

Long-term studies of the natural history of asthma in childhood

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Hans Bisgaard, MD, DMSc, and Klaus Bønnelykke, MD, PhD

Activity Objectives

1. To appreciate the natural history of asthma and its implications in predicting the onset and severity of asthma, preventing disease, and allowing for individualization of disease management.
2. To become familiar with the evidence from the available long-term studies on the natural history of asthma from birth to adulthood.
3. To become familiar with the genetic markers that have been identified as risk factors for asthma.
4. To understand the role of lung function in predicting the natural history of asthma.
5. To understand the strengths and limitations of longitudinal asthma studies.

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Segmentation of children with asthma and other wheezy disorders remains the main research challenge today, as it was when described 2 centuries ago. Early childhood wheezy disorders follow different temporal trajectories, probably representing different underlying mechanisms (endophenotypes). Prospective identification of endophenotypes allowing accurate prediction of the clinical course is currently not possible. The variability of the clinical course remains an enigma and difficult to predict. Three of 4 school-aged children with asthma have outgrown disease by midadulthood. The risk of persistence increases with severity, sensitization, smoking, and female sex. Genetic risk variants might help disentangle

the heterogeneity of asthma and other wheezy disorders. At early school age, children with asthma have reduced lung function. It is an important and unresolved question whether the airflow limitation associated with asthma already existed at birth or developed along with symptoms. Likewise, the association between the infant's bronchial responsiveness and development of asthma and other wheezy disorders is unclear. Neither primary prevention through manipulation of environmental factors nor secondary prevention through the use of inhaled corticosteroids can effectively halt the long-term disease progression in childhood. In conclusion, the natural history of asthma and the associated airway changes is still poorly understood, and we have not managed to translate findings from long-term studies into a deeper understanding of the underlying endophenotypes or improved disease management. We propose the need for a translational research approach based on long-term clinical studies of birth cohorts with comprehensive and objective assessments of intermediate phenotypes and environmental exposures combined with interdisciplinary basic research and a systems biology approach. (*J Allergy Clin Immunol* 2010;126:187-97.)

Key words: Birth cohort, asthma, natural history

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Abbreviations used

ALSPAC: Avon Longitudinal Study of Parents and Children birth cohort
 CAMP: Childhood Asthma Management Program
 COAST: Childhood Origins of ASThma
 COPSAC: Copenhagen Study on Asthma in Childhood
 FLG: Filaggrin
 ICS: Inhaled corticosteroid
 MAAS: Manchester Asthma and Allergy Study
 MAS: German Multicenter Allergy Study

- *Segmentation of children with asthma and other wheezy disorders remains the main research challenge today.*

In the early 19th century, misclassification of asthma was identified as a central problem for disease management: “*Asthma, the word which properly signifies difficulty of breathing, has been as much misused, and has been made the cognomen of as many different diseases as any word in medicine,*” and it was realized that further understanding of “*the real disease, the structural alteration and preternatural sensibility of the bronchial membrane*” was needed.¹ Misclassification of a heterogeneous and poorly understood condition is the remarkably accurate description of what remains the central challenge in pediatric asthma research today.² This heterogeneity complicates understanding of the natural history of childhood asthma, suggesting there are not one but several histories to learn. Adding further to this complexity is the feature of a disease process that changes throughout life, with the peak prevalence during childhood and remissions and relapses thereafter. It is often initiated in early childhood or maybe even before birth. Therefore long-term studies investigating children from birth to adulthood are needed to understand the development of the disease and to describe the temporal pattern of symptoms and the underlying changes in the airways. Prospective studies are needed to identify unbiased associations between exposures and the initiation, development, and persistence of disease, with the aim of establishing causal inferences. Several such studies have been performed and have provided important information about subtypes (phenotypes) of asthma and other wheezy disorders with different temporal patterns and disease characteristics and have identified a number of potential risk factors. In spite of these efforts, the research aim defined almost 2 centuries ago is as relevant as ever. Asthma and its natural histories are still poorly understood, and the knowledge gained from long-term studies has had little effect on clinical disease management. We still cannot effectively predict or prevent disease, and the current treatment of asthma and other wheezy disorders in children is inadequate, particularly in early life.^{2,3} We need to take the essential step from description of phenotypes to identification of endophenotypes defined by specific underlying molecular mechanisms and treatment responses to allow improved and individualized disease management.^{4,5}

This review aims to summarize the essential evidence from long-term studies on the natural history of the clinical features of asthma and other wheezy disorders from birth to adulthood. The strengths and limitations of such studies are critically appraised to define the remaining key research questions, and strategies are proposed for future long-term studies.

NATURAL HISTORY OF SYMPTOMS IN CHILDREN WITH ASTHMA AND OTHER WHEEZY DISORDERS

- *Early childhood wheezy disorders follow different temporal trajectories probably reflecting different endophenotypes.*
- *There is no available evidence allowing prospective identification of these temporal patterns of early childhood wheeze.*
- *3:4 of school aged children with asthma have outgrown disease by mid-adulthood.*
- *Risk of persistence increases with severity, sensitization, smoking and female gender.*

Preschool age

Most cases of chronic asthma begin in preschool age. Adults with chronic asthma had a median age of symptom onset of 3 years, and 80% to 90% of cases had onset before the age of 5 years.⁶⁻⁸

Temporal patterns of wheezy disorders in early life were studied systematically in the Tucson Children's Respiratory Study of 1,246 unselected subjects followed from birth, with 66% follow-up on symptoms to age 6 years.⁹ Forty-eight percent of parents reported wheezing in the child at some point during the first 6 years of life, and 3 temporal patterns were characterized: (1) 20% presented with transient wheezing (≥ 1 respiratory tract illnesses with wheezing before the age of 3 years but no wheezing at age 6 years); (2) 15% presented with late-onset wheezing (no wheezing before the age of 3 years but wheezing at age 6 years); and (3) 14% had persistent wheezing (wheezing both before age 3 years and at age 6 years).⁹ These analyses were limited by the dichotomized outcome at 2 age points, which by default only allows these 3 temporal phenotypes: basically describing children growing out of symptoms, growing into symptoms, or continuing to have symptoms. Still, risk factors seemed to differ between the groups; persistent and late-onset wheeze at school age was associated with atopy, whereas transient wheeze was associated with maternal smoking, which supported that they might indeed represent different endophenotypes.

