Epidemiology, Risk Factors and Natural History of Asthma

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SECTION

Asthma

Chapter Outline

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KEY POINTS

- Asthma is a clinical diagnosis characterized by bronchial hyperresponsiveness and reversible airflow obstruction
- The reported prevalence of asthma is higher in developed countries, ranging from 1.6 to 28%. In India, the prevalence varies from 2–20% in different parts
- Children who have been diagnosed with asthma may have about 20–25% risk of persistence of symptoms till adulthood
- Recognition of specific pathways of inflammation that are activated in asthma has helped to define specific asthma endotypes
- Atopy in the child or the parent(s) constitutes one of the most important risk factor for the development of asthma in the child
- Various genes have been linked to development of asthma and to its severity
- There is improved understanding of the influence of diet and early life changes in gut and airway microbiome on the subsequent development of atopy and asthma
- With the knowledge of potential risk factors and factors that influence the severity, there have been attempts to prevent asthma by early antenatal and postnatal interventions and to alter the natural history of asthma by modifications in diet and environment

DEFINITION OF ASTHMA

Asthma is a clinical diagnosis characterized by bronchial hyper-responsiveness (BHR) and reversible airflow obstruction that produces recurrent respiratory symptoms of wheeze, shortness of breath, and cough, which usually responds to bronchodilators and anti-inflammatory therapy. External factors like exposures in fetal life and environmental exposures act in concordance with genetic susceptibility and personal or family history of atopy to produce the clinical symptomatology of asthma.[1]

While BHR can be measured objectively, its presence alone may not imply a diagnosis of asthma, as 10% of the normal population and 30% of those with allergic rhinitis may demonstrate this phenomenon.[2] The term reactive airway disease, which may signify this bronchial hyperreactivity, cannot be used interchangeably with asthma and its use should, therefore, be abandoned.[3] Our current knowledge of asthma has developed over the decades but what clearly constitutes asthma has not been uniformly applied across all the prospective studies carried out over the last few decades. Other methodological differences like different case selection methods, variable periods of follow-up, and the different methods of evaluation bring considerable heterogeneity to the data collected from these studies. Some of the large prospective studies with long durations of follow-up and their important findings are discussed here.

NATURAL HISTORY OF ASTHMA

Almost every pediatrician who is caring for a child with recurrent wheezing or asthma is confronted with questions from their parents like "Is my child suffering from asthma?", "Will my child outgrow his asthma?" or "Will my child continue to have asthma as an adult?" It is important to provide satisfactory answers to these questions and counsel them properly to ensure parental cooperation, compliance with therapy, and regular follow-up. Asthma is an entity that affects not only the family involved but also the society as a whole and there is high prevalence of this condition, with high rates of hospitalization and emergency department visits, especially in those with uncontrolled disease. Hence, a thorough understanding of the natural history of asthma is essential in order to provide the most rational, evidence-based answers to these above-mentioned queries.

EPIDEMIOLOGY OF ASTHMA IN INDIA

Asthma is the most common chronic illness in children. It is the most common reason for children's absence from school. The social stigma attached to asthma contributes to the loss of self-esteem which results into a significant stress to the child and his family.

The reported prevalence of asthma is higher in developed countries, ranging from 1.6 to 28%.[4-11] The highest rates have

been observed in studies carried out in Australia and New Zealand, with moderate rates in the United Kingdom (UK) and North America and lowest in the Scandinavian countries. There is some evidence that asthma is less common in developing countries, although in certain regions, higher rates similar to those observed in the developed countries have been reported. While these differences may be partly related to methodological issues, including how asthma is defined, true regional differences may exist.

The International Study of Asthma and Allergies in Childhood (ISAAC), established in 1991,[12] is a global initiative aimed at studying the prevalence of childhood asthma in different countries using uniform methodology. The study in phase I, completed by children aged 13–14 years in 155 centers in 56 countries, was based on a written and a video questionnaire. Data showed two- to twenty-fold differences in crude prevalence rates in different regions depending on the symptoms compared. A comparison of prevalence rates in 14 centers that carried out this study in India shows wide variations, ranging from 2% to almost 18–20%. In general, prevalence in urban areas has been found to be greater than that in the rural areas.

A study conducted in India as a part of phase III of ISAAC at 15 centers for age groups 6–7 years and at 18 centers for the age group 13–14 years during 2001–03 reported prevalence of 5.35% and 6.05% for age group 6–7 years and 13–14 years, respectively. Highest prevalence of 22.99% in 6–7 year age group and 15.36% in 13–14 year age group was noted in Kottayam, Kerala.[13] Another study conducted at Jaipur during participation in phase III of ISAAC study noted prevalence of wheeze in past 12 months (current wheeze) up to 5.43% and 5.37% in the 6–7 year age group and 13–14 year age groups, respectively. Prevalence of severe asthma was 3.42% and 2.89% in 6–7 years and 13–14 year age group, respectively.[14] Prevalence varies between urban and rural centers with prevalence of asthma in urban area of Mumbai of 6.1%[15] while in rural area in south India, prevalence was noted to be 10.3% among 6–15 years aged children.[16]

Pokhrel et al. in their study on 2,000 school children in rural Haryana reported a prevalence of 2%,[17] while Chhabra et al.[18] from Delhi reported a current prevalence of asthma of 11.9% in the age group of 5–16 years. The current prevalence of total wheezing (current plus probable asthmatics including those with cold-associated and exercise-induced asthma) was 16.4%. Using a standardized questionnaire, 9,090 students in the 9–20 years age range were studied in Chandigarh. The observed prevalence of asthma was 2.6% among boys and 1.9% in girls. Presence of one or more respiratory symptoms was reported by 31% students.[19]

In 1999–2000, using a simplified version of the ISAAC questionnaire, children less than 12 years of age were studied in urban and rural areas of Chennai.[20] Symptoms suggestive of asthma were present in 18% of children. The prevalence of diagnosed childhood asthma was about 5% in both urban and rural areas, pointing to a gross underdiagnosis. A school survey in 12 schools on 6,550 children in the age group of 6–15 years was undertaken for prevalence of asthma in Bangalore.[21] Wide variation in prevalence was found within the city depending upon the location of the school and the socioeconomic status of children. The range was 11–31%. Another study carried out as a part of ISAAC-III in Lucknow[22]

in children aged 6–7 years and 13–14 years reported a low prevalence of asthma (2.3–3.3%). However, a higher prevalence of wheeze was reported as compared to asthma among children from both age categories (6.2% and 7.8%, respectively).

INTERNATIONAL PROSPECTIVE STUDIES

From the middle of the 20th century, an increasing number of hospital- and clinic-based and whole-population cohort studies have been reported (Table 1). Cross-sectional studies carried out among those with asthma are plagued with significant recall bias and possibility of inclusion of transient wheezers. Retrospective studies do not have comparability because of differing definitions of asthma, its severity, and the length of follow-up. Thus, prospective studies provide the best method of estimation of the natural course of wheezing and asthma in infancy and childhood.

