

Epidemiology of Asthma and Recurrent Wheeze in Childhood

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Introduction

Recurrent wheezing and asthma in childhood are important public-health problems, and are associated with significant health care costs. Wheezing lower respiratory-tract illnesses (LRIs), such as bronchiolitis, are some of the most common reasons for seeking care during the first year of life, and are a major cause of hospitalization in infancy. By the end of the first decade of life, the majority of children in the industrialized world have experienced wheeze at least once.

Although it affects fewer children, asthma is the most common chronic disease of childhood. In the early 1990s, it was estimated that asthma affected over 12 million people, and accounted for 7.1 million visits to physicians, 1.4 million visits to emergency rooms, and at least 5,000 deaths annually (1). More recent figures estimate that costs for health care of asthmatics is \$5.8 billion annually (2). Because the prevalence of asthma appears to be increasing (3,4), particularly among young children, the costs associated with asthma care are also likely to increase.

Despite the fact that recurrent wheeze is one of the major symptoms of asthma, the relation of these two entities is complex. First, while asthmatics are more likely than other children to wheeze in early life, the majority of those who wheeze with early LRIs do not develop asthma. Secondly, although viral infections appear to cause most early LRIs, they appear to be only one of several triggers for later asthma attacks, with airway inflammation associated with allergy being the underlying cause for later asthma. Finally, the risk factors for infectious wheeze differ from those for asthma, and for both outcomes, the risks vary with age. An understanding of the risk factors for and natural his-

tory of both asthma and wheeze is essential for prevention and appropriate management of these conditions.

This chapter addresses the distribution of and risk factors for wheezing and asthma in three periods: the first 3 yr of life, middle childhood, and late childhood. Much of the data reported is taken from the prospective, longitudinal Tucson Children's Respiratory Study (CRS) (5,6). This study has followed a large population of healthy children (and their families) since birth through age 16. The picture of asthma and wheeze that has emerged from this and other studies is complex, with different clinical manifestations evident at any particular age, leading to different patterns of activity over time. Thus, although children may wheeze for different reasons at a single age, most early wheezing is infectious, with later wheezing and asthma showing a stronger relation to allergy. Finally, although genetic factors are important determinants of asthma, environmental factors operating at different developmental stages also appear to influence the development and presentation of the disease.

Wheezing in the First Years of Life

Wheezing is a very common respiratory symptom. Almost half of all children wheeze at least once in the first years of life, with the prevalence being highest in infancy. In the Tucson CRS the prevalence of wheezing with LRIs among children followed for the entire year was 32.0% in the first year of life, after which it declined to 17.3% and 12.0% in the second and third year, respectively. An etiologic agent was identified, by culture and/or direct immunofluorescence for antigen detection, in 66% of LRIs (6). As anticipated, respiratory syncytial virus (RSV) was the most common agent identified, followed by parainfluenza virus type 3; similar findings have been reported in other studies of LRIs (7,8). It is worth noting, however, that parents reported additional episodes of wheeze that were not diagnosed as LRIs by the pediatricians. In the first 3 yr of life, 55.5% of parents reported that their child had wheezed at least once, as compared to 36.1% who reported their children had wheezing LRIs.

One of the most important risk factors for LRIs identified in the CRS was pre-existing lung function (9). Measures of T_{me}/T_e (the percentage of total expiratory time required to reach peak tidal expiratory flow), total respiratory conductance (the reciprocal of the resistance of air flow of the entire respiratory system), functional residual capacity, and maximal flow at functional residual capacity ($V_{max}FRC$) were obtained in 124 infants at 2 mo of age who had at least one Caucasian, non-Hispanic parent. Children who subsequently developed a wheezing LRI, and especially those who had recurrent wheezing in the first 3

yr of life, had lower mean levels of these measures prior to any LRI. This analysis suggests that the differences in lung function found after an LRI (10,11) may be attributable in part to pre-existing deficits in lung function.