A different approach was used by the British Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, in which data on wheezing were available at 7 time points from birth to 7 years of age in 6,265 (45%) of the 14,062 unselected children recruited. Wheezy phenotypes were analyzed, applying a statistical analysis not limited by an *a priori* hypothesis about specific temporal phenotypes (latent class analysis).¹⁰ This largely confirmed the temporal wheezing patterns from the Tucson Children's Respiratory Study, as well as the associated risk factors. In addition, the analysis suggested a phenotype with “intermediate-onset wheeze” (ie, onset of symptoms after 18 months of age) and another with “early prolonged wheeze” (ie, onset in the first year of life but remission at 69 months of age).

The clinical value of temporal endophenotyping is limited by the retrospective definition. A clinical predictive index based on findings from the Tucson study has been proposed but still requires a history of recurrent wheeze in addition to certain known risk factors, providing a positive predictive value of only 59% for an asthma diagnosis between 6 and 13 years of age.¹¹

School age

Persistence of asthma symptoms from school age to adulthood was studied in the oldest longitudinal asthma study, the Australian

“Melbourne Asthma Study.” In 1964, a group of 295 children 7 years of age with a past history of wheezing and a control group of 106 children of similar age without wheezing were included. A group of 83 children with severe asthma was added at the age of 10 years. Eighty-three percent of the cohort provided information on asthma symptoms at 42 years of age. This study suggested an association between severity of symptoms in childhood and persistence of asthma into adult life⁷ because 20% of children with asthma at age 7 years had persistent asthma at age 42 years, increasing to almost 50% of the group with severe asthma recruited at 10 years. Eczema, hay fever, or allergic sensitization in childhood also increased the risk of more severe asthma later in life.¹²

The Dunedin Multidisciplinary Health and Development Study assessed history of asthma-like symptoms from age 9 to 26 years at 2- to 5-year intervals in 59% of the original cohort of 1,037 unselected children and reported persistence in 27% of the population followed from age 9 to 26 years.¹³ Female sex, smoking, and atopy were associated with persistence, and earlier age of onset was associated with greater risk of relapse.

The British 1958 birth cohort assessed asthma-like symptoms at 5 time points between 7 and 33 years of age in 5,801 subjects (31% of the original cohort) and reported that 27% of children with wheeze or asthma by age 7 years continued to wheeze at age 33 years.¹⁴

A general observation in these studies was that many patients experienced years without symptoms and relapse later in life.^{13,14} This demonstrates the importance of long-term follow-up and the risk of overestimating disease remission on the basis of single time points.

Follow-up of 49% of the Tucson Children's Respiratory Study suggested that the pattern of the wheezing phenotype does not change significantly from age 6 to 16 years, with persistent and late-onset wheezers having increased frequency of wheeze throughout school age and increased risk of atopy.⁸

The German Multicenter Allergy Study (MAS) recruited 815 unselected newborns and 499 newborns with high risk of atopy, with a follow-up of 58% by age 13 years. They stratified children with current wheeze at 5 to 7 years of age by means of concurrent sensitization. This suggested that sensitization is a strong risk factor for persistence of wheeze during school age, with 46% of sensitized wheezers at early school age having persistent symptoms at 13 years of age compared with 10% of nonsensitized wheezers.¹⁵

The Childhood Asthma Management Program (CAMP) study included 1,041 asthmatic children, 5 to 12 years of age, participating in a trial of anti-inflammatory treatment for 4 to 6 years and with a 4-year subsequent observational period (89% follow-up for symptom categorization). Remission was associated with lack of sensitization and allergen exposure, milder symptoms, older age, higher FEV₁, and less bronchial hyperresponsiveness.¹⁶

Adolescence and young adulthood

In the Tucson Children's Respiratory Study approximately one third (49/181) of young adults with active asthma at age 22 years had newly diagnosed asthma between 16 and 22 years of age.¹⁷ Risk factors for onset in adolescence were female sex and parental asthma. However, two thirds of these patients already had wheezing at preschool age, and one third had wheezing at 6 years of age. This illustrates the difficulty with generalization from studies on a community-based physician's diagnosis of

asthma with unknown criteria; some of the children with a late diagnosis of asthma in this study would probably have had asthma diagnosed much earlier in other cultures with a different diagnostic tradition.

In conclusion, long-term studies have revealed a number of temporal patterns of asthmatic symptoms from preschool age to adulthood. Symptoms in the first 3 years of life are often transient, and also at school age, 3 of 4 asthmatic patients will outgrow asthma by midadulthood, with an association between severity, sensitization, and risk of persistence. These temporal patterns might reflect different endophenotypes, as demonstrated by differences in related risk factors. However, the clinical usefulness of such temporal phenotyping is limited by their retrospective definitions.