In a multicenter study performed as phase II of ISAAC which included 35 centers from 22 countries and bronchial challenge with hypertonic saline in 22 centers from 16 countries enrolling 6,826 children aged between 8–12 years noted prevalence ranged from 4.4% at Tirana (Albania) to 21.9% at Hawke's Bay (New Zealand). In Mumbai, prevalence was 6.1% and bronchial hyperreactivity after hypertonic saline inhalation was noted in 47.8% children with slope of forced expiratory volume in one second (FEV_1) decline more than 15% in 12.8% children.[15]

A multicenter, cross-sectional study during phase III of ISAAC at 233 centers in 97 countries for age group 6–7 years and 13–14 years evaluated prevalence of wheeze in past 12 months, ever diagnosis of asthma and severe asthma. For children of 6–7 years, global prevalence of wheeze in past 12 months was 11.5% versus 6.8% in Indian subcontinent, prevalence of ever diagnosis of asthma was of 9.4% globally versus 4.5% in Indian subcontinent, and prevalence of symptoms of severe asthma was 4.9% globally versus 3.5% in Indian subcontinent. Similarly, low prevalence for Indian subcontinent was also noted in age group of 13–14 years. For age group 13–14 years, global prevalence of wheeze in past 12 months was 14.1% versus 7% in Indian subcontinent, prevalence of ever having a diagnosis of asthma was 12.6% globally versus 5.6% in the Indian subcontinent, while the prevalence of severe asthma was 6.9% globally versus 4% in Indian subcontinent.[23]

The United Kingdom National Birth Cohort Study of more than 18,000 children born in March 1958 has undergone repeated surveys, with follow-ups at ages 7, 11, 16, 23, and 33 years[24-26] and in which a substantial decrease in asthma and wheezing symptoms has been noted through childhood into adolescence. Perinatal factors including maternal age, parity, and birth weight for gestation and breastfeeding, were not related to persistence.

The follow-up studies from Royal Children's Hospital, Melbourne (Australia) have been helpful in understanding the prognosis of childhood asthma. In these studies, 7-year-old children were initially recruited in 1963 and, subsequently, followed-up into mid-adult life, with a severe symptomatic group added at age 11 years.[27-32] In symptomatic children, 50% reported their first wheezing illness before 3 years of age and 18% in the first year of life. At the age of 35 years, the lung function of those with mild childhood wheezy bronchitis

TABLE 1: Prospective studies in children with asthma		
Study population	**Follow-up**	**Findings**
11,486 United Kingdom children in a 1970 birth sample[34]	Questionnaire completed by parents when children reached ages 5 years and 10 years	• 80% of 2,345 children with wheezing before age 5 years had no wheezing at age 10 years
401 Australian children, age 7 years on enrollment[44,45]	5 follow-up evaluations until age 28 years	• Wheezing abated in patients with less severe wheezing on enrollment; lung function lower at age 28 years in those with more severe wheezing
1,335 United Kingdom children in a 1958 birth sample[24]	Periodic evaluation in subjects up to age 35 years	• Of the 302 with wheezing by age 16 years, about 40% still had asthma of wheezing in the last year at age 34 years or 35 years
67 infants in the United Kingdom at risk for atopic disorder[46]	Annual evaluation through age 5 year and again at age 11 years	• Of 21 children with wheezing at <2 years, 76% were wheeze-free and 61% did not have bronchial hyperresponsiveness at age 11 years • Of 21 with wheezing at >2 years, 17 were wheezing at the age 12, were hyperresponsive at age 11 years
121 children with asthma, 167 with wheeze, and 167 controls enrolled at age 9–15 years, in Scotland[47]	Evaluation after 25 year follow-up	• Former asthmatics were more likely to wheeze, had lower lung function, and had greater airways reactivity
108 children in Sweden with a diagnosis of asthma by age 15 years[48]	Evaluation at age 20–24 years	• 28% were symptom-free and 22% had symptoms at least weekly; 48% had bronchial hyperresponsiveness
406 children, ages 8–12 years on enrollment, referred to a clinic in the Netherlands[49]	Follow-up for mean of 14.8 years to mean age of 24.7 years	• Decreased level of airway responsiveness over time and increasing percent of predicted forced expiratory volume in one second
81 children, mean age of onset of wheezy bronchitis by 10 months age[50]	Follow-up at 12 years after presentation	• 28% had ongoing symptoms at follow-up
696 children born in a single hospital in 1972–1973[51]	Evaluated at 7-year age and then followed up for 8 years	• 36% had ongoing symptoms at follow-up
63 children followed up to 16-year age[52]	Follow-up ranging from 4 to 14 years	• 8% had rare wheezing on follow-up • 51% had occasional symptoms • 19% had frequent symptoms

was indistinguishable from the asymptomatic group, with a gradient of impairment for the other categories that depended on their initial assessment of severity in childhood.[31,33]

The Dunedin (New Zealand) cohort was established in 1972–1973, and they were followed up with regard to clinical features, lung function and BHR at 9, 11, 13, 15, 18, 21, and 26 years of age. In this cohort, the prevalence of diagnosed asthma varied by age between 10% and 20%, and was initially more common in young males, with a subsequent switch towards predominance in young females. The prevalence of BHR was higher in childhood than in adolescence.[34]

The Tasmanian (Australia) birth cohort of 8,410 children was designed to compare the natural histories of wheeze and productive cough.[35-37] Of those diagnosed with asthma at age 7 years, one in four had current asthma as an adult and one in 20 had frequent asthma. In addition to childhood asthma, risk factors for adult asthma were found to be impaired lung function in childhood, female sex, coexistent eczema, and a history of maternal and/or paternal asthma.

A prospective study from Tucson, Arizona, where 1,246 children were recruited right from birth and followed up to 6 years of age, gave several insights into the natural history of asthma.[38] Of this cohort, 52% never experienced wheezing whereas 20% had transient wheezing which was defined as one or more wheezing episodes occurring before 3 years of age but none thereafter. Another 15% had late-onset wheezing (i.e., no wheezing before 3 years of age), while 14% had persistent wheezing throughout early childhood. In this study, Martinez et al. initially measured the respiratory conductance of this cohort by forced oscillometry in the newborn period and found that those who developed wheezing with or without lower respiratory tract infection had significantly lower pulmonary function right from birth; with those in the lowest third of pulmonary function testing parameters having a 10–16 times higher risk for wheezing. These children who are born with smaller than normal airways tend to develop airway edema with each episode of viral infection, and hence show significant airflow obstruction and wheezing. But these children do not necessarily go on to develop asthma, and Martinez et al. found that they were no more likely to wheeze at age 6 years than those who had never wheezed, suggesting that most of them probably outgrow from their smaller airways. Conversely, those who had later onset and/or persistent wheezing had normal pulmonary function in infancy. Similar findings have been reported in other studies.[39-43] Therefore, early wheezing and reduced pulmonary function do not necessarily lead to later asthma, but a genetic predisposition to BHR beyond infancy, in conjunction with environmental influences, are stronger contributors to the development of asthma.
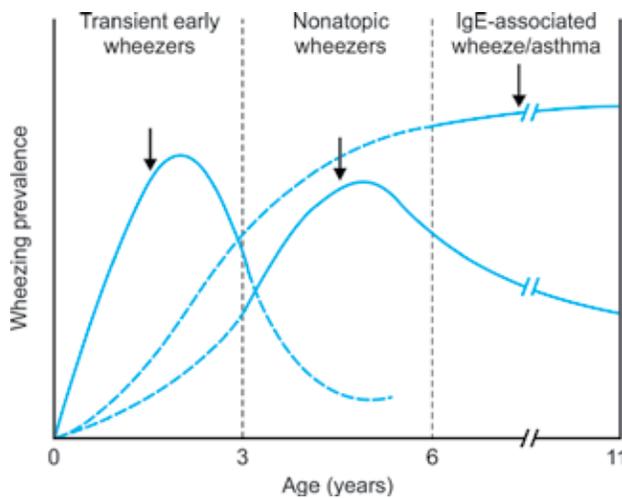
Fig. 1: The proposed wheezing phenotypes and their peak prevalence by age. The dashed lines represent the phase of overlap between the various groups. This classification does not imply that the groups are mutually exclusive

From such studies in symptomatic and whole populations, it appears that approximately 30% of 3-year-old children will have had at least one acute episode of wheezing, 60–70% will outgrow their wheeze by 6–8 years of age and much of the mild wheezing in young nonatopic children may be explained by subtle impairments of airway function that were probably present at birth. Various wheezing phenotypes (Fig. 1) may be delineated from the prospective studies, which include early transient wheezers, who usually become asymptomatic by 6 years of age. Some nonatopic wheezers may continue to wheeze into childhood but were found to have no wheezing or elevated immunoglobulin E (IgE) by 11 years of age. In contrast, children with asthma continue to wheeze throughout childhood and show a progressive decline in lung function over a period of time.