Several behavioral and/or environmental factors were also associated with incidence of LRIs, most of which alter the risk of infection and/or illness. Breastfeeding of at least 1 mo was associated with lower rates of wheezing LRIs in the first 4 mo of life (12), particularly if the child was exposed to other risk factors for acute respiratory illnesses such as sharing the room. Use of daycare in the presence of ≥ 3 children was also associated with roughly double the risk for LRI (13) from the age of 4 mo to 3 yr. Passive exposure to cigarette smoke in infancy was associated with a significantly higher rates of wheezing LRI (14), particularly if the mother smoked a pack or more per day and if the child was cared for at home (odds ratio: 2.8). In addition, maternal smoking of a pack or more per day was associated with earlier age of first LRI. In the third year of life, the risk of a wheezing LRI in the presence of a smoking caretaker was three times higher than for children who did not have a smoking caregiver (13).

To investigate the role of allergy as a possible risk factor for LRIs, the relationships between umbilical cord serum IgE levels and the incidence of subsequent LRIs in the first year of life was investigated (15). Total IgE was inversely associated with LRI rates: the percentage of those with LRI was 35.8%, 27.5%, 28.7%, and 22.2%, for those with undetectable, 0.10-<0.30 IU/mL, 0.30-<1.0 IU/mL, and 1.0+ IU/mL of IgE, respectively ($p < .005$ trend chi square). These analyses suggest that most LRIs in infancy are not allergic in nature, and that elevated serum IgE may indicate relative protection from LRIs in the first year of life. However, cord-serum IgE became predictive of LRIs occurring in the third year of life, suggesting that allergic predisposition plays an increasing role in later episodes of wheeze.

Wheezing During Middle Childhood

Numerous studies have shown that skin-test responsiveness to allergens, particularly indoor allergens, is associated with persistent wheezing among older children (16). In their classic study, Sporik et al. (17) showed a strong association between asthma and sensitization to house-dust mite (both skin test and specific IgE) among 67 children followed for 11 yr. It also appears that *early* onset of atopy may more relevant to asthma than later sensitization. Peat and her colleagues have shown (18) that children who were already atopic at 8–10 yr of age were significantly more likely to develop wheeze, asthma and BHR during subsequent years of follow-up than were children who became atopic

Table 1
Factors Associated with the Wheezing Phenotypes

	Never wheezed	Transient early wheezing	Late onset wheezing	Persistent wheezing
$V_{\max}$ FRC in infancy [n] (95% confidence intervals)	123.3 [n = 67] (110.0–138.0)	70.6 [n = 21]* (52.2–93.8)	107.1 [n = 21] (87.5–129.6)	104.6 [n = 16] (73.6–144.5)
$V_{\max}$ FRC at age 6 [n] (95% CI)	1262.1 [260] (1217–1308)	1097.7 [104] (1035–1164)	1174.9 [81] (1111–1241)	1069.7 [81]* (907–1146)
Total serum IgE (IU/mL) at 9 mo (95% CI)	3.4 (3.0–3.9)	3.7 (3.1–4.4)	3.8 (2.9–5.0)	5.2* (3.8–7.2)
Total serum IgE (IU/ml) at 6 yr (95% CI)	28.1 (22.4–35.3)	31.0 (22.3–43.1)	42.1 (26.6–66.0)	65.6* (45.3–94.4)

* $p < .01$ for comparison with children who never wheezed.

Adapted from (19).

after that age. Because wheezing LRIs may occur both in children who later become allergic as well as those who do not, it is logical that wheezing in early childhood would encompass several distinct entities with different clinical manifestations and sequelae.