NATURAL HISTORY OF LUNG FUNCTION IN CHILDREN WITH ASTHMA AND OTHER WHEEZY DISORDERS

- *It is the important research question if the early loss of lung function in asthma is a cause or a consequence of the disease.*
- *It is unclear if persistent wheeze during preschool age is preceded by neonatal airflow limitation or if such airflow limitation develops along with symptoms.*
- *Children with asthma have reduced lung function by early school age. Thereafter the lung function tracks at a fixed percentile with no evidence of a further decline in lung function.*

Asthma at school age is associated with reduced lung function, particularly in patients with severe disease. Analyses of the association between wheezing phenotypes and lung function by age 7 years in the ALSPAC birth cohort suggested that all wheezy phenotypes are associated with impaired lung function by school age.¹⁰ Similarly, the Manchester Asthma and Allergy Study (MAAS) birth cohort of 1,085 unselected newborns, with 49% and 67% having lung function measured at 3 and 5 years, respectively, reported reduced lung function in children with a history of transient and persistent but not late-onset wheeze.^{18,19} Neither of these studies accounted for the role of infant lung function in this association. Was the reduced lung function caused by the disease or causing the disease?

The important research question is whether loss of lung function associated with asthma is mainly a cause or a consequence of the disease because this will affect the strategy for preventive measures. Are children born with impaired airflow and increased responsiveness programmed for asthma and other wheezy disorders? Should we expect genetic or prenatal factors to program the disease? Or is lung function abnormality a consequence of the disease process in the early years of life? Is there an early window of opportunity to modify the disease and prevent deficits in lung function and airway remodeling?

Preschool age

The existing evidence on the association between infant spirometry and the long-term development of asthma and other wheezy disorders mainly derives from the 2 birth cohort studies: the Tucson Children's Respiratory Study (125 unselected

infants)^{8,9,17,20,21} and the Perth cohort study (243 unselected infants).²²⁻²⁷ In addition, 3 British birth cohorts reported on the short-term association between infant lung function and development of wheeze; 69 infants with 2 atopic parents from the MAAS study,²⁸ a cohort of 73 infants with at least 1 atopic parent,²⁹ and a cohort of 108 unselected infants.³⁰

The short-term follow-up from the Tucson Children's Respiratory Study^{20,21} and the Perth cohort,^{22,23} as well as 2 of the British cohorts,^{28,30} found an association between early airflow limitation and any wheeze in infancy, whereas one cohort found no such association.²⁹

The evidence from long-term follow-up is ambiguous because the Tucson Children's Respiratory Study and Perth cohorts provided conflicting answers. The Tucson cohort found an association between neonatal airflow limitation and development of transient early wheeze (100% follow-up to 6 years for 125 with infant measurements),⁹ whereas there was no such association in the Perth cohort (64% follow-up to 11 years).²⁶ Furthermore, the Tucson Children's Respiratory Study reported that infants who had persistent wheeze had normal infant lung function but significantly reduced spirometry by age 6 years,⁹ suggesting that the lung function deficit was caused by the persistent wheezy disorder in preschool years. In contrast, the Perth cohort study suggested that persistent wheeze at both 4 to 6 and 11 years of age was associated with lung function deficit in neonates, and this deficit did not seem to progress over time, suggesting that impaired infant lung function might have predetermined the development of persistent wheezy disorders.²⁶ The latter finding was supported by a cohort study of 802 unselected infants (77% follow-up) reporting association between abnormal tidal breathing patterns and asthma at 10 years of age.³¹

The Copenhagen Study on Asthma in Childhood (COPSAC) birth cohort of 411 children born of mothers with a history of asthma studied spirometry, bronchial responsiveness, and exhaled nitric oxide in neonates with a long-term diary card-based follow-up of wheezy symptoms in the first 6 years of life (76% follow-up). Exhaled nitric oxide levels (measured in 62% of the cohort) were increased in 1-month-old symptom-free babies who developed transient early wheeze but not persistent wheeze, and this was unrelated to neonatal lung function.³² This suggests a premorbid pathology that is independent of lung function abnormalities and present in asymptomatic neonates.

In conclusion, evidence from studies on the short- and long-term associations between infant lung function and the development of wheezy disorders is contradictory, partly because of few studies of limited size and with methods of little standardization. It is unknown whether lung function deficit associated with childhood asthma is a cause or a consequence of the disease.

School age

The Melbourne Asthma Cohort was followed with spirometric assessments at a 7-year interval from age 7 years until age 42 years, with 267 measured at the final review (55% follow-up).⁷ Children originally classified as having asthma had consistently lower FEV₁/FVC ratios than the control subjects. Notably, the lung function deficit was already established by the age of 7 years, with no progression occurring up to the age of 42 years, despite the fact that most patients, especially those with severe asthma, had continued symptoms throughout the follow-up period.⁷

The Dunedin Multidisciplinary Health and Development Study assessed lung function and history of asthma-like symptoms from age 9 to 26 years at 2- to 5-year intervals in 613 subjects (59% follow-up).¹³ Subjects who reported persisting or relapsing wheeze during the observation period had lower FEV₁/FVC ratios from age 9 years than children with no wheezing. The lung function deficits of these 2 groups of children remained unchanged between 9 and 26 years relative to those seen in children with milder wheezing or without wheezing.¹³

The Tucson Children's Respiratory Study confirmed that levels of lung function were established by age 6 years and did not appear to change significantly by age 16 years in children who start having asthma-like symptoms during the preschool years (n = 426, 34% follow-up).⁸ Similar findings were reported from the German MAS cohort, in which lung function in children with wheezing deficit did not progress from 7 to 13 years of age (n = 680, 52% follow-up).¹⁵

It should be noted that only the MAS cohort measured childhood lung function after bronchodilator treatment. This still showed reduced lung function in wheezing children, but the differences were attenuated. It is therefore unclear to what extent the reported lung function changes in childhood were irreversible.

