentiate between, it should be noted that the phenotypes also share similarities and pathophysiology and some children may present with a "mixed" wheezing phenotype and that phenotypes may switch within the same patient over time.

Episodic wheezing is the most common type of wheezing in preschool children, characterized by acute attacks and symptoms, with periods of being completely well in between, a seasonal variation and usually precipitated by an underlying respiratory tract infection, which triggers the inflammation that leads to airway narrowing and wheezing. The most common causative viral pathogens include human rhinovirus (HRV), respiratory syncytial virus (RSV), coronavirus, and human metapneumovirus [13]. In addition, bacterial infections are shown to be associated independently of possible concurrent viral infections with wheezing episodes. Preschool children with or without wheezing have the same type of pathogens (bacteria or viruses), and hence the type of pathogen likely is not determinant for the wheezing but rather the presence of pathogens [14]. The long-term outcomes vary: wheezing may disappear, continue into school age, or develop into multiple-trigger wheezing and later manifest asthma. The prevalence of episodic wheezing decreases with age [15].

Multiple-trigger wheezing (also called persistent wheezing) is characterized by the presence of acute attacks but also symptoms of wheeze between episodes. Usually, the airways respond to several trigger factors such as allergen exposure, tobacco smoke, respiratory infections, crying, laughing, and exercising. The condition shows less seasonal variance compared to episodic wheezing mostly linked to viral infections, and its absolute prevalence throughout childhood remains rather constant, though its proportion compared to episodic wheezing increases with age. Children with multiple-trigger wheeze have a higher risk of later asthma compared to children with episodic wheeze [16]. Yet, although most wheezing in preschool

children is associated with viral respiratory tract infections, there is insufficient evidence to show that the mechanisms driving preschool wheezing are the same as asthma [13].

Retrospectively, preschool wheezing can also be divided based on the duration of the symptoms into three groups as described in the hallmark paper from the Children's Respiratory Study in Tucson, Arizona [17]. All three types can either be defined as episodic wheezing or multiple-trigger wheezing. *Transient wheezing* typically appears before the child is 3 years of age and disappears before their sixth birthday or around school age. *Persistent wheezing* continues beyond the child's sixth birthday (or school age). *Late-onset wheezing* shows symptoms that begin after the age of 3. These definitions may be useful when discussing longitudinal studies. These studies and clinical phenotypes have been described in more detail in Chap 1.

Features of Severe Acute Wheezing in Young Children

The spectrum of symptoms is broad and varied when it comes to preschool wheezing disorders. In acute, severe disease exacerbations (or attacks) oxygen saturation can be decreased, and the patient is tachycardic and tachypneic and has to exploit additional strategies to fill the lungs with air. This is perceived as a use of accessory breathing muscles in older children and chest wall recession in younger children as well as nasal flaring. The child may not be able to communicate effectively as completing a sentence with one breath may be difficult. Characteristics affiliated with severe or moderately acute clinical presentations of wheeze attacks are displayed in Table 2.1 [18].

Several definitions for non-acute severe asthma have been suggested. The suggested factors behind these definitions include dose of medication, symptomatology, exacerbation frequency, and severity as well as spirometry results. The ERS/ATS definition only starts at 6 years of age, and there is no established definition for patients younger than that.

The definitions are presented in Table 2.2 [19, 20].

Table 2.1 Characteristics of severe and moderate acute asthma, divided by age [18]

	Age >5 years		Age 2–5 years	
	Severe acute	Moderate acute	Severe acute	Moderate acute
Oxygen saturation (%)	<92	92–95	<92	92–95
Pulse (bpm)	>125	100–125	>140	120–140
Respiratory rate (bpm)	>30	20–30	>40	30–40
Features	Clear use of accessory muscles, nasal flaring	Some use of accessory muscles, nasal flaring	Clear chest wall recession, nasal flaring	Some chest wall recession, nasal flaring
Others	Inability to complete sentence, feed	Talking in short phrases	Inability to complete sentence, feed	Talking in short phrases

Table 2.2 Exact definitions of severe asthma by ERS/ATS and GINA

European Respiratory Society (ERS)/American Thoracic Society (ATS)	Definition, all quoted from [19]
ERS/ATS definition of severe asthma for patients aged ≥6 years	*Asthma which requires treatment with guidelines suggested medications for GINA steps 4–5 (high-dose ICS and LABA or leukotriene modifier/theophylline) for the previous year or systemic CS for ≥50% of the previous year to prevent asthma from becoming "uncontrolled" or if asthma remains "uncontrolled" despite this therapy*
	Uncontrolled asthma defined as at least one of the following: *1. Poor symptom control: ACQ consistently ≥1.5, ACT <20 (or "not well controlled" by NAEPP/GINA guidelines)* *2. Frequent severe exacerbations: two or more bursts of systemic CS (≥3 days each) in the previous year* *3. Serious exacerbations: at least one hospitalization, ICU stay, or mechanical ventilation in the previous year* *4. Airflow limitation: after appropriate bronchodilator withhold FEV_1 <80% predicted (in the face of reduced FEV_1/FVC defined as less than the lower limit of normal)* *Controlled asthma that worsens on tapering of these high doses of ICS or systemic CS (or additional biologics)*
Global Initiative on Asthma (GINA)	Definition, quoted from [20]
GINA guideline definition assessed when the patient has been on regular controller treatment for several months. Criteria for severe asthma (all ages)	*Asthma that requires step 4 or 5 treatment* (e.g., *high-dose ICS/LABA) to prevent it from becoming uncontrolled or asthma that remains uncontrolled despite this treatment*

(I)CS (inhaled) corticosteroids, *LABA* long-acting β_2-agonists, *ACQ* asthma control questionnaire, *ACT* asthma control test, *NAEPP* National Asthma Education and Prevention Program, *ICU* Intensive Care Unit

Genetics and Epigenetics

Parental or sibling history of asthma remains one of the most well-established risk factors for wheezing and asthma in children, further supported by high estimates for asthma heritability in twin studies. In 2007, the first genome-wide association study (GWAS) of childhood asthma was published, and genetic variants regulating *ORMDL3* expression on chromosome 17q21 were identified as strong determinants of asthma susceptibility [21]. Since then, this gene region has been replicated for asthma and wheeze in numerous studies worldwide, and analyses stratified by age of onset suggest that *ORMDL3* variants are particularly associated with early childhood-onset asthma (below the age of 4 in this study) [22]. The *ORMDL* genes encode transmembrane proteins that are anchored into the endoplasmic reticulum and are believed to be involved in protein folding and cellular functions such as

responses to inflammation and dysregulation of sphingolipid metabolism. As a possible mechanism linking early virus infections to childhood, asthma is supported by findings that variants at the 17q21 asthma locus (including *ORMDL3*) have been specifically associated with asthma in children who had had HRV wheezing illnesses early in life, connecting genetic susceptibility, HRV infection, and asthma development [4]. Additional evidence linking viral infections to asthma genetics relates to the gene encoding for the HRV receptor (C), *CDHR3* on chromosome 7q22. *CDHR3* was first identified in a GWAS on severe preschool asthma exacerbations in children [23], and only later did experimental work lead to the identification of *CDHR3* as the virus receptor [24]. Severe bronchiolitis, most often induced by viral infections, has also been evaluated using the GWAS approach. Interestingly, KCND3, which encodes a potassium voltage-gated channel, was recently identified in a GWAS of children hospitalized for bronchiolitis. KCND3 had previously been associated with occupational asthma. Most other works on the genetics of severe preschool asthma or wheeze (and bronchiolitis) have focused on candidate genes, such as IL4 [25].

Several other genes have been implicated in childhood asthma and wheezing, such as *interleukin 33 (IL33)* with its receptor IL1RL1, known to be expressed on epithelial cells, and involved in the host response to certain environmental and infectious stimuli, Th2 genes in the locus on chromosome 5q containing *RAD50* and *IL13* and *TSLP* (thymic stromal lymphopoietin) on the same chromosome. In one of the most recent asthma GWAS, the number of confirmed asthma loci at the genome-wide significant level was reported to be 16, and functional genomics analyses suggest major role of these loci in the regulation of immunologically related mechanisms [26].

Although the genetic associations described to date, e.g., between *ORMDL3* and childhood asthma, are very robust across studies and populations, the disease risk association with a single genetic variant, or combinations of variants, is modest at best. This is expected for a complex disease such as asthma but limits the use of genetic variants for diagnostic testing or prediction algorithms for prognosis or severity.