ASTHMA IN URBAN VERSUS RURAL AREA

Prevalence of asthma varies widely geographically from nation to nation with general trend of high prevalence in developed nations. Additionally, prevalence varies within nation depending on urban, rural, and farming locations which have been an area of investigation. This is discussed in further detail in hygiene hypothesis which hypothesizes that degree of exposure to microbial products especially in early life is an important determinant of likelihood of development of asthma and allergies.[53,54] Children living in farming locations have 25% lower prevalence of asthma compared to urban children.[55] Similar observations of low prevalence of asthma in rural areas have been noted in India where traditional lifestyles include close animal contact and associated microbial exposures.[20,56]

AGE OF ONSET

Wheezing in infancy and early childhood is very common, in that more than 30% of infants experience at least one wheezing episode by their 3rd birthday and almost 50% by their 6th birthday.[38] However, approximately half of those children who wheeze before 3 years of age are asymptomatic by 6 years

of age.[57] The natural history of wheeze does appear to be influenced by age at presentation, in that children presenting less than 2 years of age only have a one in four chance of wheezing at age 11 years,[58] and onset of parent-reported asthma or wheezing before the age of 2 years is not associated with symptoms in early adulthood.[36]

The study by Sears et al.[59] shows that symptoms of asthma appeared much earlier in cases that seemed to remit during adolescence, only to relapse during early adulthood, than in remitting cases in which a relapse did not occur. These findings provide strong support for the contention that environmental factors, acting during early life and interacting with specific asthma genes, are crucial for the development of the chronic, persistent form of the disease.

A predictive tool for asthma in children with history of wheezing at least once during first 3 years of life, known as asthma predictive index (API), was developed from Tucson Children's Respiratory Study cohort. A stringent index included frequent wheezing during the first 3 years of life and either one major risk factor (parental history of asthma or eczema) or two of three minor risk factors (peripheral eosinophilia >4%, wheezing without colds, and allergic rhinitis). A loose index required any wheezing during the first 3 years of life plus the same combination of risk factors. At 6–13 years age, children with positive loose index were 2.6–5.5 times and children with positive stringent index were 4.3–9.8 times more likely to have active asthma than children with negative API.[39] These findings were validated in a population-based birth cohort in United Kingdom enrolling 1,954 children at 3 years and then comparing rates of asthma at 7 years and 10 years of age. Authors noted findings similar to Tucson cohort with 5 times increased risk of asthma at 7 years of age with positive loose API and 8 times increased risk with positive stringent API.[60]

GENDER-RELATED DIFFERENCES

Whole population studies consistently show an earlier age of presentation and a higher prevalence of asthma in pre- and peripubertal males than females.[61] The higher prevalence of asthma in young males may be explained by a combination of factors, including a smaller peripheral airway caliber before puberty[62,63] and an increased prevalence of atopy and a higher prevalence of BHR.[61]

Follow-up of the Tucson birth cohort to 13 years found that, during the first 3 years of life, males were more likely than females to be early wheezers, early frequent wheezers and to have wheezing apart from colds. The prevalence of asthma was significantly higher in males than in females at all ages up to 11 years of age, but not at 13 years.[39-41] In the Melbourne follow-up studies, a history of wheeze in the past 12 months was more common in 7-year-old males than females, a sex difference that became less obvious at 12 years and that had disappeared by 15 years. Subsequent follow-up at 21 years showed that this pattern persisted and that the male predominance of severe disease was lost by this age.

The British Birth cohort study also found a similar sex reversal between 16 years and 23 years,[24] as did a similar New Zealand cohort.[34] In adult populations, the male:female ratio is about 1:1.5, and this difference could be explained by a number of factors, including hormonal influences on airway

inflammation, airway smooth muscle function, and vascular integrity.[61] From these studies, it can be concluded that male sex is a risk factor for asthma in prepubertal children, while female sex appears to be a risk factor for persistence of asthma in the transition from childhood to adulthood.

VIRAL INFECTIONS AND BRONCHIOLITIS

Viral infections of the respiratory tract are a common occurrence early in life and bronchiolitis has been associated with recurrent episodes of wheezing in infancy and early childhood. Respiratory syncytial virus (RSV) infection is known to occur in 50% of children by 1 year of age and in almost 100% children by 2 years of age. Hence, if RSV infection is so common why do only a small proportion of children go on to have persistent wheezing throughout childhood? Occurrence of a single episode of wheezing before 2 years of age does not result in recurrent wheezing and in the absence of other risk factors does not result in asthma. Data from infants with an initial episode of bronchiolitis followed up to 7 years of age by Rooney and Williams showed that at least 56% had another episode of wheezing and 43% wheezed on 3 or more occasions.[64] Another study by Sims et al. had shown persistence of wheezing in 23% of infants with initial bronchiolitis when followed up to 8 years of age. Even infants who had mild bronchiolitis that did not require hospitalization had comparable rates of recurrence of wheezing at 6–9 years of age.[65] However, these studies do not identify whether recurrent wheezing is a direct result of RSV infection itself or if it is an expression of some underlying tendency which results in wheezing both at the time of RSV infection in infancy and later in childhood.

In fact, there is evidence to show that wheezing following bronchiolitis has several causes[66] and RSV infection might promote airway obstruction by acting on airways that are susceptible due to a number of reasons like smaller airway diameter, increased reactivity, aberrant immunological responses, and heredity. This may be corroborated by the association of recurrent wheezing following RSV infection in an atopic infant and also by the fact that the presence of eosinophilia in peripheral blood at the time of RSV infection may identify those with persistence of wheezing into the school age.[67] Even the severity of the initial RSV infection does not determine the subsequent risk of asthma, with the risk of recurrent wheezing being the same for those with mild episodes as against those with more severe forms of bronchiolitis requiring hospitalization.[68]

So far, there is no convincing evidence to show that a single RSV infection in infancy may lead to recurrent wheezing, persistent airway hyperreactivity and dysfunction, or development of atopy, in the absence of other risk factors. The association of wheezing with childhood bronchiolitis is related to the similarities in inflammatory response to viral infections and allergen exposures.[69] Viral infections usually result in the appearance of CD4 lymphocytes, eosinophils or their degranulation products, histamine and cysteinyl leukotrienes in the airway, and infants with more severe forms of RSV bronchiolitis have shown increased levels of macrophage inflammatory protein 1-α and eotaxin. In asthma, the T-helper type 2 (Th2) cytokines initiate the allergic response and they are chemotactic for lymphocytes and eosinophils, causing degranulation of mast cells, basophils, and eosinophils. Due to induction of similar terminal inflammatory responses in both situations, there is airway obstruction in susceptible hosts.