A different conclusion is reached based on the CAMP study of 1,041 asthmatic children 5 to 12 years of age participating in a trial of anti-inflammatory treatment for 4 to 6 years with a 4-year further observation (90% follow-up). They observed increased airway obstruction from 5 to 18 years of age in children with mild-to-moderate asthma but only when compared with an external cohort of healthy children.³³

These reports on estimated average lung function patterns in school-aged children probably cover a diversity of endophenotypes, including patients with progressive loss of lung function and others tracking at a fixed percentile or growing into remission. Indeed, in the CAMP cohort a subpopulation of children could be identified who had pronounced disease progression: approximately 1 in 4 children included in the study with mild-to-moderate asthma had a 1% per year or greater loss in postbronchodilator FEV₁ percent predicted, although this was not accompanied by increased symptom severity.³⁴

NATURAL HISTORY OF BRONCHIAL RESPONSIVENESS IN CHILDREN WITH ASTHMA AND OTHER WHEEZY DISORDERS

- *The association between infant bronchial responsiveness and asthma and other wheezy disorders is unclear.*
- *Infant bronchial responsiveness is probably not associated with atopy as opposed to bronchial responsiveness later in life.*

It is a challenging question whether premorbid abnormal bronchial hyperresponsiveness is a determinant factor for children to have asthma and other wheezy disorders or whether bronchial hyperresponsiveness develops as part of the asthmatic pathophysiology.

Two cohorts have reported on the association between bronchial responsiveness in infancy and the development of

respiratory disease. The Perth cohort tested bronchial responsiveness to histamine on 3 occasions during the first year of life in 202 unselected infants with a forced spirometric technique and assessed asthma by age 6 and 11 years. Bronchial hyperresponsiveness at 1 month was significantly associated with asthma by age 6 years (47% follow-up)²⁴ but not by age 11 years (76% follow-up).²⁶ Bronchial responsiveness by age 12 months was associated with asthma by age 11 years,²⁷ but this assessment of responsiveness might have been influenced by viral infection and other exposures during the first year of life. A British cohort measured bronchial responsiveness to histamine at 1 month of age in 73 high-risk infants by using a forced spirometric technique. An association was reported between neonatal bronchial hyperresponsiveness and transient early wheeze but not persistent wheeze (89% follow-up at 10 years).^{29,35} Therefore a general interpretation is unclear. Neither cohort found an association between bronchial responsiveness in infancy and at school age.^{24,35}

The COPSAC birth cohort studied bronchial responsiveness to methacholine in 402 neonates. The 17q21 gene variants (*ORMDL3*) were associated with increased bronchial responsiveness in infancy and at 4 years of age but not at 6½ years of age, suggesting a genetic determinant of neonatal bronchial hyperresponsiveness.³⁶ There was no influence from other atopic symptoms in the mother or any atopic disease in the father.³⁷ Likewise, in the Perth birth cohort infant bronchial responsiveness was not associated with a family or personal history of atopy. This contrasts the common association between bronchial responsiveness at school age and atopy,^{26,38} suggesting that different factors drive bronchial responsiveness in infancy and later in life.

Bronchial hyperresponsiveness to cold-dry air at 6 years of age was a risk factor for asthma by 22 years of age in the Tucson Children's Respiratory Study,¹⁷ and hyperresponsiveness at 5 to 12 years of age was a risk factor for persistent symptoms in asthmatic children in CAMP.¹⁶

In conclusion, it is unclear whether bronchial responsiveness is a neonatal trait predisposing to asthma and other wheezy disorders or whether it develops as a consequence of the disease's pathophysiology. Possibly the neonatal bronchial responsiveness is driven by genetics and "nonatopic" mechanisms representing a different trait from bronchial responsiveness later in life.

RISK FACTORS

- The main environmental risk factors known from long-term studies to be associated with asthma and other wheezy disorders are genetics, virus, bacteria, tobacco exposure, and allergic sensitization.

Long-term studies on risk factors influencing the natural history of asthma generally belong to the more recent birth cohort studies, reflecting a changing paradigm in the past decades. While the pioneering long-term studies described above primarily focused on disease presentation, recent cohort studies have increasingly emphasized the gene-environment interactions in the natural history of disease.

There are few risk factors documented for asthma and other wheezy disorders in long-term studies, mainly genetics, viruses, bacteria, tobacco exposure, and allergic sensitization.

Genetics

Asthma is a complex genetic disease with marginal effects from multiple genetic variants that interact with multiple environmental factors to modify both susceptibility and the severity of the disease. It is likely that genetics contributes to the different natural histories of asthma.

The initial candidate gene approach was largely disappointing, with marginal effects and poor replication between studies.³⁹ The genetic effects uncovered are generally small (odds ratio, <1.5), and since the completion of the first genome-wide analyses, it is unlikely that variants with larger effects will be found with this 1-dimensional approach.

Still, the gene variants with strong replications are fascinating examples of how genetics might help our understanding of asthma and its natural history. The risk variants in the gene coding for the skin barrier protein filaggrin (*FLG*) is the strongest known genetic risk factor for eczema.⁴⁰ Detailed long-term phenotyping in the COPSAC birth cohort suggested an *FLG*-associated pattern of atopic disease in early childhood characterized by very early onset of eczema, followed by early onset of acute severe asthmatic exacerbations and later development of sensitization (Fig 1, A).⁴¹ An association with wheeze and asthma both in the first years of life and at school age has also been reported from other cohorts.^{42,43} The pathway leading from skin barrier dysfunction to asthma is unknown, and the temporal pattern suggests that this is not mediated by sensitization. Importantly, *FLG* seems only to be expressed in the skin, suggesting that *FLG* might define a specific asthma endophenotype initiated by impaired skin barrier function, proposing a novel disease mechanism in asthma.