Epigenetics can be defined as the array of mechanisms that regulate changes in gene expression, which cannot be explained by variations in the underlying DNA sequence. Epigenetic changes may persist over a number of cell generations and can potentially be transmitted from parents to offspring. Epigenetic mechanisms regulate where and when different genes are active. DNA methylation is one of the regulatory mechanisms, and recent studies have found that genetics, aging, and environmental factors can influence the level of methylation globally or in specific genes, and early-life factors have been particularly studied. There are very strong associations between maternal smoking during pregnancy and DNA methylation changes at birth, as well as later during childhood [27]. Studies on 4- and 8-year-old children show that asthmatics have a lower degree of DNA methylation in certain immune cells than healthy controls, particularly in the eosinophils, which play a critical role in the asthmatic inflammation [28]. However, no association was seen between methylation in identified genes in cord blood and later asthma, which sug-

gests that these particular changes were acquired during early childhood. Interestingly, the identified methylation marks were associated with transcriptomics patterns that suggest reduced activity of naive T cells and increased activity of effector and memory CD8 T cells and natural killer cells. This methylation-expression pattern in children with asthma may be due to different environmental factors such as air pollution, tobacco smoke exposure, or viral/bacterial infections, although definite mechanisms remain to be elucidated. In other methylation studies on children with asthma, association with several known immune/asthma genes, including *IL13* and *RUNX3*, has been described [29]. Associations between methylation status in newborns and later asthma at school age have also been reported [30].

Chapter 15 will expand into the genetics and genomics of childhood asthma.

Atopy is defined as the hereditary tendency toward developing specific IgE antibodies against harmless stimuli (allergens) and the IgE-mediated allergic reactions that result when exposed to such stimuli. Occurrence can be measured either as a positive serum-specific IgE (sIgE) test or a positive skin prick test. Atopy encompasses several endotypes and manifests with many different phenotypes [31]. A phenotype encompasses observable traits or characteristics of a condition (e.g., allergic dermatitis or sensitization in allergic versus non-allergic asthma), whereas an endotype refers to an etiological (physiological or pathological) mechanism behind a disease. Persistent childhood wheezing is associated with atopy, and in turn, atopy is one of the strongest risk factors for later asthma and is related to an increased severity of asthma [32]. Atopic children, especially those with multiple sensitization, with asthma tend to be at higher treatment steps and have decreased lung function and more severe asthma in general [33]. In infants, sensitization to egg and milk typically occurs first, later to be followed by sensitization to other foods and airborne allergens. Depending on the geographical region and allergen load, different allergens are associated with asthma and multi-trigger (persistent) wheezing (e.g., mites, cockroaches, grass, or tree pollens) in different countries. Although atopic sensitization may be more commonly associated with multiple-trigger wheezing, it may also be associated with viral wheezing, since the clinical phenotype based on symptom pattern does not incorporate atopic status.

Preschool children who wheeze should undergo sensitization tests as these may aid in the prediction and prevention of future asthma and may guide optimal management. Results from longitudinal cohort studies suggest that the wheezing phenotypes most strongly associated with atopy (and airway responsiveness) are characterized by onset after age 18 months [34]. Also, a high blood eosinophil count may be a sign of an increased risk of persistent wheezing and atopy [35]. As such, early eosinophilia, allergic sensitization, and elevated total IgE levels indicate immune responses associated with persistent wheezing, asthma development, and asthma severity [36, 37]. Both skin prick tests and sIgE analyses have their pros and cons. Although the results between skin prick tests and sIgE are not always concordant, they may complement each other and, in general, serve as reliable markers of atopy and specific allergy. The effect of other aspects of sensitization in the prediction and prevention of wheezing and asthma, e.g., allergen exposure or avoidance, is discussed further down in the text.

Environmental Risk Factors

There are several potentially modifiable risk factors that affect the incidence, manifestation, and response to treatment of childhood wheezing disorders and asthma. Educating parents of preschool children with wheezing symptoms about beneficial vs harmful exposures is important as they affect disease occurrence and severity. These exposures or factors are presented in Table 2.3 and Fig. 2.1.

Factors That are Associated with an Increased Risk of Wheezing and Asthma

Impaired Lung Function Impaired lung function in infants is associated with wheezing during the first 2–3 years [38]. Specifically, a small caliber of the airways assessed at birth or shortly thereafter is associated with increased risk of transient wheezing that improves gradually with age. In contrast, persistent wheezing that debuts in the second or third year of life is not associated with the same deficit at birth, but signs of airway obstruction are often seen later during childhood, when asthma has developed [39–40]. Bronchial hyperresponsiveness in infancy (e.g., wheezing in conjunction with laughing, crying, or exposures such as cold air and tobacco smoke exposure) has been linked with a decreased lung function in children between the ages of 5 and 9 [41] and is also a risk factor for the development of asthma.

Viral Infections Viral infections are the leading cause of acute asthma symptoms such as wheezing. Airway infections in preschoolers may lead to subsequent repeating episodes of wheezing, and children with a history of viral bronchiolitis are at increased risk of developing recurrent wheezing and asthma later in life. The host

Table 2.3 Exposures that are associated with increased or decreased risk of wheezing and asthma in preschool children

Increased risk for preschool wheeze
Parental or sibling asthma
Impaired lung function
Viral infections
Tobacco smoke
Air pollutants
Prematurity
Insufficient vitamin D intake
Mold or dampness
Maternal obesity
Decreased risk
Microbiological exposures (e.g., traditional cattle farming lifestyle)
Exclusive breastfeeding

Fig. 2.1 Exposures that are associated with increased or decreased risk of wheezing and asthma in preschool children. Clockwise from the top (*increased risk in blue color*): parental or sibling asthma, impaired lung function, viral infections, tobacco smoke, air pollutants, prematurity, insufficient vitamin D intake, mold or dampness, maternal obesity, microbiological exposures (e.g., traditional cattle farming lifestyle), exclusive breastfeeding (*decreased risk in green color*)

response and the clinical manifestations of the respiratory tract infection may predict subsequent respiratory illness, rather than the pathogen [42]. It is not clear why some children with viral infections develop airway obstruction and some do not, although genetic factors have been suggested to play an important role (see section on "Genetics" above) [4, 43]. In addition, the combination of a respiratory tract viral infection and atopy may synergistically increase the risk of exacerbations [44].

Table 2.4 Some of the most common respiratory virus species, their subgroups, and type of genetic material

Virus species	Subgroups	Type
Adenovirus	A–F	DNA
Coronavirus	I, II	RNA
Human bocavirus	1–3	DNA
Influenza	A–C	RNA
Metapneumovirus	1–4	RNA
Parainfluenza	1–4	RNA
Respiratory syncytial virus	A, B	RNA
Rhinovirus	A–C	RNA

It has been estimated that up to 95% of all wheezing illnesses in preschool children are associated with viral respiratory tract infections [45]. In children under the age of 2, 75% of those who have had bronchiolitis report recurrent wheezing. In particular, respiratory syncytial virus (RSV) and human rhinovirus (HRV) have been linked to an increased risk of recurrent wheezing episodes during childhood. Although RSV and RV are the most common causative pathogens in bronchiolitis, there are several other viral pathogens that may cause the same disease. These viruses are listed in Table 2.4. RSV and HRV, the two most studied viruses in association with preschool wheezing, will be discussed in more detail.

Respiratory Syncytial Virus (RSV) Nearly every child under 2 years of age is seropositive for RSV, but not all children show the same severity of symptoms during infection. RSV bronchiolitis has been linked to wheezing, current asthma, and impaired lung function [46]. More than half of children below the age of 3 with bronchiolitis due to respiratory tract infection with confirmed RSV etiology will experience wheezing in the 2 weeks after discharge from the hospital. Approximately 50% of these children will experience wheezing during the following year and another 15% admitted to hospital due to a (new) severe wheezing episode [47].

Children who present with severe bronchiolitis, requiring emergency care or hospitalization, carry a higher risk of later asthma than those with no or mild symptoms. Fortunately, the risk is not equally high when a child has had an RSV-related wheezing without hospitalization [48]. It is unclear if a more severe disease manifestation is a result of congenitally impaired lung function or if RSV damages the developing lungs. To be able to assess the risk of later wheezing episodes after an RSV infection during the first year of life, presence of airflow limitation (wheezing) should be evaluated during auscultation. Infants with signs of limited airflow during an RSV infection have a higher risk of later recurrent wheezing [49].

Human Rhinovirus (HRV) Similar to RSV, HRV has a broad spectrum of disease severity. Respiratory illness caused by HRV before the age of 3 has also been linked to an increased risk of developing asthma [50]. These patients often have an atopic predisposition and seem to respond to anti-inflammatory asthma treatment [51]. In older children with diagnosed asthma, HRV infections may give more severe symp-

toms and a longer duration of the illness as well as a greater impairment of lung function. This may partly be due to a malfunction in the aborting of virus replication in asthmatic children [52].