This issue was investigated by identifying categories of children with reference to whether wheeze in the past year was reported at age 6 and whether they experienced early wheezing LRIs (19). Although more than half of the children (51.5%) had never wheezed, 164 (19.9%) wheezed only with early LRIs (“transient early wheezers”), 124 (15.0%) wheezed at age 6 but not in the first 3 yr of life (“late wheezers”), and 113 (13.7%) wheezed both before 3 yr of age and at age 6 (“persistent wheezers”). Thus, of the 277 children who had wheezing LRIs during the first 3 yr of life, 60% were transient wheezers, who did not wheeze at age 6. The main risk factor associated with transient early wheezing was lung function prior to any LRI. $V_{\max}$ FRC was significantly lower in infancy for transient wheezers (70.6 mL/s) compared with never wheezers (123.3 mL/sec, $p < .01$). This group had no other risk factors for asthma as shown in Table 1: they had normal levels of IgE, were no more likely to be atopic at age six, had no increased history of maternal asthma, and did not have eczema in early life.

In contrast, persistent wheezers were significantly more likely to have allergic risk factors for asthma (see Table 1). Although there was no difference in total IgE at birth, persistent wheezers had significantly higher IgE levels at 9 mo and 6 yr than never wheezers. In addition,

they were significantly more likely to be skin-test positive to aeroallergens, to have a maternal history of asthma, and to have had eczema in infancy. Persistent wheezers did not differ from never wheezers in infant lung function. Risk factors for late wheezing were similar to those for persistent wheezing (*see* Table 1).

As shown previously, total IgE at birth was not predictive of wheezing phenotype, but by 9 mo of age, persistent wheezers had significantly higher IgE compared to the other groups. This suggests that persistent wheezers may develop a different immunologic response to exposures and events in the first year of life. Welliver et al. (20) had previously shown a correlation between RSV-IgE titer at the time of an RSV LRI, and subsequent wheezing, suggesting that such altered immune responses might be evident at the time of an LRI. We assessed both eosinophil levels and total IgE at the time of acute LRIs in comparison to a specimen obtained when the children were well. Children with persistent wheezing had significantly higher levels of total serum IgE during the acute LRI compared to the convalescent phase, whereas acute and convalescent IgE levels in transient early wheezers were unchanged by the acute LRI. Further, persistent wheezers lacked the characteristic eosinopenic response associated with the acute LRI seen among the transient wheezers (21). Because production of eosinophils and IgE are regulated by interleukin (IL)-4 and IL-5, these findings suggest that the persistence of symptoms in some children may be revealing a predisposition toward predominant T-helper (Th2)-like responses already present at the time of the acute illness.

Wheezing and Asthma in Later Childhood and Early Adolescence

Symptoms

Most epidemiologic studies have found that although the onset of new wheeze declines as children age, the incidence of asthma increases, particularly among females. In one study of adolescents between the ages of 16 and 19 yr, the yearly incidence of new cases of asthma was as high as 0.8–1.3%, with an incidence in females that was almost twice that in males (22,23). In another study of over 14,000 children followed from age 7–33 (23,24), males were more likely than females to develop asthma until age 16, but after this age the ratio was reversed.

In the CRS, although the point prevalence of wheeze declined, the prevalence of active asthma diagnosed by a physician increased at each survey until age 16, the last age at which data were available. In addition, distinct gender differences were evident (Fig. 1). Early in life, boys were significantly more likely to wheeze, especially at age 6 and 8, and active wheeze became less common with increasing age. In contrast, a

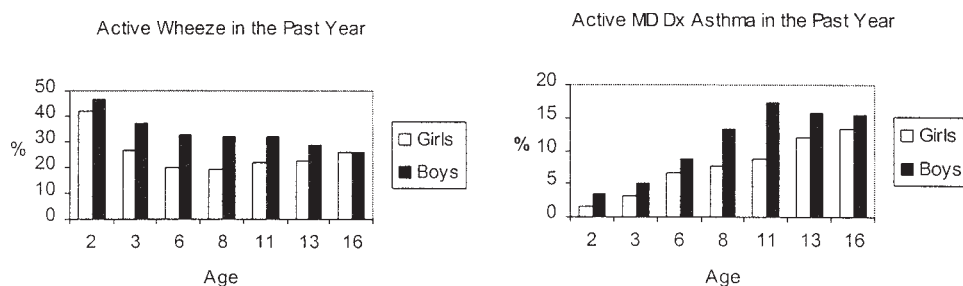


Fig. 1. Rates of wheeze and active MD asthma in the past year, by age and gender.

