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# The Potential to Predict The Course of Childhood Asthma

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## Abstract

Many children experience pre-school or early childhood wheezing. In a significant proportion symptoms disappear as the child grows, but others have persistent and troublesome asthma which can be life-long. Tools to predict course of disease in young children are a priority for families and clinicians. This review summarizes evidence from several longitudinal population-based birth-cohort studies that have identified risk factors for persistence and remission of childhood asthma. These factors include clinical characteristics, environmental and other exposures, familial factors, biomarkers of allergic inflammation, measurements of lung function and airway responsiveness, and genetic variants. This review also introduces the concept of polygenic risk and genetic risk scores, and describes results from a recent study that suggests promise for the use of genetic information in predicting the course of childhood asthma. We conclude with a discussion of implications and future directions.

Asthma is the commonest chronic non-communicable disease of childhood. Prevalence figures vary, but up to 20% of children report recurrent wheezing. In some, early childhood wheezing disappears, but others have persistent and troublesome life-long asthma.[1–4] Identification of children whose symptoms will persist and who will develop more troublesome disease is a clinical priority. Which children should be more actively treated for asthma in the hope of reducing long-term morbidity? Can we use clinical characteristics, physiological measurements, biomarkers or genetics to more precisely determine outcomes? When can we reassure parents that their child will “outgrow” asthma? Sensitive and specific tests to determine which children will suffer persistent symptoms and which will recover remain a work in progress, but longitudinal population-based birth-cohort studies provide insights into risk factors for persistent disease.[3,5–11]

## Sex and Age at Onset

Persistence is more frequent in boys in most longitudinal studies tracking asthma from early to middle childhood,[8,10] although not all studies find sex differences.[9] In studies with a longer duration of follow-up, asthma persistence after puberty is more frequent in girls.[3,5] Earlier age of onset is associated with increased risk of asthma persistence. In the Tucson Children’s Respiratory Study, asthma onset by age-6 years and persistent wheezing in early life predicted 7-fold and 14-fold increases in odds of chronic asthma at age-22 years.[5] In the Dunedin longitudinal study, each 1-year increase in age at asthma onset predicted an 11% decrease in the odds of persistent asthma.[3]

## Symptom Severity

More frequent/severe childhood symptoms predict increased risk of asthma persistence. In a report from Tasmania, only 25% of children continued to wheeze as adults,[1] whereas in a simultaneous report from Melbourne, the rate of persistence was 70%.[12] This discrepancy was due to the Melbourne cohort being “enriched” with children with more severe asthma.[13] Many studies confirm that more severe symptoms predict a doubling or tripling of the odds of persistence.[6,8,14,15]

## Rhinoconjunctivitis and Eczema

Rhinoconjunctivitis and eczema increase the likelihood of persistence.[14] In the Tasmanian study, 29.7% of persistent atopic asthma was attributable to concomitant childhood eczema or rhinitis; the combination of these two risk factors predicted a nearly 12-fold increase in the odds of adult atopic asthma.[16,17] In the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, eczema before age-4 years more than doubled the odds that early symptoms would persist to become overt clinical asthma at age 7–8 years.[8]

## Allergy

Allergic sensitization, a major driver of development of asthma, is also related to persistence of disease.[18] In the German Multicentre Allergy Study (MAS), sensitization to indoor (mite, cat and dog) allergens by age-3 years gave a positive predicted value (PPV) of 57% for asthma at 11–13 years; when exposure to cat, dog or mite allergen before age-3 years was in the upper quartile of the distribution in the total MAS population, PPV for persistent asthma was 83%.[7] Early childhood allergic sensitization also predicted diminished lung function and airway hyper-responsiveness at ages 7–13 years in the MAS cohort.[19] Allergens of interest differ according to location; in the Tucson cohort, sensitization to *Alternaria alternata* by age-6 years trebled the odds of chronic asthma at 22 years.[5]

## Infection

In the Isle of Wight study, persistence to age-10 years was doubled in those with a history of recurrent chest infections at 2 years.[20] In the PIAMA cohort, respiratory tract infections 1–2 times per year between birth and 4 years almost doubled the risk of asthma at age 7–8 years while ≥3 infections per year almost trebled the risk.[8] Among 198 sensitized children in Perth, the risk of subsequent persistent wheeze was 49% with 3 severe lower respiratory tract illnesses in the first 2 years of life, increasing to 75% with 6 such episodes.[21] Early-childhood infections may also predispose to other risk factors for asthma persistence such as atopy, although whether viral infection is causal of asthma or instead acts to reveal latent disease is uncertain.[22]