While some studies suggest that an early HRV wheezing attack or bronchiolitis event is an important marker of risk for later asthma, others suggest that the number, not the particular viral species, of lower respiratory tract infection episodes in the first years of life is of primary importance for later asthma development [53, 54]. Host factors affect the risk of being infected with HRV, and recent studies have indicated that genetic susceptibility may play an important role both indirectly and directly. CDHR3, a member of the cadherin family, was shown to be downregulated in preschool-aged patients with HRV-induced wheezing [55]. Children of mothers with atopic asthma have an increased risk of HRV bronchiolitis, and variants in known asthma genes have also been reported to modify asthma risk following HRV infection (see section "Genetics" above).

Tobacco Smoke and nicotine exposure One of the best-studied and most significant risk factors for respiratory disease in children (and adults) is tobacco smoke exposure. Tobacco smoke contains numerous harmful chemicals and toxins that may cause damage to developing lungs pre- or postnatally. Maternal smoking has been associated with deficient lung growth and wheezing, thus establishing a link between in utero exposure to tobacco smoke and a later phenotype of wheezing [56]. Secondhand tobacco smoke exposure early in life has been associated with reduced lung function in preschoolers, development of wheezing and asthma, a higher susceptibility to airway infections, and more severe manifestations of respiratory tract illnesses. Exposure to tobacco smoke is harmful due to both its inducing and exacerbating effect and is shown to be linked with more severe wheezing disorders in preschoolers [57]. Children exposed to tobacco smoke before birth and in infancy are also more susceptible to wheezing when exposed to other risk factors like traffic-related air pollutants; thus it seems that smoking may lead to damage and increased vulnerability in preschoolers' lungs [58].

E-cigarettes are electronic vessels that transport nicotine to the lungs in an act called vaping. Instead of combusting tobacco, nicotine and other components are transported to the lungs along with an aerosol from a special e-liquid containing a mixture of propylene glycol, glycerin, and flavorants. This is why e-cigarettes are thought to be less carcinogenic than the typical cigarette [59]. The long-term effects of e-cigarettes are unknown [60]. Furthermore, the effects of passive vaping on children and particularly infants and preschoolers with developing respiratory organs are unknown. Children near to adults who vape are still exposed to components of the aerosol, including nicotine [61], as the measured levels of a nicotine marker, cotinine, do not differ between conventional smokers and vapers [62].

Exposure to nicotine among children under the age of 2 in the USA is increasing, and, furthermore, nicotine has been shown in several studies to impair lung development and function pre- and postnatally [63, 64].

In addition to nicotine, the flavorants, composed often of aldehydes, diacetyls, and acetyl propionyls, have irritative and partially unknown effects on the respiratory system when inhaled [65]. Parental vaping is not only harmful due to smoke exposure, it also leads to an increased incidence of conventional smoking in adolescents [66].

Air Pollutants Air pollution (outdoor and indoor) is a global problem and one of the most important environmental determinants for human health. According to recent estimates from the World Health Organization (WHO), more than 90% of children worldwide breathe toxic air. Ambient air pollution consists of organic and inorganic liquid and solid particles suspended in air (particulate matter – PM), as well as different gases such as ozone (O_3), nitrogen oxides (NO_x), and carbon monoxide (CO), and vapors such as volatile organic carbons (VOCs). The primary sources of ambient air pollutants are fuel combustion from motor vehicles, heat and power generation, industry and agriculture, as well as residential cooking and heating. In addition, natural sources (e.g., dust) also contribute significantly. Air pollutants may induce airway inflammation, increased airway responsiveness, and lung damage, and this is partly due to generation of free radicals and oxidative stress. Studies investigating exhaled nitric oxide support that inflammatory processes may partially account for the observed effects of air pollution exposure on childhood wheezing and asthma. Fractional exhaled nitric oxide (FeNO) is an established biomarker of eosinophilic airway inflammation, and several studies show a relation between exposure and increased FeNO levels [67]. Other studies suggest a mixed inflammation response following exposure, including a predominant neutrophil airway inflammation. It is likely that the air pollutant source (traffic, combustion processes, biomass burning, etc.) in combination with host factors (genetics, preexisting conditions, co-exposures, etc.) will influence the type of individual response. Dietary intake has been suggested to modify the negative health effect of exposure. As an example, higher omega-3 intake was recently associated with diminished harmful effect of particle exposure on symptoms and asthma severity in children age 5–12 years, while higher omega-6 intake was associated with an amplified effect [68].

Young children are considered particularly vulnerable since they are more exposed to air pollutants compared to adults relative to their size, due to higher ventilation per minute, and an immature immune system that cannot optimally handle toxic agents. Exposure to traffic-related air pollution has been negatively associated with lung growth and lung function (primarily FEV_1) in children in several studies, leading to increased risk of clinically important deficits [67]. In studies from the Swedish BAMSE (Barn/Children Allergy Milieu Stockholm Epidemiology) cohort, conducted in the Stockholm area with air pollution exposure levels well below the current WHO guidelines, exposure during the first year of life seemed to have the largest impact on school age lung function [69]. There is now robust evidence that air pollution exposure is linked to recurrent wheezing in young children, and recent studies also suggest increased risk of acute lower respiratory infection below the age of 2 [70, 71]. Further, early-life exposure is associated with increased risk of asthma and wheezing throughout childhood [72, 73].

Similar to tobacco smoke exposure, there is also evidence for significant associations between prenatal exposures to NO_x and PM and the risk of wheezing and asthma development in childhood [74].

Prematurity Approximately 5–15% of all pregnancies result in preterm birth (before 37 weeks of gestation), which is strongly associated with neonatal morbidity and mortality, as well as later health effects. In children born at a very low gestational age, i.e., very or extremely prematurely (below 32 or 28 weeks, respectively), bronchopulmonary dysplasia (BPD) is a major health challenge [75]. There is compelling evidence that preterm birth, in particular very or extreme preterm birth, increases the risk (1.7–3-fold) of wheezing disorders and asthma [76] (Fig. 2.2). Dose-response effects (i.e., the more preterm, the higher risk of wheeze or asthma) support the notion that immature lungs and airways are vulnerable to early-life exposures, including respiratory tract infections, which may trigger symptoms. Although children with BPD are often regarded as having asthma and are frequently treated with asthma medications, the mechanisms underlying BPD are considered different from asthma and typically do not involve eosinophilic inflammation. Instead, the lungs and airways in children with BPD are characterized by immature lung tissue affected by reparative processes, impaired alveolarization, and dysmorphic vascular growth [77]. In agreement with these findings, the evidence supporting beneficial effects from asthma drugs in preterm BPD subjects is scarce. An increasing body of studies suggests that even moderately preterm birth (gestational age 32–36 weeks) is associated with later adverse health outcomes, such as wheezing, asthma-like symptoms, and lung function impairment [78].

Allergen Exposure The association between allergen exposure and sensitization and wheezing and asthma has been much debated throughout the years. Studies have shown allergen exposure may increase or decrease the risk of disease or, in some cases, have no effect at all, i.e., no relationship observed between allergen exposure early in life and concurrent or later allergies [79]. Sensitization (and subsequent allergen exposure) should, however, be viewed as a prognostic marker,

Fig. 2.2 The airways and lungs of preterm babies are vulnerable to outside exposures, and preterm birth is associated with later manifestations of respiratory tract diseases

since early wheezing disorders combined with current allergy are an important risk factor for asthma later in life [80].

Studies in inner-city children in the USA report that 3-year-old children with the highest exposures to allergens and bacteria during their first year of life had a decreased risk of periodic wheezing compared to children the same age with less exposure. In addition, singling out cockroach, mouse, and cat allergen exposure, these three allergens were shown to have an inverse relationship with later wheezing [81]. The relationship of cat or dog allergen exposure early in life and later wheezing and sensitization has been evaluated in numerous studies, often with mixed results (Fig. 2.3). Pooled analysis of data from 11 prospective European birth cohorts that recruited a total of over 22,000 children showed no association between keeping furry pets early in life and asthma in school age, and the study conclusion was that "Advice from health care practitioners to avoid or to specifically acquire pets for primary prevention of asthma or allergic rhinitis in children should not be given" [82]. In cases where hereditary factors are involved (e.g., maternal atopy or presence of a genetic variant), exposure to allergens may be associated with a different risk [83], but due to challenges with residual confounding and the difficulties to draw firm conclusions about lifestyle factors and disease risk in observational studies, no clear picture has emerged in the literature.

It is well-known that children who have been diagnosed with severe wheezing or asthma show more severe and more frequent wheezing patterns as well as hospitalizations if exposed to the allergens they are sensitized to [44]. Although house dust mite exposure during early life is a strong risk factor for allergic sensitization, studies conducted in Europe, Australia, and the USA have found no clear association between house dust mite allergen concentrations and the development of childhood wheezing or asthma [84–86]. However, children diagnosed with asthma and house dust mite sensitization between the ages of 3–17 showed fewer and milder exacerbations of existing asthma when avoiding house dust mite exposure by using special bedding [87]. Hence, persistent house dust mite exposure may exacerbate existing asthma when sensitized children are exposed.