Studies looking at the role of RSV bronchiolitis in causing long-term airway damage or airway hyperreactivity have found that these children have reduced airflow in the terminal airways later in life but the changes were milder than those with atopic asthma.[70] Others have looked at the relationship of this lung dysfunction following bronchiolitis with the atopic status of the host and they found that in those with multiple episodes of wheezing-associated lower respiratory illness (WLRI) in infancy, lung function appeared to be determined by the presence of atopy.[71] Martinez et al.[38] also found that nonatopic children with wheezing in early infancy had smaller airways to begin with (based on lung function studies at birth) and a mild degree of airflow limitation was still present in later childhood, suggesting that their small airways had predisposed them to wheeze in relation with viral infection. But atopic children in their cohort who had wheezing in early infancy actually had normal airflow in infancy but began to lose lung function in later childhood, suggesting that it was atopy and not bronchiolitis alone that was related to postbronchiolitis lung dysfunction and airway hyperreactivity.

Several cross-sectional studies have also shown an inverse relation between asthma at school age and the burden of respiratory infections early in life. Anderson and coworkers[72] showed that respiratory infections were more common among children living in the highlands in Papua New Guinea with simultaneous lower prevalence of asthma as against those from the coastal areas where asthma was much more frequent. Similar differences were noted by Flynn[73] among indigenous Fijians, who showed a higher rate of pneumonia as against Fiji Indians whose infection rates were lower than that of former but asthma admission rates were three times higher. Other workers have found similar differences between East and West European countries[74] giving birth to the hypothesis that whether repeated viral exposures can induce a Th1-like immune response that can counteract allergic responses, and hence reduce the development of atopy in these children. These findings have led to the development of the hygiene hypothesis (discussed here).

ATOPY AND ASTHMA

Atopy in the child or the parent(s) constitutes one of the most important risk factor for the development of asthma in the child. Children of atopic parents are twice as likely to wheeze by age 5 years, with one half of them having experienced at least one episode of wheezing by that age. Two or more episodes of wheezing occur by 4 years in about 25% of children with atopic parents.[75]

The epidemiology of atopy and asthma has been evaluated with the help of two types of studies—(1) longitudinal studies of atopic subjects or those at higher risk of atopy (such as infants of atopic parents), and (2) general population cohort studies. Among the former group, the study by Clough et al.[58] involved 104 infants with recent onset wheeze, who had one atopic parent, and had no history of RSV bronchiolitis. They assessed factors which included: personal atopy (IgE level >1

SD above age-related normal and/or eczema and/or positive skin tests); parental atopy; number of siblings; age at first wheeze; sex; serum-soluble interleukin-2 receptor (sIL-2R); proliferation of peripheral blood mononuclear cells (PBMC) to β-lactoglobulin and to *Dermatophagoides pteronyssinus*; production of interferon-gamma on stimulation of PBMC with β-lactoglobulin and with *D. pteronyssinus*. Among the study cohort, 49.5% required prophylactic anti-asthma treatment within 1 year and predictor variables for persistent wheeze among these children were assessed by univariate and multivariate logistic regression analysis. Although persistence of wheeze was strongly correlated with older, atopic children with biparental atopy, the best predictors were age of onset and sIL-2R levels.

Among the general population cohort studies where children with one atopic parent were followed up to define the natural history of atopy and its relation to asthma, the findings were more or less uniform. Van Asperen and Kemp[76] evaluated 79 infants every 4 months from birth to 20 months and then again at 5 years of age and performed skin testing to common antigens at regular intervals. They found an overall prevalence of 50% for both atopic dermatitis and prolonged, continuous rhinitis in the first 12 months of life, with onset around 4–8 months of age, but most cases remit by 5 years of age. In their cohort, asthma was present in one in every three children with an atopic parent, with one-half of this having onset of wheezing before 1 year of age. Similar findings were also reported by Cogswell et al.,[77] who followed 73 children, and found that 89% of asthmatics at age 5 years had at least one positive skin test from among a battery of six antigens.

In addition, these studies found that specific reactivity to dust mites increases by age 2 and 4, about 15–20% of children with an atopic parent are skin-test positive to dust mite.[77] Animal reactivity to dog or cat reaches a cumulative prevalence of 10% by age 4 in this cohort, but pollen reactivity generally begins later, probably related to more intermittent exposure to it than others. By age 5, 25% of Cogswell's subjects reacted to grass and similar high prevalence was also reported among the Tucson cohort. The Tucson Respiratory Study group cohort was also evaluated prospectively for the development of allergic rhinitis, with repeated skin testing and evaluation of IgE levels.[78] One-half of those with allergic rhinitis at age 6 had its onset before 1 year of age and these children were also more likely to have asthma, but interestingly they had less likelihood of having positive skin tests.

Overall, the data suggests that atopically predisposed individuals (as measured by serum IgE and skin testing) are much more likely to manifest asthma in later childhood and adulthood and environmental factors may play a crucial role in allowing the atopic gene(s) to be expressed.

GENETIC INFLUENCES

The studies of genetic influences on asthma have been done using either genome-wide genetic screen followed by positional cloning (Table 2) and by candidate gene association studies (Table 3).[79] Numerous twin studies have shown that there is significant increase in concordance of asthma among monozygotic twins as compared to dizygotic twins, with the estimated effect of genetic factors on disease susceptibility ranging from 35 to 70% among various populations.[80] However,

TABLE 2: Candidate genes identified by positional cloning

Gene locus	Gene	Phenotype
6p21-24	• Major histocompatibility complex	Strongest evidence for linkage to asthma phenotypes
11q13-21	• Clara cell secretory protein (*CCL21*) • β-chain for high affinity receptor for IgE • Glutathione S-transferase P1	Very high linkages in various studies
20p13	• *ADAM33*	Significant association with bronchial hyperresponsiveness

TABLE 3: Genetic factors associated with asthma severity based on candidate gene studies[77]

Gene	Polymorphism	Associated phenotype
Interleukin-4	• C589T	• Forced expiratory volume in one second <50%
	• Intron-2 repeat	• Fatal/near-fatal asthma • Asthma severity
IL-4 receptor α	• Q576R	• Asthma severity • Severe airway obstruction
β2-adrenergic receptor	• R16G	• Nocturnal asthma • Steroid-dependent asthma • Severe asthma • Not associated with fatal/near fatal asthma
Tumor necrosis factor-α	• A308G • T857C	• Not associated with Fatal/near-fatal asthma
Leukotriene C₄ synthase (LTC4S)	• A444C	• Aspirin-intolerant asthma
Interleukin 13	• 5q31 • T1111C (promoter gene) • A110G	• Th2 cytokine response associated

in addition to common genes, twins may be living in common environments as well and these factors play an important role in the pathogenesis of the disease. But, Laitinen et al. showed that the incidence of asthma in twins with affected parents was increased fourfold as compared to those without affected parents,[81] suggesting that asthma recurring in families is more likely due to shared genes than due to shared environments alone.

The question of the heritability of the severity of asthma has not yet been addressed convincingly and very few studies have examined phenotypes relating to asthma severity. Sarafino et al. assessed asthma severity (measured by frequency and intensity of asthma episodes) among 39 monozygotic twin pairs and 55 same-sex dizygotic twin pairs and they found that severity was significantly correlated for monozygotic pairs but not for dizygotic pairs.[82] A large epidemiologic study did show a modest correlation between the severity of parents' airway hyperresponsiveness and those of their child[83] but Sarafino et al. did not find this

correlation either with parents' asthma severity or even the number of parents with asthma.[84] Other studies have found significant parent of origin effects for atopy and early wheezing and it is the maternal genotype that strongly correlates with the risk of expression of asthma.[85]

In addition to disease susceptibility genes, several other genes may modify the course of the disease and a complex interaction between susceptibility genes, environmental and treatment related factors may exist. These putative candidate genes may have association with the measures of asthma severity and a number of these genes that have been identified so far are listed in table 3.