The chromosome 17q21 locus (*ORMDL3*) was the first asthma gene variant to be discovered by means of genome-wide association analysis.⁴⁴ Longitudinal clinical phenotyping in the COPSAC birth cohort suggests that this genetic variation is associated with a nonatopic asthma phenotype characterized by bronchial hyperresponsiveness in newborns and in young children, early-onset acute severe asthmatic exacerbations but without conferring risk of eczema, rhinitis, or allergic sensitization (Fig 2, B).³⁶

DENND1B gene variants were discovered in a second genome-wide association study as a risk factor for childhood asthma and replicated in both white and African American populations. *DENND1B* is upregulated in effector memory T cells, suggesting a role in the adaptive immune response. The gene effect was strongest for early-onset asthma, but the detailed phenotype associated with this genetic variation still needs to be described.⁴⁵

FLG, *ORMDL3*, and *DENN* gene variants are likely to represent different disease mechanisms and exemplify how genetics might help define novel asthma endophenotypes.

Viruses

Viral infection is associated with acute disease worsening and a putative causative factor.⁴⁶ Long-term population-based studies reported that infants with respiratory syncytial virus-induced bronchiolitis had abnormal pulmonary function, wheezing, and asthma in childhood.⁴⁷⁻⁵⁰

The Childhood Origins of Asthma birth cohort study (COAST) followed a birth cohort of 289 children at high risk for asthma, focusing on viral infections during wheezy episodes in the first year of life. Rhinovirus in association with wheezy episodes appeared to be a strong predictor of asthma by age 6 years (90% follow-up).^{51,52} However, other long-term studies reported that

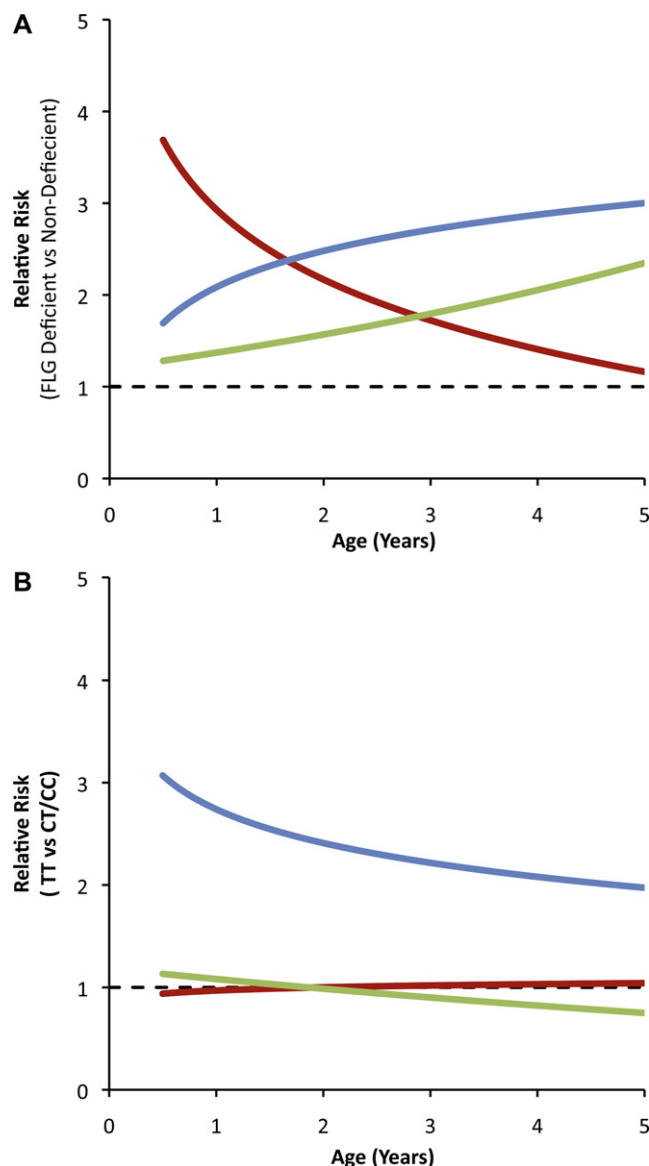


FIG 1. Genetic variants might define novel endophenotypes with different underlying mechanisms. Close clinical symptom monitoring in the COPSAC birth cohort suggested that *FLG* and *ORMDL3* variants define 2 distinct endophenotypes. The logarithmic regression lines were calculated from the observed relative risks previously published.^{36,41} **A**, *FLG*-associated endophenotype characterized by very early onset of eczema, followed by acute severe asthmatic exacerbations and later development of sensitization.⁴¹ **B**, *ORMDL3*-associated endophenotype (rs7216389) characterized by a strong effect on early development of recurrent wheeze with acute severe asthmatic exacerbations but no effects on eczema or allergic sensitization.³⁶ Red line, eczema; blue line, acute severe asthmatic exacerbations; green line, allergic sensitization.

predisposition to asthma and atopy^{53,54} and early wheezy symptoms⁵⁵ were associated with increased risk of lower respiratory tract infection and respiratory syncytial virus hospitalization. Furthermore, increased concordance of severe respiratory syncytial virus infection in identical twins suggested that genetics is the major determinant of the response to virus.⁵⁶ Therefore the direction of causality is unknown. Do certain viral infections increase the risk of asthma or is asthma constitution increasing the risk of severe response to viral infections?

Bacteria

The bacterial burden is a major exposure in the newborn baby, who is otherwise exposed to a limited range of environmental factors. The neonatal period is particularly critical in terms of mucosal defense and immunologic priming, and it has been hypothesized that the maturation of the immune system is dependent on the bacterial milieu, with a potential skewing from an unfavorable ecology; that is, an unfavorable composition of commensal bacteria can cause immune deviation, leading to asthma, eczema, and allergy.⁵⁷⁻⁶⁰ The commensal bacteria are determined by lifestyle.