Fig. 2.3 The relationship of cat or dog allergen exposure early in life and later wheezing and sensitization has been evaluated in numerous studies, often with mixed results (Photo by L. Korppoo)

Insufficient Vitamin D Intake A link between maternal vitamin D intake during pregnancy and infant wheezing has been suggested, but there is much debate around the associations, dosages, causality, and mechanisms. Maternal supplementation with vitamin D is associated with a decreased risk of wheezing and asthma in 0–3-year-olds, and measured in cord blood, a lower level of vitamin D is linked to a higher risk of preschool wheezing [88]. Likewise, lower levels of vitamin D in 0–4-year-olds have been associated with acute wheezing [89]. However, this association is debated, as several studies have not observed a link between vitamin D levels and airway function, both regarding maternal intake and the child's intake of vitamin D [90, 91]. Meta-analysis results from two randomized controlled trials with a follow-up time of 3 years showed that vitamin D supplementation during pregnancy resulted in a significantly reduced risk of asthma or recurrent wheeze in the offspring (~25% risk reduction by 3 years), especially among women with low vitamin D (25(OH)D level <30 ng/ml) at randomization [88].

Mold or Dampness Home dampness and mold have been associated with childhood asthma in several cross-sectional studies performed across geographical regions and age-groups, with evidence of dose-response relationships [92]. In addition, studies strongly suggest causation of asthma exacerbations in children, and there is some evidence from longitudinal studies that indoor dampness may contribute to the development of new onset asthma [93]. These exposures are very common – studies from North America and Europe show that up to 20% of homes may have signs of dampness or mold. Despite clear epidemiological data, the causal exposures (including microbes) and mechanisms related to asthma remain unclear. Some studies suggest that respiratory symptoms may decrease after professional remediation of water leaks or other sources of mold/moisture in the home or school, although more research is needed to draw firm conclusions about such intervention effects [94].

Maternal Obesity Obesity is a major public health problem, both in children and adults. Following the Developmental Origins of Health and Disease (DOHaD) hypothesis, in utero exposures may predispose infants to diseases throughout the life span [95]. In this context, associations between maternal obesity in pregnancy and offspring wheezing and asthma have been suggested in several studies. A systematic review and meta-analysis concluded that maternal obesity is a significant risk factor for the development of childhood asthma or wheeze [96]. Subsequent studies have been able to confirm these associations; however, overweight in the offspring may have a mediating role [97]. Thus, prevention strategies of maternal prepregnancy and childhood obesity might be important to reduce the prevalence of childhood asthma. It is also well established that obese children have increased asthma risk and that obese asthmatic patients have more symptoms and more severe exacerbations than nonobese asthmatics [98].

Factors That are Associated with a Decreased Risk of Wheezing and Asthma

Microbial Exposures Are some newborns more prone to respiratory problems and thus experience more frequent infections, or are some non-prone newborns pushed to a trajectory of decreased lung function due to early-life respiratory tract infections? Does the pulmonary microbiota affect the incidence of asthma, or is the microbiota itself altered by asthma? There is no clear answer to these questions although the role of bacteria in allergic diseases and asthma has been and is studied and debated extensively. We know that when it comes to preschoolers, the immune and respiratory systems are only developing and that children under the age of 3 are especially sensitive. Infections have the greatest effect compared to later in life on the developing individual and may lead to persistent changes [99].

It is well established that both viral and bacterial respiratory tract infections may cause exacerbations of asthma and wheezing episodes: generally, respiratory tract infections exacerbate already existing asthma in both preschool and school-aged children and before the age of 3 are associated with an increased risk of asthma and declined lung function at school age [100, 101]. There is however no clear consensus on the relationship between early microbial exposure, airway pathogens, and later disease, and we will discuss this complex matter by introducing several aspects of microbial exposures and host reactions.

Absence of Microbes A study published in 1989 reported that children with few or no siblings had more hay fever than those who lived in families with several siblings, and based on these and previous observations, the "hygiene hypothesis" was proposed [102]. This theory noted that the observed increase in the incidence of allergic diseases was paralleled with a general increase in hygiene characterized by a modern lifestyle with smaller families and fewer children, an increase in antibiotic use, and the introduction of vaccination programs. Further to this hypothesis, it has been noted that children who live on traditional cattle farms and encounter more bacteria have less asthma and allergies [103, 104]. Comparing the effect of traditional versus industrialized styles of farming (or Amish and Hutterite farming), the greatest differences are detected in traditional farming environments such as in Amish communities where exposure to animals and ingestion of raw cow milk create a protective effect, emphasizing the importance of the type of farming [105]. In addition to the type of farming, the positioning may make a difference. Clustering farms may mimic this protective microbial diversity when compared to more scattered localizations even if the farms are of the more industrialized type [106]. The largest protective effect is seen if the child is exposed to a farming environment before birth and then continually throughout their childhood [103]. An immune system that is not frequently stimulated by pathogens will, according to the hygiene hypothesis, react to stimuli that are potentially harmless. As such, an unbalanced response, in the absence of microbes, predisposes to allergy, wheezing, and asthma. It should, however, be noted that good personal hygiene or home cleanliness is not

linked to an increased risk of allergy nor asthma [107] and there is no association between vaccinations and later allergy or asthma [108].

The Microbiota Microbiota refers to the entire community of microbes that occupies a particular environment and has a defined niche [109]. The upper airways have a microbiota that protects pathogens from colonizing the lower airways and influence the basic composition of the microbiota in the airways further down. The lower airways are not sterile but house a microbiota of their own [110]. Older siblings affect the composition of a younger sibling's microbiota over time [111]. *Staphylococcus, Streptococcus, Moraxella,* and *Corynebacterium* species have been isolated in the lung microbiota of children [111]. One study reported that children with asthma have more *Proteobacteria* in their airways than healthy controls [110]. The microbiota develops during the first years of life, and it has been shown that abnormal colonization is linked to respiratory diseases later in life – especially colonization of the lower respiratory tract with *Streptococcus* during the first year of life is a risk factor for asthma [112, 113]. Newborns and 1-year-olds with lower airway colonization with *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* individually or in combination had an increased risk of recurrent wheezing and asthma at 5 years [114].

Early use of antibiotics may influence the formation of the respiratory microbiota and predispose for future infections in the airways [115]. A link between recurrent ear infections (treated with antibiotics) and wheezing as well as asthma in childhood has been established [116].

Not only do airway infections and pathogens influence later asthma risk, the gut microbiota also seems to affect the susceptibility to asthma and later allergic disease. As with the airways, the microbiota in the gut develops with time and depends on the host's exposures. The gut microbiota is significantly involved in maturing processes of the immune system and host responses to environmental stimuli and is affected by a number of factors such as diet and use of antibiotics [117]. A decreased microbial diversity in the gut in 1-week and 1-month-old infants is associated with asthma at 7 years [118]. Gastrointestinal bacterial infections and more general gut dysbiosis early in life may be associated with later asthma and atopy [119, 120, 121]. Also, patients who later developed asthma showed a skewed composition, with more *Clostridia*, coliform bacteria, and enterococci as well as less *Bacteroidetes*, bifidobacteria, and lactobacilli as part of their normal gut microbiota [122].

Exposure to Microbes Early-life exposures to certain pathogens may influence the risk of asthma later in life, although our understanding of their role is still unclear. Infections with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* early in life have been confirmed to predispose for wheezing and asthma. An infectious etiology behind asthma mediated by *C. pneumoniae* has been confirmed [123]. *C. pneumoniae* has been detected in bronchoalveolar lavage (BAL) fluid in children aged 0–20 years with asthma [124] along with *M. pneumoniae* more often in children aged 2–14 years who wheeze compared to healthy controls [14, 125]. Likewise, early exposures to fungi may predispose to asthma [126].

Breastfeeding Breast milk is undeniably the optimal source of nutrients for infants, and in addition it has several documented health benefits. According to WHO, exclusive breastfeeding is recommended up to around 6 months of age, with continued breastfeeding along with appropriate complementary foods up to 2 years of age or beyond. An earlier introduction of complementary foods (at around 4 months of age) is currently being discussed by many pediatric associations following recent clinical trials of early food introduction for allergy prevention [127], but most national associations have yet not changed their guidelines. Numerous studies have evaluated associations between breastfeeding and childhood wheezing/asthma and allergies, often with somewhat conflicting results. There seems, however, to be a consistent pattern of decreased risk of early wheezing and asthma related to breastfeeding (around 20–25% lower risk estimated in large meta-analyses; ever vs never breastfeeding), in particular at age 0–2 years, but with diminishing effects over time [128].

Attempts at Early Prediction of (Severe) Asthma

Recognition of at-risk preschoolers is crucial for the efficacy of preventive measures and appropriate pharmacological treatment. Overtreatment of wheezing among preschoolers is gratuitous and increases the total disease burden and risk of potential side effects – this should especially be noted as a large portion of wheezing preschoolers only experience transient periods with respiratory symptoms that ultimately resolve. Severe wheezing at preschool age is, however, associated with decreased lung function and an increased risk of later asthma not only into adolescence but also into adulthood and should thus be optimally prevented, monitored, and aptly treated [80, 129–131].