In addition to severity, genetic influence upon the effectiveness of therapy may be related to the β-2 agonist receptor polymorphisms, influencing the response to β-agonist.[86] Glucocorticoid responsiveness may be related to the expression of glucocorticoid receptor-β, with increased expression being present among steroid insensitive subjects with severe asthma.[87] Similarly, a repeat-length polymorphism in the promoter of 5-lipoxygenase (5-LO) enzyme gene may modify transcription factor binding and reporter gene expression, resulting in reduced responsiveness to 5-LO inhibitor therapy.[88]

There is increasing recognition of epigenetic changes in deoxyribonucleic acid (DNA) that are heritable and can explain the phenotypic variation that cannot be explained by gene candidates identified by Genome Wide Association Studies (GWAS). Deoxyribonucleic acid methylation occurs at the cytosine nucleotides in individual CpG dinucleotides as well as within clusters of CpG rich areas that are called CpG islands. A study comparing the DNA methylation patterns and gene expression in 6–12 years old urban children with asthma with healthy control subjects found 81 differentially methylated regions, and several immune genes (*IL13*, *RUNX3*, and *TIGIT*) were hypomethylated in asthma. While 11 of these differentially methylated regions were associated with higher serum IgE concentrations, another 16 were associated with lung function in subjects with asthma. A case-control study performed in India in children aged 1–15 years provided evidence of increased risk of asthma in children due to interaction between mutant genotype of IL-13 and heterozygous genotype of *IL4R*, while homozygous genotypes of both genes shown protective association with asthma.[89]

ENVIRONMENTAL INFLUENCES

Asthma is a disorder in which the airways become over-responsive to the inhaled environment. There has been much focus on the way that allergens interface with the mucosal immune response to genetic Th2-type inflammation involving IgE switching, and the recruitment and activation of mast cells, basophils, eosinophils, and monocytes/macrophages involving T cell selection. Another aspect of the hyperresponsive airway (BHR) in asthma is acute broncho-constriction provoked by a variety of inhaled stimuli such as exercise, cold air, sulfur dioxide (SO_2), fog and air pollutants. The majority of the stimuli differ from the classical methods to assess BHR with inhaled methacholine or histamine in that to evoke airway narrowing they stimulate the release of secondary mediators from mast cells or nerves.

The common factor tying all these stimuli together is a defect in the epithelium, which in asthma exhibits features of chronic injury and repair. For example, an alteration in the ability of the epithelial cell to transport water sufficiently quickly to the airway lumen results in a hyperosmolar environment that activates primed mast cells and basophils for mediator secretion. A defective physical barrier will also increase access of allergens to underlying effector cells as well as exposing afferent nerve endings that are especially sensitive to such stimuli as SO_2 and ozone (O_3). Evidence that the epithelium in asthma is more susceptible to injury comes from bronchial biopsy studies, showing increased epithelial apoptosis that is sustained *in vitro* even after several passages and increased apoptotic cell response on exposure to oxidant stimuli, e.g., hydrogen peroxide and O_3.

At every level, the cellular response to these environmental stimuli is under genetic control. Thus, polymorphic variation in cytokine receptors (e.g., *IL4R*), antioxidant enzymes (e.g., *GSTP1*, SOD), protease inhibitors (e.g., *SPINK5*), cell adhesion molecules (e.g., cadherins), and mucin genes (e.g., *MUC8*) contribute to the altered epithelial response in asthma. Similarly, altered secretion of growth factors linked to remodeling (TGFβ) or the mesenchymal cell response to these (e.g., *ADAM33*) predisposes the asthmatic airway towards chronicity and reduced response to corticosteroids.

Hence, a combined gene-environment interaction occurs in genetically predisposed individuals with underlying risk factors for the development of asthma and this interaction may have its beginnings during the *in utero* period itself (discussed later).

GENE ENVIRONMENT INTERACTIONS AND "THE HYGIENE HYPOTHESIS"

The rising incidence of asthma and allergic disorders in the Western societies, with its rapidly changing patterns and huge variations across different populations, has led to increased focus on possible environmental interactions and western lifestyle as the underlying factors. This led to the generation of the concept that has been labeled as the hygiene hypothesis.[54] This hypothesis originated from the coupling of observations on the allergy-protective effect of sibship size/birth-order with the emerging concept of helper T cell polarization into two counter-regulatory subsets; proinfection Th1 and proallergy Th2.[90,91] Supported by some experimental and clinical evidence,[92-94] the pathogenetic mechanism that could potentially explain the recent rise in allergic disorders among children growing up in affluent, urbanized societies includes a preferential programming of the T lymphocytes towards a predominance of the proallergy Th2 responses, which may be driven by the overall decline in early life infections (as a result of improved hygiene, increased immunization rates, decreased sibship size, and more prevalent antibiotic use).[95] However, with the increasing recognition of additional immune mechanisms involving T regulatory cells and cytokines in the pathogenesis of allergic inflammation, there has been additional support for the hygiene paradigm due to the role of infections in generating such cells and mediators. Development of immune response in early life is influenced by microbial burden exposure with final result being decreased risk of Th2 responses including asthma and allergies. In early childhood, being raised in farm, exposure to farm milk, attending day care, and exposure to

dogs have been noted to decrease the risk of asthma providing evidence of role of environmental factors interacting with genetic determinants. These factors are associated with microbial exposure, increased endotoxins.[96-100] These findings are further supported by comparing similar genetic ancestries and lifestyles of Amish and Hutterite children with differences in prevalence of asthma and allergic sensitization being 4–6 times lower in Amish population, but having airborne endotoxin levels 6.8 times higher in Amish population suggesting considerable role of environment and innate immunity in providing protection against asthma.[101]

It is also suggested that due to increased modernization we are living in static, artificial, micro-niches (the so-called artificial habitats) which are optimized for our convenience, but which bear little resemblance to the dynamic inputs provided by the environments that nurtured our evolution.[102] Since we are increasingly living within an array of artificial habitats designed to handle us very well, but we may well not be equipped to handle them. Asthma, according to this view, becomes a manifestation of our respiratory maladaptation to modern lifestyles. On other hand, in rural areas, close living with animals, mud flooring and walls, and regular domestic cow dung use in rural homes increases the load of microbial components such as endotoxin and other toll-like receptor ligands,[103] thereby reducing the subsequent risk of asthma and atopy.

OTHER FACTORS

Data from a number of longitudinal studies of wheezing in childhood suggest that atopy, and particularly eczema, is the single most important risk factor in the development of wheezing illness and its persistence (as discussed earlier). In addition, susceptibility to wheezing and to asthma seems to be determined by certain factors, exposures, or events that exert their influence in very early life, perhaps even before birth, and these include fetal nutrition,[104,105] duration of pregnancy,[105] tobacco smoke exposure,[43,106] environmental air pollution,[107] postnatal nutrition, breastfeeding, family size,[106,108] maternal age,[119] socioeconomic status, and allergen exposure.[110] By paying attention to such factors, it becomes possible to identify children who have at least a 50% chance of developing asthma in the future.