The gut flora have been the prime focus for the working hypothesis targeting bacterial ecology in the development of asthma. However, prospective studies found no association between infant microbiota of the gut and risk of recurrent wheeze before 2 years of age.⁶¹

Colonization of the airways has only been studied recently, probably because of the common misconception that the lower airways are sterile, when in fact the bronchial tree contains a characteristic microbiota that is disturbed in asthmatic airways.⁶² COPSAC is a long-term clinical birth cohort study with deep phenotyping, objective exposure assessments, and genomic research. COPSAC showed a strong association between colonization of the airways with common pathogenic bacteria (measured in 321 children [78%] of the cohort) and development of asthma by age 5 years (Fig 2).⁶³ Similar to viruses, it is unknown whether the bacterial colonization acts as the environmental trigger in genetically predisposed persons or whether this colonization is merely a marker of the underlying genetic asthmatic constitution.

Some aspects of living on a farm in early life appear to protect against the development of allergic diseases,⁶⁴ and subsequent studies have suggested environmental exposure to bacterial products (endotoxins) also in non-farm environments to protect against allergic asthma but not non-atopic wheeze,⁶⁵ which could relate to exposure to a beneficial bacterial ecology.

Tobacco exposures

Tobacco exposure is probably the strongest known environmental modifier of the natural history of asthma. The mother's smoking status was associated with a 7% deficit in lung function among newborns in a comprehensive risk analysis in the COPSAC cohort.³⁷ Prenatal and postnatal smoke exposure has been linked to asthma and other wheezy disorders, particularly to disease in the first years of life and less strongly to asthma later in life.⁶⁶⁻⁶⁸

Allergic sensitization

The German MAS cohort showed that early and persistent sensitization was associated with asthma,³⁸ although only in children with an atopic family history, indicating that the relationship between sensitization and asthma is interacting with genetic factors.⁶⁹ High levels of early allergen exposure combined with sensitization to perennial allergens before 3 years of age were associated with loss of lung function and development of airway hyperresponsiveness at school age.¹⁵

A machine-learning approach for detection of latent classes of sensitization in the British MAAS cohort suggested that a pattern of multiple early sensitizations is a particular strong risk factor, proposing a heterogeneity in the pattern of sensitizations relevant for the risk of asthma.⁷⁰

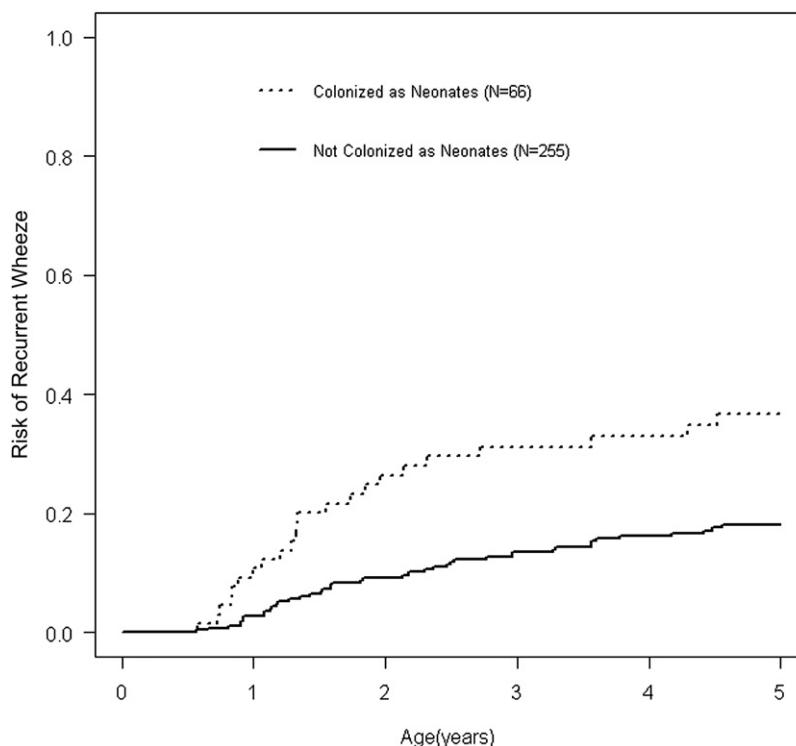


FIG 2. Risk of recurrent wheeze. COPSAC showed a strong association between colonization of the airways with common pathogenic bacteria and development of recurrent wheeze and asthma.⁶³ The close clinical monitoring of age of onset for exposure and outcome allows survival statistics as a powerful statistical tool, as illustrated here by the inverse Kaplan-Meier plot. Copyright 2007 *New England Journal of Medicine*.

Perennial and multiple allergies are rare in the first years of life, and this mechanism can only explain a minority of asthma in the population and an even smaller proportion of preschool wheeze. The population attributable risk of allergic sensitization for current asthma in children and adults is less than 40% based on analyses of both cross-sectional and longitudinal studies.⁷¹ The population attributable risk decreases to only 4% in relation to exposure to the common indoor allergen from house dust mite.⁷² This indicates that any important role of allergy or allergen exposure in the primary causation of asthma assumes interaction with other independent factors.