The Asthma Predictive Index (API) is a clinical tool used to evaluate a wheezing preschooler's risk of later asthma. After providing information on the number of wheezing episodes, parental asthma, current eczema, rhinitis, and eosinophilia, the treating doctor obtains either a positive or negative result that indicates the likelihood of their patient developing asthma and can use it as a basis for treatment based on the GINA guidelines [132]. mAPI, the modified Asthma Predictive Index, is even more accurate compared to API in predicting asthma correctly when obtaining a positive result, with the addition of criteria such as parent's allergy to airborne allergen and patient's allergy to foods such as egg, milk, or peanuts [133].

Several prediction models have been constructed to enhance asthma prediction capability. Prediction of persistent asthma was shown to be most affected by sensitization, heredity for asthma, and atopic dermatitis in a study developing a persistent asthma predictive score [134]. Other models have utilized, for example, atopy, heredity, parental education, history of wheezing, sensitization, current eczema, and rhino-conjunctivitis as well as in vitro cytokine production, although all studies show that the negative predictive power was more prominent due to the lower positive predictive values [135, 136]. The most prominent factor repeating in several models is allergen sensitization. Sensitization at preschool age may predict asthma

in general at school age: allergy to cat, dog, mold, or pollen (Fig. 2.4) was highly predictive of later asthma at preschool age both in a secondary healthcare and research setting [8]. IgE measurement can be used as a way of differentiating between high- and lower-risk patients (86% vs 45% risk of asthma development when measuring airborne allergen sensitization) as well as in choosing possible therapeutic measures [9]. Predictors may, however, change according to wheezing phenotype or debut age, reflecting the natural variance of wheezing [8, 137].

A recent study in Leicester, UK, constructed a prediction score investigating 1–3-year-olds with wheeze and the prevalence of asthma 5 years later. The noninvasive model included ten predictors (wheeze frequency, activity disturbance, and parental history of asthma/bronchitis to name a few) and showed promising results with sensitivity and specificity around 70%, PPV 49%, and NPV 86% [138]. Replication in the German MAS cohort supported the applicability of the score [139]. A study by Devulapalli et al. identified that assessing relatively straightforward markers such as the frequency, severity, and number of hospitalizations due to wheezing at the age of 2 predicts later asthma [140].

Biomarkers introduced to prediction models include FeNO, which is today used clinically as a biomarker of eosinophilic airway inflammation and may also serve as a predictor for asthma [141]. FeNO improved the prediction of asthma later in life; a study introducing a novel API with FeNO showed that preschool children with higher FeNO values had a higher risk for asthma at school age [142, 143]. The advantages of FeNO include that it is a noninvasive measuring technique; its disadvantages include that single-breath technique is mostly unachievable for preschoolers and alternative measuring techniques need to be used [144]. One alternative is that of measuring volatile organic compounds (VOCs) in exhaled breath. In one paper, 17 VOCs that differed between asthmatic and transient wheezing preschoolers were identified and that information of VOCs in predictive scores or API improved the prediction of later asthma in a preschool-age population [145, 146].

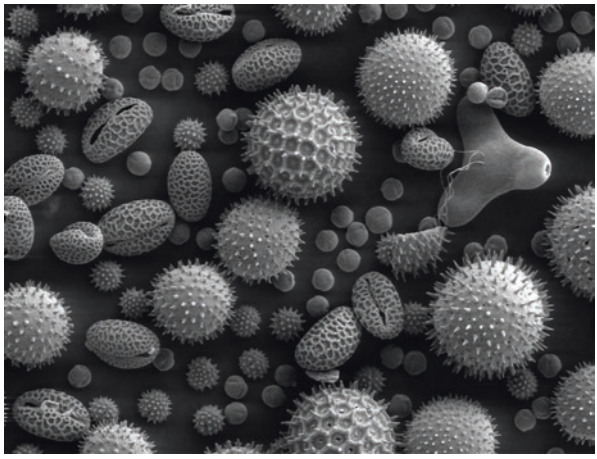

Fig. 2.4 Different allergens such as tree pollen have been associated with asthma and multi-trigger wheezing. Pollen grains with a 500 × magnification. (Courtesy of Dartmouth College Electron Microscope Facility, Dartmouth, NH)

At one end models are noninvasive and collect information on, e.g., frequency of asthma exacerbations or family history, whereas at the other end, more extended models perform additional testing in the form of, for example, blood sampling for specific IgE determination. Computational intelligence may be one way to help overcome the complexity of prediction of asthma: a sophisticated system using principal component analysis and other statistically potent methods was able to predict asthma outcomes with a success rate of approximately 95% [147].

As of today, the clinical utility of prediction models is still debated, and no particular model type has emerged as superior in predicting asthma development [11]. Concerns arise from generalizability of questions, absence of a global standard diagnosing system for childhood asthma, and validity of the models. Any efforts aimed at constructing models and predictive indices for asthma should address external validity and meticulously identify predictors that are previously identified risk factors from epidemiological studies to correctly describe and predict future asthma – albeit they are predictors from clinical examinations, questionnaires, lung function tests, or biomarker measurements [148].

Natural History and Prognosis

Early wheezing disorders, in particular multi-trigger wheezing, are well-known risk factors for the development of asthma later in life. Although longitudinal cohorts show that children with virus-induced wheezing symptoms during the first years of life often outgrow their symptoms later in childhood (i.e., transient wheezing), as a group, they do not completely overcome their lung function impairment [149, 150]. These associations suggest that early wheezing may not be such a harmless condition after all. In addition, if a child develops recurrent wheeze or asthma following lower respiratory tract infection in infancy, he or she may be at increased risk for a further deterioration of lung function (the two-hit hypothesis) or develop an increased susceptibility to experience respiratory problems following later environmental exposures such as tobacco smoke. Whether these early and later lung function insults are related to independent risk factors and pathways or instead share a genetically determined susceptibility remains to be elucidated.

Regarding atopic vs nonatopic asthma predictions, there are suggestions that clinical markers can be useful in that sensitization, eczema, and HRV etiology (of wheezing) at preschool age predict later atopic asthma, whereas virus-negative etiology, parental smoking, and age of wheezing onset below 1 year predict nonatopic asthma at school age [151].

In conclusion, childhood and especially preschool wheezing and asthma are heterogeneous conditions with several risk factors and highly varying outcomes. The increased understanding of the effect of different risk factors is crucial for our capability of identifying at-risk individuals but also predicting the outcome and prognosis of early-life wheezing. Clinical observations and data gathering of, for example, number of wheezing episodes, specific infections, heredity, and sensitization are useful for both research and clinical purposes, although improvement of the accuracy for individual predictions is needed.

References

1. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. Lancet. 2018;391(10122):783–800.
2. Keller T, Hohmann C, Standl M, Wijga AH, Gehring U, Melén E, et al. The sex-shift in single disease and multimorbid asthma and rhinitis during puberty – a study by MeDALL. Allergy. 2018;73(3):602–14.
3. Croisant S. Epidemiology of asthma: prevalence and burden of disease. Adv Exp Med Biol. 2014;795:17–29.
4. Calışkan M, Bochkov YA, Kreiner-Møller E, Bønnelykke K, Stein MM, Du G, Bisgaard H, et al. Rhinovirus wheezing illness and genetic risk of childhood-onset asthma. N Engl J Med. 2013;368(15):1398–407.
5. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, Cabana MD. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. Pediatrics. 2016;137(6):e20154496.
6. Bisgaard H, Szefler S. Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol. 2007;42(8):723–8.
7. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. Clin Exp Allergy. 2003;33(5):573–8.
8. Matricardi PM, Illi S, Grüber C, Keil T, Nickel R, Wahn U, Lau S. Wheezing in childhood: incidence, longitudinal patterns and factors predicting persistence. Eur Respir J. 2008;32(3):585–92.
9. Boersma NA, Meijneke RWH, Kelder JC, van der Ent CK, Balemans WAF. Sensitization predicts asthma development among wheezing toddlers in secondary healthcare. Pediatr Pulmonol. 2017;52(6):729–36.
10. Bacharier LB. The recurrently wheezing preschool child-benign or asthma in the making? Ann Allergy Asthma Immunol. 2015;115(6):463–70.
11. Smit HA, Pinart M, Antó JM, Keil T, Bousquet J, Carlsen KH, et al. Childhood asthma prediction models: a systematic review. Lancet Respir Med. 2015;3(12):973–84.
12. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225–32.
13. Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. Eur Respir J. 2008;32(4):1096–110.
14. Bisgaard H, Hermansen MN, Bønnelykke K, Stokholm J, Baty F, Skytt NL, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. BMJ. 2010;341:c4978.
15. Jurca M, Pescatore AM, Goutaki M, Spycher BD, Beardsmore CS, Kuehni CE. Age-related changes in childhood wheezing characteristics: a whole population study. Pediatr Pulmonol. 2017;52(10):1250–9.
16. van Wonderen KE, Geskus RB, van Aalderen WM, Mohrs J, Bindels PJ, van der Mark LB, Ter Riet G. Stability and predictiveness of multiple trigger and episodic viral wheeze in preschoolers. Clin Exp Allergy. 2016;46(6):837–47.
17. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332(3):133–8.
18. Okpapi A, Friend AJ, Turner SW. Acute asthma and other recurrent wheezing disorders in children. Am Fam Physician. 2013;88(2):130–1.
19. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343–73.
20. Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. J Allergy Clin Immunol Pract. 2014;2(5):489–500.

21. Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007;448(7152):470–3.
22. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J, et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. N Engl J Med. 2008;359(19):1985–94.
23. Bønnelykke K, Sleiman P, Nielsen K, Kreiner-Møller E, Mercader JM, Belgrave D, et al. A genome-wide association study identifies CDHR3 as a susceptibility locus for early childhood asthma with severe exacerbations. Nat Genet. 2014;46(1):51–5.
24. Bochkov YA, Watters K, Ashraf S, Griggs TF, Devries MK, Jackson DJ, et al. Cadherin-related family member 3, a childhood asthma susceptibility gene product, mediates rhinovirus C binding and replication. Proc Natl Acad Sci U S A. 2015;112(17):5485–90.
25. Amat F, Louha M, Benet M, Guiddir T, Bourgoin-Heck M, Saint-Pierre P, et al. The IL-4 rs2070874 polymorphism may be associated with the severity of recurrent viral-induced wheeze. Pediatr Pulmonol. 2017;52(11):1435–42.
26. Demenais F, Margaritte-Jeannin P, Barnes KC, Cookson WOC, Altmüller J, Ang W, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. Nat Genet. 2018;50(1):42–53.
27. Joubert BR, Felix JF, Yousefi P, Bakulski KM, Just AC, Breton C, et al. DNA Methylation in newborns and maternal smoking in pregnancy: genome-wide consortium meta-analysis. Am J Hum Genet. 2016;98(4):680–96.
28. Xu CJ, Söderhäll C, Bustamante M, Baïz N, Gruzieva O, Gehring U, et al. DNA methylation in childhood asthma: an epigenome-wide meta-analysis. Lancet Respir Med. 2018;6(5):379–88.
29. Yang IV, Pedersen BS, Liu A, O'Connor GT, Teach SJ, Kattan M, et al. DNA methylation and childhood asthma in the inner city. J Allergy Clin Immunol. 2015;136(1):69–80.
30. Reese SE, Xu CJ, den Dekker HT, Lee MK, Sikdar S, Ruiz-Arenas C, et al. Epigenome-wide meta-analysis of DNA methylation and childhood asthma. J Allergy Clin Immunol. 2019;143(6):2062–74. https://doi.org/10.1016/j.jaci.2018.11.043.
31. Custovic A, Lazic N, Simpson A. Pediatric asthma and development of atopy. Curr Opin Allergy Clin Immunol. 2013;13(2):173–80.
32. Carroll WD, Lenney W, Child F, Strange RC, Jones PW, Whyte MK, et al. Asthma severity and atopy: how clear is the relationship? Arch Dis Child. 2006;91(5):405–9.
33. Lu KD, Phipatanakul W, Perzanowski MS, Balcer-Whaley S, Matsui EC. Atopy, but not obesity is associated with asthma severity among children with persistent asthma. J Asthma. 2016;53(10):1033–44.
34. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax. 2008;63(11):974–80.
35. Miller EK, Avila PC, Khan YW, Word CR, Pelz BJ, Papadopoulos NG, et al.; Microbes, Allergy, and Asthma Committee. Wheezing exacerbations in early childhood: evaluation, treatment, and recent advances relevant to the genesis of asthma. J Allergy Clin Immunol Pract 2014;2(5):537–543.
36. Just J, Nicoloyanis N, Chauvin M, Pribil C, Grimfeld A, Duru G. Lack of eosinophilia can predict remission in wheezy infants? Clin Exp Allergy. 2008;38(5):767–73.
37. Sharples J, Gupta A, Fleming L, Bossley CJ, Bracken-King M, Hall P, et al. Long-term effectiveness of a staged assessment for paediatric problematic severe asthma. Eur Respir J. 2012;40(1):264–7.
38. Young S, Arnott J, O'Keeffe PT, Le Souef PN, Landau LI. The association between early life lung function and wheezing during the first 2 yrs of life. Eur Respir J. 2000;15(1):151–7.
39. Borrego LM, Stocks J, Leiria-Pinto P, Peralta I, Romeira AM, Neuparth N, et al. Lung function and clinical risk factors for asthma in infants and young children with recurrent wheeze. Thorax. 2009;64(3):203–9.
40. Håland G, Carlsen KC, Sandvik L, Devulapalli CS, Munthe-Kaas MC, Pettersen M, Carlsen KH, ORAACLE. Reduced lung function at birth and the risk of asthma at 10 years of age. N Engl J Med. 2006;355(16):1682–9.

41. Delacourt C, Benoist MR, Le Bourgeois M, Waernessyckle S, Rufin P, Brouard JJ, et al. Relationship between bronchial hyperresponsiveness and impaired lung function after infantile asthma. PLoS One. 2007;2(11):e1180.
42. Everard ML. The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children. Curr Opin Allergy Clin Immunol. 2006;6(1):56–61.
43. Bønnelykke K, Coleman AT, Evans MD, Thorsen J, Waage J, Vissing NH, et al. Cadherin-related family member 3 genetics and rhinovirus C respiratory illnesses. Am J Respir Crit Care Med. 2018;197(5):589–94.
44. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, Custovic A. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax. 2006;61(5):376–82.
45. Saglani S. Viral infections and the development of asthma in children. Ther Adv Infect Dis. 2013;1(4):139–50.
46. Zomer-Kooijker K, van der Ent CK, Ermers MJ, Uiterwaal CS, Rovers MM, Bont LJ, RSV Corticosteroid Study Group. Increased risk of wheeze and decreased lung function after respiratory syncytial virus infection. PLoS One. 2014;9(1):e87162.
47. Eriksson M, Bennet R, Nilsson A. Wheezing following lower respiratory tract infections with respiratory syncytial virus and influenza A in infancy. Pediatr Allergy Immunol. 2000;11(3):193–7.
48. Kotaniemi-Syrjänen A, Laatikainen A, Waris M, Reijonen TM, Vainionpää R, Korppi M. Respiratory syncytial virus infection in children hospitalized for wheezing: virus-specific studies from infancy to preschool years. Acta Paediatr. 2005;94(2):159–65.
49. Bont L, Van Aalderen WM, Versteegh J, Brus F, Draaisma JT, Pekelharing-Berghuis M, et al. Airflow limitation during respiratory syncytial virus lower respiratory tract infection predicts recurrent wheezing. Pediatr Infect Dis J. 2001;20(3):277–82.
50. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol. 2005;116(3):571–7.
51. Jartti T, Smits HH, Bønnelykke K, Bircan O, Elenius V, Konradsen JR, et al.; EAACI Task Force on Clinical Practice Recommendations on Preschool Wheeze. Bronchiolitis needs a revisit: distinguishing between virus entities and their treatments. Allergy 2019;74(1):40–52.
52. Heymann PW, Platts-Mills TA, Johnston SL. Role of viral infections, atopy and antiviral immunity in the etiology of wheezing exacerbations among children and young adults. Pediatr Infect Dis J. 2005;24(11 Suppl):S217–22; discussion S220–1
53. Jartti T, Nieminen R, Vuorinen T, Lehtinen P, Vahlberg T, Gern J, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. J Allergy Clin Immunol. 2015;135(3):691–8. e9
54. Bønnelykke K, Vissing NH, Sevelsted A, Johnston SL, Bisgaard H. Association between respiratory infections in early life and later asthma is independent of virus type. J Allergy Clin Immunol. 2015;136(1):81–6. e4
55. Stenberg Hammar K, Niespodziana K, van Hage M, Kere J, Valenta R, Hedlin G, Söderhäll C. Reduced CDHR3 expression in children wheezing with rhinovirus. Pediatr Allergy Immunol. 2018;29(2):200–6.
56. Landau LI. Parental smoking: asthma and wheezing illnesses in infants and children. Paediatr Respir Rev. 2001;2(3):202–6.
57. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, et al.; U-BIOPRED Study Group. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. Eur Respir J, 2015;46(5):1322–1333 . Erratum in Eur Respir J. 2017;49(6). pii: 1550780.
58. Sonnenschein-van der Voort AM, de Kluizenaar Y, Jaddoe VW, Gabriele C, Raat H, Moll HA, Hofman A, et al. Air pollution, fetal and infant tobacco smoke exposure, and wheezing in preschool children: a population-based prospective birth cohort. Environ Health. 2012;11:91. https://doi.org/10.1186/1476-069X-11-91.