VITAMIN D AND ASTHMA

Vitamin D does not occur naturally in humans and is acquired by sunlight exposure or through supplements. In last few decades, vitamin D deficiency and insufficiency are increasingly noted due to inadequate sun exposure, and changes in diet and lifestyle.[111] For the majority of asthma patients, asthma symptoms are typically well controlled on inhaled corticoid medications if adherence and follow-up with physicians are maintained. Despite these, significant numbers of individuals with asthma remains symptomatic and at risk of exacerbations. There are increasing numbers of studies suggesting linkage between low vitamin D in children with mild to moderate asthma and its association with poor asthma control, increased medication use and frequent exacerbations.[112,113] Children with severe and therapy-resistant asthma are noted to have significantly lower serum vitamin D3 levels than children with moderate asthma.

Additionally, they were noted to have increased airway smooth muscle mass, worse lung function, poor asthma control and more steroid use, which provides an important link between vitamin D, airway structure and function. These findings suggest vitamin D supplementation may be useful in children with severe and therapy-resistant asthma. In a randomized, double-blind study performed in India enrolling children with moderate to severe asthma noted significantly less exacerbations, reduction in steroid dose use, better asthma control and reduction in emergency room visits in vitamin D treatment group receiving 1200 IU per day over 6 months compared to placebo group.[114] A Cochrane systematic review reported clinically and statistically significant protective effect of vitamin D against severe exacerbation of asthma and no convincing evidence of an increase in serious adverse events. People who received vitamin D experienced decreased numbers of exacerbations, fewer asthma attacks needing treatment with oral steroids, decreased need to attend hospital with acute asthma attack but had little or no effect on lung function or day-to-day asthma symptoms. Vitamin D is likely to offer protection against severe asthma attacks and should be considered for patients who have severe and therapy-resistant asthma.[115]

PARASITIC INFESTATIONS AND ASTHMA

Prevalence of asthma varies widely across the globe. Higher prevalence is noted in developed countries and urban areas while lower prevalence is noted in rural, nonurban, and developing countries where parasitic infestations are endemic. Common environmental allergen stimulate IgE responses and produce allergic disorders, but the allergens that produce most potent IgE responses originate from helminthic parasites.[116] Parasitic infestations are endemic in India, so understanding relationship between parasitic infections and asthma is relevant. Allergic diseases and helminth infestations share important immune responses, such as Th2 dominating cytokine milieu associated with upregulation of IL-4, IL-5, and IL-13 mediated mast cell production and eosinophilia. These responses are typically protective against parasitic infection, while they are central to pathogenesis of allergic diseases.[117] Helminthic infections decrease the risk of allergies by stimulating the production of high levels of polyclonal IgE which are capable of blocking Fc receptors on mast cells preventing aeroallergen from triggering allergic responses or by promoting high levels of regulatory cytokines which are capable of downregulating allergic responses.[118] For children living in urban areas with low socioeconomic status, light parasitic load of *Ascaris lumbricoides* was found to be a protective factor against asthma while heavy parasite load was noted to be a risk factor contributing to high prevalence of asthma among these children.[119] In a systemic review, it was noted that any relation between intestinal parasite infection and asthma risk is likely to be helminthic species specific, with *A. lumbricoides* being associated with increased risk, hookworm with marked decreased risk, and with other intestinal parasites without clear effect.[120]

ASTHMA ENDOTYPES

Several studies that have elaborated the mechanism of airway inflammation in asthma have led to the recognition of

biologic pathways that express a specific clinical phenotype and these have been referred to as endotypes. Based on a combination of clinical, laboratory, and lung function parameters, two broad endotypes that have emerged include Th2 and non-Th2 endotypes. The Th2 endotype refers to the activation of the T-helper type 2 cells and their associated cytokines such as IL-4, IL-5, and IL-13, which are associated with allergies, eosinophilic airway inflammation and IgE production. This endotype is better defined due to its early onset phenotype and responsiveness to inhaled steroids. Development of biologic therapies that target several key mediators, such as anti-IgE monoclonal antibody (omalizumab, quilizumab, and ligelizumab), anti-IL-5 monoclonal antibody (mepolizumab, reslizumab, and benralizumab), and anti-IL-13 monoclonal antibody (lebrikizumab, tralokinumab) have shown promise in the subset of patients with eosinophilic airway inflammation with a severe clinical phenotype.

The non-Th2/low-Th2 endotype is less well defined with predominance of either neutrophilic inflammation or paucigranulocytic inflammation. The cytokines involved include IL-8, IL-17, and IL-23 and these patients are generally not as responsive to inhaled corticosteroids. Besides use of long-acting muscarinic antagonists and/or long-acting β-agonists, therapeutic options for this subset remains limited. Further research into the mechanisms of inflammation in these patients might help develop specific interventions along the theme of personalized medicine based on each individual patient's inflammatory and cytokine profile.

MICROBIOME CHANGES IN EARLY LIFE AND THE RISK OF ASTHMA

Advanced molecular techniques (16S rRNA sequencing and bioinformatics) have allowed the quantification of complex bacterial communities and their diversity in the gut and the airways in early life. Diversity of the bacterial species in the airways is inversely associated with airway hyperresponsiveness and specific bacterial taxa have been linked to disease severity and response to treatment. However, most of this data comes from cross-sectional studies and direct causation cannot be implied until longitudinal data is available. Nevertheless, there is enough longitudinal data regarding intestinal microbiota and the subsequent development of allergies and asthma. Studies of the germ-free mouse model have shown exaggerated Th2 responses in the ovalbumin model of asthma leading to increased airway hyperresponsiveness, mucus hypersecretion, and increased airway eosinophils. In addition, neonatal studies have shown reduction of *Bifidobacteria* and *Escherichia coli* and increase in *Clostridia* prior to the development of asthma. In addition, dietary modifications to alter the intestinal microbiome have been shown to affect the subsequent development of allergies and asthma. Several studies have also evaluated the impact of high-fiber diets in pregnancy and probiotics in early life, but the results have been mixed. Further studies are needed to characterize the changes in the microbiome of the gut and lower airways from early life up to the development of asthma, and additional studies of adults with asthma will help track the changes that occur with progression of the disease over time. Studies that also explore the complex interactions between gut-lung axis and their respective bacterial communities can provide some important insights into the regulation of the developing immune system and the subsequent development of atopy and asthma.

BREASTFEEDING

In prospective studies and in systematic reviews, breastfeeding has been shown to confer protection from asthma, atopy and allergic disorders.[121-123] However, there are some studies that have not demonstrated such protective effects.[124] Different groups analyzing the data from the same population in a survey in the United States have reached contradictory conclusions about the role of breastfeeding.[125,126] In a global study, no risk reduction was noted for asthma in children who were ever breastfed.[127] While a study performed in southern India noted that 74% rural children were exclusively breastfed compared to 20% urban children. In their study, exclusive breastfeeding was noted to be strongest independent predictor of lower atopy providing some evidence of protective role for breastfeeding against childhood asthma and atopy. Additionally, their rural children were in close animal contact and mud flooring, which also might be contributing to lower prevalence of atopy in rural children.[103]

Reasons for this controversy include methodological differences and flaws in the studies performed to date, the immunologic complexity of breast milk itself and, possibly, genetic differences among patients that would affect whether breastfeeding is protective against the development of allergies or is in fact sensitizing.[128] The development of WLRI in the first year of life and the presence of atopy are both independently associated with an increased risk for current diagnosis of asthma in childhood. Since their effects are mediated via different causal pathways, their presence together could have an additive effect. Exclusive breastfeeding protects against asthma via effects on both these pathways, as well as through other as yet undefined mechanisms. Furthermore, exclusive breastfeeding may protect against asthma and may reduce the incidence of lower respiratory illness, especially RSV.[129]