slight increase in wheeze was evident for girls after infancy. Consequently, gender differences in wheeze became borderline at age 13 ($p < .08$), and disappeared completely by age 16 ($p < .96$). Similarly, although MD-diagnosed asthma was more common in boys at all ages, it increased during the first decade of life but then declined for boys starting at age 11. For girls, however, active asthma continued to increase through age 16. Data on severity of symptoms are not yet available for the 16 yr olds in the CRS. However, other studies have found that severity of symptoms, as measured by hospitalizations (25–27), mortality (28), level of BHR (29), frequency of symptoms (30), and decreased lung function (25), is greater among females than males.

Although asthma is a chronic condition, with onset in childhood being associated with wheezing in adult life (31), there is some evidence that asthma may be “outgrown” during adolescence (32,33). Studies of childhood asthmatics in their teens have shown that many patients, particularly those with mild illness, stop having respiratory symptoms during adolescence (34). However, estimates of remission of asthma symptoms in various populations ranges from 30–80% (35–37). In one study of children with diagnosed asthma at age 7 who were re-interviewed at age 33 (38), 35% never experienced symptoms again, 60% had intermittent symptoms, and only 5% had persistent symptoms. Remission of symptoms also appears to be confined mainly to males (34,37,39).

The relation between early wheezing history and both mild and frequent wheeze at age 11 was assessed in the CRS. As shown in Fig. 2, there was a highly significant relationship between wheezing phenotype in the first 6 yr of life with wheezing at age 11 (left) and at age 16 (right). More than 60% of persistent wheezers at age 6 were still wheezing at 11. For children with mild wheeze at age 11, the proportion with continued wheeze at age 16 was highest among those who had persistent wheezing at age 6. Eighty percent of children who reported frequent wheeze at age 11 still wheezed at age 16, regardless of their wheezing phenotype by age 6.

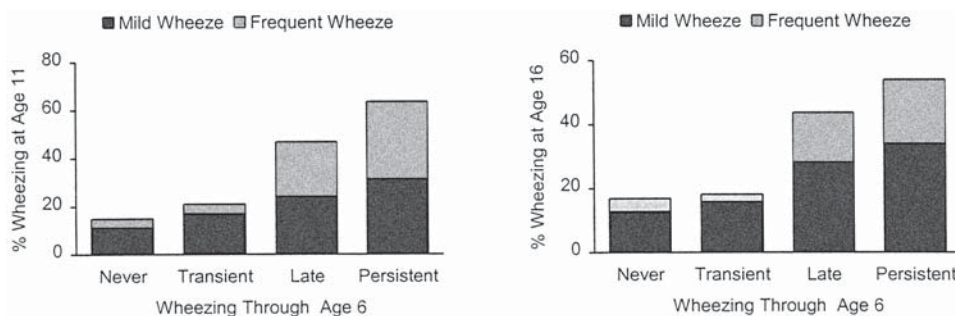


Fig. 2. Percent wheezing at age 11 and age 16 by previous wheezing history.

Risk Factors

Many of the risk factors for wheezing and asthma in late childhood and early adolescence are allergic. In the desert environment of Tucson, the mold *Alternaria* is the allergen most strongly associated with the development of asthma (40). For example, the incidence of asthma by age 11 increased with atopy and specifically with sensitization to *Alternaria*, being 13% among nonatopic children; 24% among atopic children who were sensitized to neither *Dermatophagoides farinae* nor *Alternaria*; 33% for children who were sensitized to *D. farinae* but not *Alternaria*; and 43% for those who were sensitized to *Alternaria* ($p < .00001$). Only sensitization to *Alternaria* was associated with a significantly higher risk of asthma than the risk associated with atopy in general.