## Socioeconomic Status

In the PIAMA and Generation R cohorts respectively, medium or low parental education was associated with a 50% and 60% increase in the odds of persistent childhood asthma relative to children with highly educated parents.[8,10] These associations likely reflect a combination of physical and social environmental factors.[23]

## Allergic Inflammation

Blood eosinophils have been measured for decades as markers of allergic inflammation, and have a modest predictive role with respect to persistent asthma. Eosinophilia >470/$mm^3$ was a risk factor ($p<0.001$) for persistence of wheezing to age-6 in a clinical cohort of infants in

France.[24] Blood eosinophilia ≥4% is included in the minor criteria of the Asthma Predictive Index.[25] Measurements of serum IgE from birth onwards have often been assessed for their predictive role in the development of asthma, but may also predict persistence. In the PIAMA cohort, specific IgE measured at 4 years predicted an almost three-fold increase in the odds of wheezing and asthma at 8 years after adjustments for clinical status.[26] In the MAS cohort, elevated total IgE at 3 years in children with wheeze before age-3 trebled the risk of wheezing at 11–13 years.[7]

## Lung Function

In the Tucson cohort, low airway function at 6 years, defined as flow rates in the lowest quartile of VmaxFRC, doubled the risk of chronic asthma at 22 years.[5] Abnormal interrupter resistance (Rint) measured at age-4 years in PIAMA was associated with wheezing at age-6 years, independently of the clinical history, but not at 7 and 8 years.[26] In the Dunedin cohort, study members with persistent adult asthma were found to have had low lung function from the first measurement at age-9 years, suggesting airflow obstruction developed at a young age in those destined to have persistent disease.[3]

Airway hyper-responsiveness (AHR) measurements likewise have predictive value. In the Tucson cohort, AHR measured by cold air challenge at 6 years predicted a more than four-fold increase in the odds of chronic asthma at 22 years.[5] In the Dunedin cohort, children with positive methacholine challenges in childhood were at a three-fold increased risk of persisting asthma in young adulthood.[3] In the Norwegian birth cohort, AHR at age-10 years appeared a weak predictor of persistence at age-16 years.[27] However the predictive value improved substantially when results were stratified by severity; 54% of those with the greatest degree of AHR ($PD_{20}$ ≤1 μmol) at 10 years had active asthma at 16 years.[28]

Exhaled fraction of Nitric Oxide (FeNO) had predictive value both in relation to onset of new asthma[29] and persistence. In the PIAMA cohort, each IQR increase in log-10 FeNO measured at 4 years predicted a 60% increase in odds of wheezing and asthma at 8 years, even after adjusting for IgE and clinical history.[26]

## Genetics

A positive family history of asthma or atopy is associated with increased risk of asthma persistence. In the PIAMA, Generation R, and MAS cohorts, ‘any parental asthma’ more than doubled the odds of asthma persistence.[7,8,10] Evidence is mixed as to whether the sex of the parent with asthma matters to risk of transmission.[9,24]

Genetic variants discovered in genome-wide association studies (GWAS) may also provide prognostic information about the course of asthma. GWAS have identified genes that modulate aspects of the natural history of asthma such as atopy, lung development, and susceptibility to more severe disease, suggesting promise for genetic prediction of the course of asthma.[30] GWAS of the course of asthma are not yet feasible because relatively few data exist that follow children in to adulthood.[31] GWAS have discovered loci associated with childhood onset of asthma [32–35] and revealed asthma to be highly polygenic—influenced by many different genetic factors, each which making small contributions to pathogenesis.[36] A promising approach to studying polygenic conditions is to use “genetic risk scores” that summarize information from a set of discovered risk variants to produce a continuously distributed index of genetic liability.[37–42] Because genetic risk scores aggregate information from multiple risk variants, they measure a larger genetic effect and can be studied in much smaller samples than are required for GWAS. Genetic risk scores thus provide an opportunity to test how genetic risks discovered in GWAS relate to persistence of asthma.[43]

A genetic risk score study of the natural history of asthma to age-38 years has been conducted in the Dunedin cohort.[11] The score used in that study comprised 15 variants discovered in the GABRIEL Consortium asthma GWAS of over 26,000 cases and controls.[35] In the Dunedin cohort, a higher genetic risk score not only predicted asthma with onset early in childhood, atopy and AHR, but also predicted life-course-persistence of asthma and development of incompletely reversible airflow obstruction, more days missed from school and work due to asthma and increased likelihood of admission to hospital. Within the 21% of the cohort who had developed asthma by age-13 years, those with higher genetic risk were more likely to suffer symptoms through age-38 years; each standard deviation increase in the genetic risk score predicted a 20% increase in the risk of persistent asthma through midlife.