PARENTAL SMOKING

There is a remarkably increased risk of asthma in children who are exposed to second-hand smoke. Passive exposure of pregnant women to environmental tobacco smoke during the third trimester is positively associated with asthma and allergy-related symptoms in their preschool age children.[130] In children, passive smoke exposure from mother and father both importantly increase the risk of asthma and allergy-related symptoms. An association between current maternal smoking and current asthma symptoms was noted in a multicenter phase III ISAAC study, which examined association between tobacco smoke exposure and the risk of asthma, rhinoconjunctivitis and eczema in children. Higher risk for 6–7 years than 13–14 years age group was noted (Odds ratio 4.07 for 6–7 years age, and 2.22 for 13–14 years age). It was concluded that magnitude of the association was greater for current smoking by mothers than fathers, which may be due to children and adolescents spending more time in the presence of their mothers than their fathers. Additionally,

increased risk of symptoms was noted with maternal smoking during first year of child's life than current maternal smoking.[131] Similar association of greater risk of asthma with maternal smoking was noted in another study during phase III of ISAAC performed in India. In this study, odds of asthma in children exposed to maternal smoking were 2.7 times higher for age 6–7 years and 2.1 times higher for age 13–14 years than those not exposed to maternal smoking,[13] emphasizing the importance of prevention of smoke exposure, especially maternal smoking.

EFFECTS OF ENVIRONMENTAL POLLUTION

Due to increasing industrialization-related environmental pollution, there is an expanding interest in exploring relationship of air pollution and asthma. Important indoor pollutants include passive tobacco smoke, radon decay products, carbon monoxide, nitrogen dioxide, formaldehyde, asbestos fibers, microorganisms, and aeroallergens.[132] In urban setting, outdoor air pollution constitutes various pollutants which contribute to respiratory illnesses including carbon monoxide, SO_2, nitric oxide (NO_2), acid aerosols, ozone, and particulate material (PM) which constitutes complex aerosol of solid and liquid organic and inorganic material that may include dust, soot, smoke, pollens, acid droplets, and secondary aerosols.[133] Respiratory health issues related to air pollution include increased airway reactivity, lung inflammation with influx of inflammatory cells, altered mucociliary clearance, altered macrophage function, increased respiratory infections, decreased lung function, increased asthma exacerbations, and increased utilization of health care resources.[134] Suspended PM has acute health effects, even at short-term low levels of exposure, which includes daily morbidity, hospital admission rates for exacerbation of respiratory diseases, fluctuations in the prevalence of bronchodilator use. Such effects depend on particle size and concentration and can fluctuate with daily fluctuations in PM10 (particulate matter ≤10 μm in aerodynamic diameter) or PM2.5 (particulate matter ≤2.5 μm in aerodynamic diameter) levels. The relation between PM10 or PM2.5 exposure and acute health effects is linear at concentrations below 100 μg/m^3. Currently, no threshold has been reported below which no effects occur.[135] Exposure during early infancy to PM2.5, NO_2, and soot are associated with increased prevalence of asthma symptoms and asthma.[136] Similarly, another study noted association of exposure to PM2.5, PM10, and increased CO concentration to increased respiratory infections, asthma severity and increased medication use, in children with mild to moderate asthma.[137] A study performed in Delhi/India noted significantly higher mean indoor level of suspected particulate material (SPM) than outdoor SPM level. Their results suggested that both indoor and outdoor particulate exposure may be an important risk factor for development of respiratory illness in children.[138]

DIETARY INFLUENCE

Various studies have tried to evaluate the effect of modification of diet on asthma control. Yusoff et al. observed that even over the short time period of 8 weeks, an egg- and milk-free diet can reduce atopic symptoms and improve lung function in asthmatic children.[139] The effect of dietary fat has also been evaluated. There are reports indicating a beneficial role for omega 3 (n-3) fatty acids in the diet.[140,141] Vitamin E supplementation has not been found to be beneficial.[142]

Based on the existing available literature, the following factors are implicated in increasing the risk of developing asthma (Box 1).

Box 1	Risk factors for development of asthma

Definite (multiple studies show statistical significance)
- Family history of atopy/asthma
- Early lung disease/bronchiolitis
- Elevated immunoglobulin E
- Positive skin tests or radioallergosorbent test
- Maternal smoking
- Concurrent allergic rhinitis, especially if onset before 1 year of age
- Concurrent atopic dermatitis, especially if early onset
- House dust/dust mite allergy
- High dust mite levels in home (with positive family history of atopy)
- Male sex

Probable (multiple studies show statistical significance; occasional studies do not)
- Immediate/early food reactivity
- House dampness
- Presence of furred animal in home (with positive family history)
- Blood eosinophilia (adult >children)
- Low birth weight
- Maternal smoking while pregnant
- Black race

Possible (some studies show statistical significance and a similar number do not, or a single study showed statistical significance and not evaluated in other studies)
- Air pollution
- Nasal eosinophilia in early childhood
- Skin test reactivity to milk, egg, and peanut under 1 year of age
- Not breastfed as an infant
- Paternal smoking
- Cockroach allergy (with positive family history)
- Young maternal age (<20 year)
- Season of birth
- Childhood obesity
- Hispanic ethnicity
- Day-care attendance
- Central city residence
- Low family income
- Presence of wood/charcoal burning stove in home
- Cord immunoglobulin E levels

Unlikely (most studies do not show statistical significance)
- History of urticaria
- Delayed food reactions
- Lower respiratory tract infections after infancy

No association
- Immunoglobulins A, immunoglobulin G levels
- Presence of gas stove in home
- Proportion of protein/fish in diet

LUNG FUNCTION STUDIES IN CHILDREN WITH ASTHMA

The association of smaller airways at birth with recurrent wheezing in early life has been discussed above and most of these children tend to outgrow their wheezing as they grow older. However, those who continue to have wheezing in later childhood tend to show a progressive decline in lung function. Prospective studies evaluating the lung function of children with recurrent wheeze followed up to 16 years showed that transient early wheezers with smaller airways and lower lung function at birth who did not have persistence of wheeze in later childhood subsequently showed improvement in lung function as they grew older. However, those with persistent wheeze had a persistent and gradual decline in lung function. Lung function data from 28-year follow-up of children from Melbourne[143] showed that those children who had been wheeze free for at least 3 years, even if asthma had been persistent in childhood, had normal lung function and no increased bronchial reactivity. Airway obstruction persisted in mid-adult life persisted mainly in those with moderately severe asthma.

Studies suggest that lung function decline in children with asthma may occur predominantly in younger or preschool-age children[144,145] Available evidence suggests tracking of lung function by age, such that patients with more severe asthma early in life are at greater risk of lung function deficits throughout childhood and into adulthood.[45,143,146] For the cohort of 5–12-year-old children with mild-to-moderate persistent asthma enrolled in the Childhood Asthma Management Program (CAMP) study, lung function remained stable throughout childhood and adolescence regardless of treatment status. On follow-up of this cohort, approximately 25% had a decline in FEV_1 of greater than 1% predicted per year during a 5-year period, again regardless of their treatment status.[147] It is possible that this decline in lung function in this population was related to early structural changes that occurred at the onset of the disease, or due to continuing inflammation, or a combination thereof. If the loss is indeed due to a structural change, it may not be reversible with later interventions. But, on the other hand, if ongoing inflammation is the culprit, then perhaps use of either higher doses or earlier initiation of corticosteroid therapy, or other alternative treatment strategies, are necessary to prevent this decline in lung function in the later years.