59. Peterson LA, Hecht SS. Tobacco, e-cigarettes, and child health. Curr Opin Pediatr. 2017;29(2):225–30.
60. Lee-Sarwar KA, Bacharier LB, Litonjua AA. Strategies to alter the natural history of childhood asthma. Curr Opin Allergy Clin Immunol. 2017;17(2):139–45.
61. Makadia LD, Roper PJ, Andrews JO, Tingen MS. Tobacco use and smoke exposure in children: new trends, harm, and strategies to improve health outcomes. Curr Allergy Asthma Rep. 2017;17(8):55. https://doi.org/10.1007/s11882-017-0723-0.
62. Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. Inhal Toxicol. 2013;25(2):91–101.
63. Kamboj A, Spiller HA, Casavant MJ, Chounthirath T, Smith GA. Pediatric exposure to E-cigarettes, nicotine, and tobacco products in the United States. Pediatrics. 2016;137(6):e20160041.
64. Gibbs K, Collaco JM, McGrath-Morrow SA. Impact of tobacco smoke and nicotine exposure on lung development. Chest. 2016;149(2):552–61.
65. Dinakar C, O'Connor GT. The health effects of electronic cigarettes. N Engl J Med. 2016;375(14):1372–81.
66. Chatterjee K, Alzghoul B, Innabi A, Meena N. Is vaping a gateway to smoking: a review of the longitudinal studies. Int J Adolesc Med Health. 2016;30(3) https://doi.org/10.1515/ijamh-2016-0033. Review
67. Schultz ES, Litonjua AA, Melén E. Effects of long-term exposure to traffic-related air pollution on lung function in children. Curr Allergy Asthma Rep. 2017;17(6):41.
68. Brigham EP, Woo H, McCormack M, Rice J, Koehler K, Vulcain T, et al. Omega-3 and omega-6 intake modifies asthma severity and response to indoor air pollution in children. Am J Respir Crit Care Med. 2019;199(12):1478–86. https://doi.org/10.1164/rccm.201808-1474OC.
69. Schultz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, et al. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. Am J Respir Crit Care Med. 2012;186(12):1286–91.
70. Bloomberg GR. The influence of environment, as represented by diet and air pollution, upon incidence and prevalence of wheezing illnesses in young children. Curr Opin Allergy Clin Immunol. 2011;11(2):144–9.
71. Horne BD, Joy EA, Hofmann MG, Gesteland PH, Cannon JB, Lefler JS, et al. Short-term elevation of fine particulate matter air pollution and acute lower respiratory infection. Am J Respir Crit Care Med. 2018;198(6):759–66.
72. Gehring U, Wijga AH, Hoek G, Bellander T, Berdel D, Brüske I, et al. Exposure to air pollution and development of asthma and rhinoconjunctivitis throughout childhood and adolescence: a population-based birth cohort study. Lancet Respir Med. 2015;3(12):933–42.
73. Nordling E, Berglind N, Melén E, Emenius G, Hallberg J, Nyberg F, et al. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology. 2008;19(3):401–8.
74. Hehua Z, Qing C, Shanyan G, Qijun W, Yuhong Z. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: a systematic review. Environ Res. 2017;159:519–30.
75. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007;357(19):1946–55.
76. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, Sheikh A. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS Med. 2014;11(1):e1001596.
77. Baker CD, Alvira CM. Disrupted lung development and bronchopulmonary dysplasia: opportunities for lung repair and regeneration. Curr Opin Pediatr. 2014;26(3):306–14.
78. Thunqvist P, Gustafsson PM, Schultz ES, Bellander T, Berggren-Broström E, Norman M. Lung function at 8 and 16 years after moderate-to-late preterm birth: a prospective cohort study. Pediatrics. 2016;137(4) https://doi.org/10.1542/peds.2015-2056.

79. Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, Newman Taylor AJ. Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. Thorax. 2004;59(10):855–61.
80. Goksör E, Amark M, Alm B, Gustafsson PM, Wennergren G. Asthma symptoms in early childhood—what happens then? Acta Paediatr. 2006;95(4):471–8.
81. Lynch SV, Wood RA, Boushey H, Bacharier LB, Bloomberg GR, Kattan M, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. J Allergy Clin Immunol. 2014;134(3):593–601.e12.
82. Lødrup Carlsen KC, Roll S, Carlsen KH, Mowinckel P, Wijga AH, Brunekreef B, GALEN WP 1.5 'Birth Cohorts' working group. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. PLoS One. 2012;7(8):e43214.
83. Brussee JE, Smit HA, van Strien RT, Corver K, Kerkhof M, Wijga AH, et al. Allergen exposure in infancy and the development of sensitization, wheeze, and asthma at 4 years. J Allergy Clin Immunol. 2005;115(5):946–52.
84. Casas L, Sunyer J, Tischer C, Gehring U, Wickman M, Garcia-Esteban R, et al. Early-life house dust mite allergens, childhood mite sensitization, and respiratory outcomes. Allergy. 2015;70(7):820–7.
85. Tovey ER, Almqvist C, Li Q, Crisafulli D, Marks GB. Nonlinear relationship of mite allergen exposure to mite sensitization and asthma in a birth cohort. J Allergy Clin Immunol. 2008;122(1):114–8.e1–5.
86. Dick S, Friend A, Dynes K, AlKandari F, Doust E, Cowie H, et al. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. BMJ Open. 2014;4(11):e006554.
87. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing severe asthma exacerbations in children. A randomized trial of mite-impermeable bedcovers. Am J Respir Crit Care Med. 2017;196(2):150–8.
88. Wolsk HM, Chawes BL, Litonjua AA, Hollis BW, Waage J, Stokholm J, et al. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: a combined analysis of two randomized controlled trials. PLoS One. 2017;12(10):e0186657.
89. Stenberg Hammar K, Hedlin G, Konradsen JR, Nordlund B, Kull I, Giske CG, Pedroletti C, et al. Subnormal levels of vitamin D are associated with acute wheeze in young children. Acta Paediatr. 2014;103(8):856–61.
90. Chawes BL, Bønnelykke K, Stokholm J, Vissing NH, Bjarnadóttir E, Schoos AM, et al. Effect of vitamin d3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. JAMA. 2016;315(4):353–61.
91. Anderson LN, Chen Y, Omand JA, Birken CS, Parkin PC, To T, Maguire JL, TARGet Kids Collaboration. Vitamin D exposure during pregnancy, but not early childhood, is associated with risk of childhood wheezing. J Dev Orig Health Dis. 2015;6(4):308–16.
92. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. Environ Health Perspect. 2011;119(6):748–56.
93. Thacher JD, Gruzieva O, Pershagen G, Melén E, Lorentzen JC, Kull I, Bergström A. Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. Allergy. 2017;72(6):967–74.
94. Sauni R, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T, Verbeek JH. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma (Review). Evid Based Child Health. 2013;8(3):944–1000.
95. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. Am J Clin Nutr. 2011;94(6 Suppl):1754S–8S.
96. Forno E, Young OM, Kumar R, Simhan H, Celedón JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. Pediatrics. 2014;134(2):e535–46.