The small magnitude of the genetic effect means that even for children with asthma who have very low or very high genetic risk scores, course is uncertain; one in three children with a genetic risk score 2 standard deviations (SD) below the mean may be expected to suffer persistent symptoms, while one in three with a genetic risk score 2 SD above the mean may be expected to experience remission. Genetic effects were similarly modest for other outcomes. Further, among cohort members who never developed asthma, genetic risk was normally distributed—meaning that a proportion of individuals with very high genetic risk scores never developed asthma. Therefore, these results require a cautious approach regarding the clinical implementation of genetic testing in asthma care.[44] Additionally, replication is needed of the observations from the Dunedin cohort.

It is uncertain whether even large increases in GWAS sample size will substantially improve genetic prediction for asthma.[45,46] The next step in translating GWAS discoveries into tools useful to the clinician is therefore to integrate information about genetics with information about the environment.[44][47] New evidence that the 17q21 locus repeatedly replicated in asthma GWAS is made more virulent by childhood exposure to rhinovirus[48] highlights the potential in such gene-environment interaction research. Other promising environments to examine in relation to GWAS discoveries include early-life allergen and microbial exposures, both in cases where evidence for association with asthma is conflicting, such as breast-feeding[49,50] and dog and cat ownership,[51] and cases where risk and protective effects are well established, such as microbial exposures associated with growing up in a farm environment.[52–54] As additional gene-environment interactions in asthma are documented, it may be possible to develop algorithms that generate sufficiently sensitive and specific predictions to be useful in the clinic.

Can we currently predict the course of asthma? In 2008, an ERS Task Force proposed a new classification to divide the heterogeneous population with early childhood wheezing into “episodic (viral) wheeze” and “multi-trigger wheeze” on the basis of published scientific findings and expert opinion.[55] In a recent analysis of PIAMA study data, Savenije and colleagues[56] found the ERS taskforce classification showed little correspondence with wheezing phenotypes derived from longitudinal latent class analysis[57] or hypothesis-based definitions of transient early or persistent wheeze as originally described in the Tucson study[58]. Other published prediction rules to identify preschool children having asthma at school age[25,59] were considered of limited value. The path to improved prediction will require refinement of existing approaches—increasing precision of risk factor definitions, more precise phenotyping with objective measures, combining non-invasive measures with prediction rules—incorporation of novel biomarkers—DNA sequence variants, gene expression and epigenetic marking profiles—and identification and incorporation of interactions among environmental, genetic, and phenotypic risk factors.[56]

In conclusion, there is broad agreement among population studies that childhood wheezing that is frequent and severe, and is associated with atopy, impaired lung function and airway hyperresponsiveness, is likely to be persistent throughout childhood and into adulthood. The possibilities of genomic prediction, including genetic risk scores, gene-environment interactions, and transcriptomic and epigenetic signatures, are just beginning to be explored. Much more remains to be done before we can, with a high level of confidence, predict on an individual level which children will have persistent asthma.

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## Key Issues

1. Childhood asthma is common. For many children, asthma is a childhood-limited problem, but for others symptoms persist across the life course.
2. Risk factors for persistent asthma have been identified from birth cohort studies that follow un-selected samples of children over time and track the onset and course of asthma.
3. Risk factors for persistent asthma include young age at onset, manifestation of severe symptoms including airway hyper-responsiveness and airflow obstruction in early childhood, rhinoconjunctivitis and eczema, childhood allergic sensitization, respiratory infections, and family history of asthma.
4. Genome-wide association studies have discovered asthma-associated genetic variants and revealed that most of the population carries some degree of genetic risk for asthma, while smaller groups are at especially low or especially high risk.
5. Children with asthma who carry higher levels of genetic risk may be predisposed to a persistent course of disease, according to one birth cohort study, although genetic predictions have low sensitivity and specificity.
6. Despite efforts to combine information across risk factors, it is not yet possible to predict course of childhood onset asthma with accuracy and existing predictive algorithms often yield conflicting results.
7. More precise definitions of risk factors and standardized approaches to phenotyping asthma are needed to improve accuracy of predictive algorithms.
8. Integrating genomic information into prediction algorithms may also improve accuracy, especially if interactions among genomic, phenotypic, and environmental factors can be quantified.