ASTHMA IN ADOLESCENTS

A significant number of children who have wheezing in early childhood will remit during adolescence, especially for males, but it may persist in a few. Obesity and female sex are associated with persistence of symptoms, probably related to the effects of increased estrogen on immune function. Experimentation with smoking is also seen in this age group and it may have an impact on lung function. Even a single cigarette smoked per day for a short period of 3 years may be associated with as much as 10% reduction on maximal growth in FEV_1.[148]

In one of the largest adolescent asthma surveys from the United States, undiagnosed frequent wheezing was significantly associated with female gender, current smoking, exposure to household smoke, low socioeconomic status, allergies, and ethnicity.[149]

ASTHMA IN ADULTS

In early adulthood (ages 16–35 years), the lung function is near maximal and symptoms are therefore likely to be minimal. The Melbourne Study cohort showed that the symptom status at age 14 correlates with lung function at ages 14 years and 21 years.[44] Since there is secular trend for the symptoms to decrease in early adulthood as a result of lung growth, those small proportion of individuals who continue to be symptomatic tend to have the lowest levels of lung function. The best indicators of asthma continuing into adulthood are presence of BHR, early age of onset, sensitization to house dust mites, and reduced lung function. Adults with asthma and airway hyperresponsiveness show a persistent decline in lung function. The Lung Health Study[150] showed a relationship between airway responsiveness (AR) and early onset of chronic obstructive pulmonary disease in both men and women, and those adults with increased AR who continued to smoke had the most significant declines in lung function.

CAN WE PREVENT ASTHMA?

There have been efforts by various groups to prevent asthma in high-risk children by allergen avoidance and dietary modification. These studies have enrolled the subjects antenatally and followed them up. For children with a family history of asthma, Peat JK et al.[141] reported the effects of avoidance of house dust mite allergen exposure, and the addition of omega-3 fatty acids in their diet. The atopic children in the active diet group showed a significant reduction in the prevalence of cough [10.0%; 95% confidence interval (CI), 3.7–16.4; p = 0.003; number needed to treat = 10], but there was nonsignificant change (1.1%; 95% CI, -7.1 to 9.5) in cough among nonatopic children. While the active allergen avoidance group showed a 7.2% (95% CI, 10.11–14.3; p = 0.05; number needed to treat = 14) reduction in sensitization to house dust mite, there were no significant differences in wheezing with either intervention. These results and other recent studies suggest that public health interventions that are simple to execute in early childhood may possibly have a role in preventing allergies and asthma. Similar results have been reported by other authors.[151,152]

Probiotics have been studied to evaluate their role in prevention of asthma. Kalliomaki et al.[94] evaluated the role of administration of *Lactobacillus* GG prenatally to mothers on the outcome of atopic disease in the first years of life. In this study, the frequency of atopic eczema in the probiotic group was half that of the placebo group [15/64 (23%) vs 31/68 (46%); relative risk 0.51 (95% CI, 0.32-0.84)].

CAN WE ALTER THE NATURAL HISTORY OF ASTHMA?

The ideal scenario would be to apply primary prevention measures for altering the natural history of asthma but it has to be large public health measures that will have to be

applied to a large and poorly characterized proportion of the population. More general efforts could be directed towards factors like smoking cessation and improvement of home environment, which could have an indirect impact by way of risk reduction. In addition, by focusing on critical stages in the development of atopic sensitization or in the evolution of lung damage from repeated infection, relatively brief and therefore more acceptable interventions more akin to immunization procedures may be developed.

The next possible question would be—can we reverse the course of severe asthma once it is established? The prevention of the development of airway remodeling and chronic airway obstruction as potential therapeutic targets may have an impact on the overall morbidity and the outcome related to asthma. So far, inhaled steroids are the only agents that have shown an impact on the reduction on inflammatory parameters and improvement in lung function but their effects do not appear to have long-lasting or disease-modifying value. The fact that they are effective only as long as they are administered was demonstrated by the twin studies from the Dutch Chronic Nonspecific Lung Disease Study Group.

In their first study,[153] the group sought to determine whether long-term budesonide therapy would result in clinical asthma remission during therapy and they found that of the 53 children randomized to receive budesonide, 60% achieved an 8-month clinical remission at some point during the 3-year study. At study conclusion, only one-third were in remission and 15% showed a normal FEV_1 (>90%), suggesting that budesonide improved asthma symptoms but did not cure the disease.

In their second follow-up study,[154] 28 children from the original cohort who had received budesonide initially, were now randomized again to either continue receiving it or to be tapered off it completely. About 40% of those tapered off had to be withdrawn from the study during the 6-month follow-up period and 25% required oral prednisone therapy due to poorly controlled asthma, as against none among those who continued to receive budesonide. In addition, much of the gain in lung function and BHR obtained in these children during the 2–3-year therapy with inhaled steroids was completely lost by the end of the 6-month period. Thus, steroids could induce only a short-lived remission, which lasted only as long as they were continued.

Similar observations also came forward from the CAMP study which was a multicentric study designed to assess the effect of three different treatment strategies on lung development and the course of asthma. It was started in 1993 when 1,000 children between the ages of 5–12 years were randomized to receive either inhaled nedocromil, inhaled budesonide or inhaled placebo and were followed up for symptoms, pulmonary function and need for additional therapy.[145] After the treatment phase came to a close in 1999, there was a 4-month washout period and the results showed good response and safety profile with steroid therapy. But the reduction in AR that was achieved during the treatment phase was lost completely in the 4-month washout period. In addition, there was no significant effect on lung function on lung growth at the end of the study.

Most patients in CAMP study had asthma of at least 5 years' duration; therefore, earlier introduction of steroids could be one possible intervention. Since majority of asthma has its origin in early life, considerable decline in lung function may have already occurred by the time aggressive anti-inflammatory therapy is begun. Hence, prompt evaluation and recognition of poor lung function early in life along with initiation of anti-inflammatory therapy may provide some long-term benefit. Assessment of lung function is difficult in children less than 5 years of age and recent developments in infant lung function testing techniques could help overcome this limitation.

Since there is no known effective treatment that can consistently induce a long-lasting remission from the disease, there is a need for developing a greater understanding of the onset and progression of the airway inflammation and its persistence. Use of measures of airway hyperrresponsiveness and determination of the type of inflammatory reaction, in guiding of further therapy, seems like a promising approach that needs verification through large-scale clinical studies. Development of new classes of medications like anti-IgE (omalizumab), cytokine antagonists (anti-IL-4) and transcription factor inhibitors could help augment the anti-inflammatory effect of steroids and may be a step further in this direction.

To conclude, the clinical axiom of "all that wheezes is not asthma" still holds true, and one needs to look at the clinical profile of each patient with regards to their history and physical exam, family history and other risk factors, environmental factors, and lung function parameters before one can safely say that the diagnosis of asthma is certain. Transient wheezers may symptomatically be treated and in the absence of other risk factors, about 70% of them are likely to outgrow their recurrent wheezing. Since a number of conditions may present with wheezing symptoms, a broad differential diagnosis should be kept in mind when dealing with young infants presenting with wheezing for the first time. In addition, those who have unusual lack of response to standard therapy, the diagnostic label of asthma should always be questioned. As more research unravels the mystery surrounding the pathogenesis and treatment of asthma, we will be able to give better care and provide better answers to the parents' questions about long-term outlook for their children.

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