97. Ekström S, Magnusson J, Kull I, Lind T, Almqvist C, Melén E, Bergström A. Maternal body mass index in early pregnancy and offspring asthma, rhinitis and eczema up to 16 years of age. Clin Exp Allergy. 2015;45(1):283–91.
98. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141(4):1169–79.
99. van Meel ER, Jaddoe VWV, Bønnelykke K, de Jongste JC, Duijts L. The role of respiratory tract infections and the microbiome in the development of asthma: a narrative review. Pediatr Pulmonol. 2017;52(10):1363–70.
100. van Meel ER, den Dekker HT, Elbert NJ, Jansen PW, Moll HA, Reiss IK, et al. A population-based prospective cohort study examining the influence of early-life respiratory tract infections on school-age lung function and asthma. Thorax. 2018;73(2):167–73.
101. Dondi A, Calamelli E, Piccinno V, Ricci G, Corsini I, Biagi C, Lanari M. Acute asthma in the pediatric emergency department: infections are the main triggers of exacerbations. Biomed Res Int. 2017;2017:9687061.
102. Strachan DP. Hay fever, hygiene, and household size. BMJ. 1989;299(6710):1259–60.
103. von Mutius E, Radon K. Living on a farm: impact on asthma induction and clinical course. Immunol Allergy Clin North Am. 2008;28(3):631–47. ix-x
104. Ege MJ, Mayer M, Normand AC, Genuneit J, Cookson WO, Braun-Fahrländer C, et al.; GABRIELA Transregio 22 Study Group. Exposure to environmental microorganisms and childhood asthma. N Engl J Med 2011;364(8):701–709.
105. Ober C, Sperling AI, von Mutius E, Vercelli D. Immune development and environment: lessons from Amish and Hutterite children. Curr Opin Immunol. 2017;48:51–60.
106. Müller-Rompa SE, Markevych I, Hose AJ, Loss G, Wouters IM, Genuneit J, et al.; GABRIELA Study Group. An approach to the asthma-protective farm effect by geocoding: good farms and better farms. Pediatr Allergy Immunol 2018;29(3):275–282.
107. Weber J, Illi S, Nowak D, Schierl R, Holst O, von Mutius E, Ege MJ. Asthma and the hygiene hypothesis. Does cleanliness matter? Am J Respir Crit Care Med. 2015;191(5):522–9.
108. Swartz J, Aronsson B, Lindblad F, Lindblad F, Järnbert-Pettersson H, Scheynius A, et al. Vaccination and allergic sensitization in early childhood – the ALADDIN birth cohort. EClinicalMedicine. 2018;4–5:92–8.
109. Earl CS, An SQ, Ryan RP. The changing face of asthma and its relation with microbes. Trends Microbiol. 2015;23(7):408–18.
110. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010;5(1):e8578.
111. Mortensen MS, Brejnrod AD, Roggenbuck M, Abu Al-Soud W, Balle C, Krogfelt KA, et al. The developing hypopharyngeal microbiota in early life. Microbiome. 2016;4(1):70.
112. Teo SM, Mok D, Pham K, Kusel M, Serralha M, Troy N, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe. 2015;17(5):704–15.
113. Biesbroek G, Tsivtsivadze E, Sanders EA, Montijn R, Veenhoven RH, Keijser BJ, Bogaert D. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. Am J Respir Crit Care Med. 2014;190(11):1283–92.
114. Bisgaard H, et al. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med. 2007;357(15):1487–95.
115. Man WH, de Steenhuijsen Piters WA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. Nat Rev Microbiol. 2017;15(5):259–70.
116. Eldeirawi K, Persky VW. History of ear infections and prevalence of asthma in a national sample of children aged 2 to 11 years: the Third National Health and Nutrition Examination Survey, 1988 to 1994. Chest. 2004;125(5):1685–92.
117. Noverr MC, Huffnagle GB. The 'microflora hypothesis' of allergic diseases. Clin Exp Allergy. 2005;35(12):1511–20.
118. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low gut microbiota diversity in early infancy precedes asthma at school age. Clin Exp Allergy. 2014;44(6):842–50.

119. Moraes TJ, Sears MR. Lower respiratory infections in early life are linked to later asthma. Thorax. 2018;73(2):105–6.
120. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, CHILD Study Investigators. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med. 2015;7(307):307ra152.
121. Fujimura KE, Sitarik AR, Havstad S, Lin DL, Levan S, Fadrosh D, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. Nat Med. 2016;22(10):1187–91.
122. Huang YJ, Boushey HA. The microbiome in asthma. J Allergy Clin Immunol. 2015;135(1):25–30.
123. Webley WC, Hahn DL. Infection-mediated asthma: etiology, mechanisms and treatment options, with focus on Chlamydia pneumoniae and macrolides. Respir Res. 2017;18(1):98.
124. Webley WC, Salva PS, Andrzejewski C, Cirino F, West CA, Tilahun Y, Stuart ES. The bronchial lavage of pediatric patients with asthma contains infectious *Chlamydia*. Am J Respir Crit Care Med. 2005;171(10):1083–8.
125. Esposito S, Blasi F, Arosio C, Fioravanti L, Fagetti L, Droghetti R, et al. Importance of acute *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections in children with wheezing. Eur Respir J. 2000;16(6):1142–6.
126. Qureshi MH, Garvy BA. Neonatal T cells in an adult lung environment are competent to resolve *Pneumocystis carinii* pneumonia. J Immunol. 2001;166(9):5704–11.
127. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015;372(9):803–13.
128. Dogaru CM, Nyffenegger D, Pescatore AM, Spycher BD, Kuehni CE. Breastfeeding and childhood asthma: systematic review and meta-analysis. Am J Epidemiol. 2014;179(10):1153–67.
129. Goksör E, Gustafsson PM, Alm B, Amark M, Wennergren G. Reduced airway function in early adulthood among subjects with wheezing disorder before two years of age. Pediatr Pulmonol. 2008;43(4):396–403.
130. Piippo-Savolainen E, Remes S, Kannisto S, Korhonen K, Korppi M. Asthma and lung function 20 years after wheezing in infancy: results from a prospective follow-up study. Arch Pediatr Adolesc Med. 2004;158(11):1070–6.
131. Goksör E, Åmark M, Alm B, Ekerljung L, Lundbäck B, Wennergren G. High risk of adult asthma following severe wheezing in early life. Pediatr Pulmonol. 2015;50(8):789–97.
132. Mulholland A, Ainsworth A, Pillarisetti N. Tools in asthma evaluation and management: when and how to use them? Indian J Pediatr. 2018;85(8):651–7.
133. Chang TS, Lemanske RF Jr, Guilbert TW, Gern JE, Coen MH, Evans MD, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. J Allergy Clin Immunol Pract. 2013;1(2):152–6.
134. Vial Dupuy A, Amat F, Pereira B, Labbe A, Just J. A simple tool to identify infants at high risk of mild to severe childhood asthma: the persistent asthma predictive score. J Asthma. 2011;48(10):1015–21.
135. Sly PD, Boner AL, Björksten B, Bush A, Custovic A, Eigenmann PA. Early identification of atopy in the prediction of persistent asthma in children. Lancet. 2008;372(9643):1100–6.
136. Caudri D, Wijga A, CM AS, Hoekstra M, Postma DS, Koppelman GH, et al. Predicting the long-term prognosis of children with symptoms suggestive of asthma at preschool age. J Allergy Clin Immunol. 2009;124(5):903–10.e1–7.
137. Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Predictors for wheezing phenotypes in the first decade of life. Respirology. 2008;13(4):537–45.
138. Pescatore AM, et al. A simple asthma prediction tool for preschool children with wheeze or cough. J Allergy Clin Immunol. 2014;133(1):111–8.e1–13.
139. Grabenhenrich LB, Reich A, Fischer F, Zepp F, Forster J, Schuster A, et al. The novel 10-item asthma prediction tool: external validation in the German MAS birth cohort. PLoS One. 2014;9(12):e115852.
140. Devulapalli CS, Carlsen KC, Håland G, Munthe-Kaas MC, Pettersen M, Mowinckel P, Carlsen KH. Severity of obstructive airways disease by age 2 years predicts asthma at 10 years of age. Thorax. 2008;63(1):8–13.

141. Pijnenburg MW. The role of FeNO in predicting asthma. Front Pediatr. 2019;7:41.
142. Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. Thorax. 2010;65(9):801–7.
143. Singer F, Luchsinger I, Inci D, Knauer N, Latzin P, Wildhaber JH, Moeller A. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. Allergy. 2013;68(4):531–8.
144. Vilmann L, Buchvald F, Green K, Nielsen KG. Fractional exhaled nitric oxide and multiple breath nitrogen washout in preschool healthy and asthmatic children. Respir Med. 2017;133:42–7.
145. Smolinska A, Klaassen EM, Dallinga JW, van de Kant KD, Jobsis Q, Moonen EJ, et al. Profiling of volatile organic compounds in exhaled breath as a strategy to find early predictive signatures of asthma in children. PLoS One. 2014;9(4):e95668.
146. Klaassen EM, van de Kant KD, Jöbsis Q, van Schayck OC, Smolinska A, Dallinga JW, et al. Exhaled biomarkers and gene expression at preschool age improve asthma prediction at 6 years of age. Am J Respir Crit Care Med. 2015;191(2):201–7.
147. Chatzimichail E, Paraskakis E, Sitzimi M, Rigas A. An intelligent system approach for asthma prediction in symptomatic preschool children. Comput Math Methods Med. 2013;2013:240182.
148. Garcia-Marcos L, Edwards J, Kennington E, Aurora P, Baraldi E, Carraro S, et al. EARIP Collaboration. Priorities for future research into asthma diagnostic tools: a PAN-EU consensus exercise from the European asthma research innovation partnership (EARIP). Clin Exp Allergy. 2018;48(2):104–20.
149. Hallberg J, Thunqvist P, Schultz ES, Kull I, Bottai M, Merritt AS, et al. Asthma phenotypes and lung function up to 16 years of age-the BAMSE cohort. Allergy. 2015;70(6):667–73.
150. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172(10):1253–8.
151. Lukkarinen M, Koistinen A, Turunen R, Lehtinen P, Vuorinen T, Jartti T. Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age. J Allergy Clin Immunol. 2017;140(4):988–95.