MODIFYING THE NATURAL HISTORY OF ASTHMA

- *Neither primary prevention through manipulation of environmental factors nor secondary prevention through use of ICS can effectively halt the long-term disease progression in childhood asthma or the progression from episodic to persistent wheezing.*

It is an attractive hypothesis that remodeling of the airways developing over years of persistent asthma could evoke an irreversible airway obstruction phenotype. However, there is little evidence to support this concept, and there is currently no consensus on whether disease progression requires airway inflammation, airway remodeling, or their combination. There is scarcely any proof of a direct association between objective measures of airflow obstruction and remodeling. Neither the degree of thickening of the reticular basement membrane nor the increase in airway smooth muscle mass correlates consistently with the duration or severity of

asthma.⁷³ Indeed, a number of patients have substantial remodeling but have disease that remains well controlled.⁷³

Primary prevention of asthma through allergen avoidance has shown inconsistent results in randomized controlled trials⁷⁴⁻⁷⁸ and is generally not recommended in international guidelines.

Secondary prevention of asthma progression with inhaled corticosteroids (ICSs) was initially suggested from a randomized controlled trial in adults with asthma, suggesting that asthmatic patients who started treatment 2 years late did not achieve the same recovery of lung function as those starting early.⁷⁹ A large multinational trial randomized patients 5 to 66 years of age within 2 years of onset of asthma, mostly mild persistent asthma, to ICSs or placebo for 3 years. ICSs reduced the mean decrease in FEV₁/FVC ratio among adults during treatment, confirming ICSs as a good controller treatment also in mild asthma.^{80,81} The treatment effect was less marked among children younger than 11 years than among adults and was insignificant among adolescents. Importantly, the study did not assess a possible differential effect on lung function recovery from early or delayed use of ICSs.

Secondary prevention of asthma in children from ICS treatment was suggested from a retrospective uncontrolled report.⁸² However, the disease-modifying effect from ICSs could not be confirmed in a controlled long-term trial in children with moderately severe asthma and an average 5-year history of confirmed asthma.⁸³ Long-term studies reviewed above suggested that the main deficit in lung function is already present at age 6 years and might indeed be present from an early onset. Therefore the disease-modifying effect of ICS treatment was subsequently tested in young children from age 3 years with an average

2-year asthma history,⁸⁴ young children of 1½ years with a 1-year history of wheezy symptoms,⁸⁵ and eventually in infants from the first verified wheezy episode.⁸⁶ None of these large-scale, double-blind, randomized, controlled long-term trials found any indication of a disease-modifying effect from use of ICSs.

STRENGTHS AND LIMITATIONS OF LONG-TERM STUDIES

- *Long-term, classical epidemiological studies are at high risk of misclassification with imprecise outcome and exposure assessments.*
- *Long-term clinical cohort studies gain power from deep phenotyping with accurate time-of-onset and objective clinical information and exposure assessments.*

Prospective long-term studies aim to describe disease progression and identify unbiased associations between specified exposures and subsequent development of disease outcomes with the aim of establishing causal inferences. Such studies provide unique evidence, generally of high validity, that provides insight into natural history not obtainable otherwise. Still, a number of important limitations to the long-term cohort design should be considered.

The early cohort studies on asthma in childhood recruited children at school age. Later, it became clear that programming had to occur in early life because asthma and wheezy disorders present in very young children, which led to a focus on birth cohorts. More recently, there has been an increasing emphasis on the importance of the gene-environment interactions occurring during pregnancy and perinatal life, and hence pregnancy cohorts are currently being recruited for long-term studies of the origins of asthma.

Observational studies can only suggest associations. Randomized controlled trials of interventions aimed at modifying suspected exposures will be needed to prove their causal effects. Furthermore, confounding of associations in observational long-term studies remains a risk, despite extensive attempts to adjust for covariates, because underlying variables are either unknown or unavailable.

Accurate information on age of onset for exposure and outcome might help in identifying disease mechanisms and the relevant timing of preventive measures. Genetic studies^{36,87,88} and risk factor studies⁶³ have demonstrated that age of onset might be an important characteristic of endophenotypes (Figs 1 and 2).

Disease-related modification of exposure (inverse causality) concerns the interaction between cause and effect. The effect from breast-feeding is a classic example in which inverse causation might lead to erroneous conclusions. Debut of symptoms of eczema or wheezy disorder tends to prolong the duration of exclusive breast-feeding because of the general belief in its protective effect.^{89,90} Such inverse causation could be misinterpreted as the duration of breast-feeding leading to eczema or wheezy disorder, when in fact, the disorders lead to longer breast-feeding. Only long-term observations of the start and end of exposure and disease can account for such bias.⁹¹

Differential loss to follow-up, in which adherence might relate to symptoms or risk, is critical to long-term studies. Some of the reported follow-up studies only included half of the population with a potential bias from overrepresentation of symptomatic subjects and loss of external validity.

Representation of the general population is often biased. Cohorts of predefined high-risk populations are limited by a lack of external validity. A similar but more subtle confounding might be caused by subjects willing to participate in “unselected” cohort studies, who are generally more likely to have a history or risk of related diseases.

The comparator chosen is critical for the analysis. In case-control designs subjects without any symptoms are often chosen as control subjects. However, there are indications that such children are distinctly different,⁹² and the long-term cohort design allows inclusion of a more appropriate disease spectrum as a control.

Differential bias regarding baseline characteristics and recall bias of symptoms and exposure can only be minimized with close prospective follow-up and preferably the use of diary records.

Misclassification of outcomes caused by interobserver variation is a particular risk for classical epidemiologic studies based on information from registries or questionnaires when analyzing complex diseases, such as asthma, in which the clinical presentation is instrumental to the diagnosis. Asthma is a syndrome of traits with little consensus and classification of symptoms, which is subject to large differences among patients, physicians, and cultures and changes in diagnostic tradition over time, as well as with a capricious clinical course. Further risk of misclassification is introduced by reliance on parental reports of wheezing without corroborating clinical assessment. Many studies are community-based parental reports of wheezing history based on the regrettable tradition of defining asthma specifically from the term wheeze. However, *wheeze* carries little specific meaning outside the Anglo-Saxon languages and has no translation in many countries. Even within the English-speaking cultures, many studies have documented that laypersons and even specialists have difficulties recognizing wheeze. Other studies have shown that other symptoms, including persistent cough, are as closely related to asthma as wheeze.⁹³⁻⁹⁹

Physician-diagnosed asthma is often used to qualify the diagnosis, but clearly there is little consensus on asthma diagnosis between physicians, and this problem is particularly pronounced in young children, in whom there are no objective measurements available in clinical practice. In many countries physicians hesitate to use the term asthma until school age, with an obvious effect on long-term epidemiologic studies.

Traditional paradigms will bias the common diagnostic practices in the community. For example, many doctors are more likely to use the term asthma if a child is known to be allergic, hence capturing a particular phenotype while excluding others.

The concept of asthma and wheeze has changed in the past decades. Probably the term asthma is more inclusive today than previously with physicians' diagnoses including many children with milder symptoms who might previously not have had an asthma diagnosis. Also, there is a generally increased awareness of the disease, which is likely to increase reporting.

Objective assessments are important for unbiased measurement of outcomes and exposure variables. This is likely to reduce misclassification and variance, leading to improved resolution of true differences.

Long-term studies with careful attention to all of the above issues present a terrifying challenge. Studies involving close clinical follow-up and objective assessments are often limited in sample size by the huge resource requirements. However, the

advantages of prospective clinical cohort studies with deep phenotyping and objective assessments of exposures provide an important novel approach to understanding the natural history of the asthma disease.

FUTURE LONG-TERM STUDIES OF THE NATURAL HISTORY OF ASTHMA IN CHILDHOOD

The burden of uncontrolled asthma reflects in part the failure of previous segmented research strategies. Indeed, the extent to which it will be possible to relate findings at the molecular level to clinical phenotypes is a central and general problem for current medical science.¹⁰⁰

Large-scale, long-term observational studies have provided much insight into the nature of asthma and wheezy disorders. However, very little of the research has affected clinical management. New research alliances and novel analytic approaches are needed to achieve more than just interesting observations of statistically significant associations.

Imprecision of phenotyping of asthma together with the disease's heterogeneity and age-dependent presentation confounds the end point in any genetic and risk factor analysis. There is a need for long-term studies of the natural history of the disease in cohorts starting before birth with longitudinal deep phenotyping: repeated objective assessments to differentiate the age-dependent disease processes, to identify intermediary phenotypes and early predictors of disease progression, and to disentangle the current broad-based disease definitions. In addition, objective exposure assessments are needed to assess interactions of specific environmental factors in the induction or repression of asthma-related genes.

The statistical approaches to longitudinal data reported hitherto have only inadequately described the complexity of phenotypic variation in a clinical setting, and long-term epidemiologic research has primarily focused on analyses of monocausal effect. This is unlikely to reveal the divergent molecular mechanisms and gene-environment interactions underlying different endophenotypes. Novel methodologic approaches, such as principal component analyses and techniques clustering subjects with similar intermediate traits or trajectories of symptom history, may provide novel paradigms for the classification of asthma and wheezing illnesses in children^{10,101,102} and optimize the value of the multidimensional data from the more comprehensive long-term cohort studies. A systems biology analysis framework might overcome past limitations of genome-wide association studies and reduce the requirement of an enormous number of samples.¹⁰³⁻¹⁰⁵ It might identify protein complexes or pathway/network subcircuits associated with disease, allowing us to understand the basis for disease susceptibility and environmental influence, and offer an explanation for the different phenotypic manifestations of the same disease to define disease prognosis with greater accuracy and to refine and individualize disease treatment for optimal therapeutic efficacy.^{106,107}

An unbiased translational research approach based on long-term clinical studies of birth cohorts with deep phenotyping and exposure assessment combined with genotyping, insight into the genetic regulation of basic biological processes, and a state-of-the-art systems biology approach holds the promise to improve our understanding of the processes causing disease in individual patients and the interaction between heredity and environment. This might lead to the discovery of novel susceptibility genes and

disease pathways, providing the basis for the development of novel diagnostic tests, identification of molecular drug targets, and the possibility of tailoring treatment for personalized medicine.

What do we know?

- Early childhood wheezy disorders follow different temporal trajectories, probably reflecting different endophenotypes.
- Three of 4 school-aged children with asthma have outgrown disease by midadulthood.
- Risk of persistence increases with severity, sensitization, smoking, and female sex.
- Children with asthma have reduced lung function by early school age. Thereafter the lung function seems to track at a fixed percentile in the majority of children.
- The main risk factors associated with asthma and other wheezy disorders in long-term studies are genetic variants, viruses, bacteria, tobacco exposure, and allergic sensitization.
- Neither primary prevention through manipulation of environmental factors nor secondary prevention through use of ICSs can effectively halt the long-term disease progression in childhood asthma or the progression from episodic to persistent wheezing.
- Studies on asthma in early life have a high risk of disease misclassification.
- Long-term clinical cohort studies gain power from deep phenotyping with objective assessments of disease and exposures and age-of-onset information.

What is still unknown?

- Segmentation of children with asthma and other wheezy disorders remains the main research challenge today.
- It is an important research question whether the early loss of lung function in asthma is a cause or a consequence of the disease.
- Evidence is contradictory on the relation between airflow limitation in neonates and development of asthma and other wheezy disorders. It is unclear whether persistent wheeze during preschool age is preceded by neonatal airflow limitation or whether such airflow limitation develops along with symptoms.
- Likewise, the direction of causality is uncertain between infant bronchial responsiveness and asthma and other wheezy disorders is unclear.
- There is a need to translate findings from long-term studies into a deeper understanding of the underlying endophenotypes to improve disease management.

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