Similarly, asthma is associated with higher total serum IgE levels. At age 6, total IgE is higher among children whose asthma began before that age, and total IgE at age 11 is higher in both those who already have asthma and those who develop it by age 16 (41). The relation between asthma and allergy is further supported by findings regarding bronchial hyperresponsiveness. Airway reactivity as measured by methacholine challenge was strongly associated with total serum IgE levels measured at age 6 and 11, and with atopy as indicated by skin test response (42).

Finally, eosinophilia measured longitudinally was also associated with the risk for asthma. Percent eosinophils/300 white blood cell (WBC) counts ("eos") was measured at 9 mo, 6 yr, and 11 yr of age to create an index of longitudinal eosinophil status (43). Children were classified into four groups based on the number of measurements in which they had low ($\leq 2\%$) or high ($\geq 5\%$) eos, as follows: 1) persistently low eos; 2) low eos (never high eos); 3) intermittently high eos; and 4) persistently high eos ($n = 17$). There was a strong linear relation between longitudinal eos and chronic MD asthma (trend chi square

$p < .001$), which was independent of atopy. Logistic regression which adjusted for atopy and gender found a 70% increase in asthma risk associated with each increase in longitudinal eosinophil status. Parental history of asthma was associated with both longitudinal eos ($p < .001$), and, independently, with chronic asthma ($p < .001$). The stepwise increase in asthma risk associated with longitudinal eos noted earlier was reduced to 48% when parental asthma was added to the model. These results suggest that children with asthma by the end of the first decade of life appear to have a more Th2 profile, as measured by eosinophil status, atopy, and total IgE.

A number of studies have shown a relation between early LRIs and subsequent respiratory symptoms (11,44,45). However, the nature of the relationship between wheezing in early childhood and the subsequent development of asthma has been controversial (46). Although it was often thought that LRIs predisposed a child to the subsequent development of asthma by damaging the airways, having an LRI might only be a marker of some pre-existing susceptibility to both infectious wheeze and asthma. We have investigated the relation between LRIs in the first 3 yr of life caused by respiratory syncytial virus (RSV), and the subsequent development of wheezing through age 13 (47). RSV-LRIs in the first 3 yr of life were associated with an increased risk of both infrequent wheeze (OR 3.2, 95% CI: 2.0–5.0) and frequent wheeze (OR: 4.3, CI: 2.2–8.7) at age 6. However, the risk decreased markedly with age and was no longer significant by age 13. There was no association between RSV-LRIs and subsequent atopic status. These findings suggest that although RSV LRIs early in life are an independent risk factor for the development of wheezing to age 11, they show no relation with wheezing after that age. Further, the association between early RSV-LRIs and subsequent wheezing is not attributable to an increased risk of allergic sensitization.

To further confuse the picture, some early-life exposures that were associated with greater risk of having an LRI appeared to be protective against subsequent persistent wheeze. For example, exposure to other children during the first 6 mo of life, either siblings or through day care, was associated with higher rates of wheeze in the first years of life (13). However, early exposure to other children was found to be associated with *lower* rates of active MD asthma through age 13 (48). Similarly, although infants exposed to more children at home and/or day care experienced more frequent wheeze at yr 2, they had less frequent wheeze from yr 8 through yr 13. The presence, at 6 or 11 yr of age, of skin test reactivity and IgE in the 95th percentile of the distribution, were also inversely related to increased exposure to children at home or in day care during early infancy. This finding is consistent with the "hygiene" hypothesis, which speculates that early exposure to

microbes, particularly Gram negative bacteria (49) may be protective against the later development of asthma and atopy.

It is well-documented that breastfeeding is associated with reductions in respiratory illness early in life (12,50). The relation between breastfeeding and childhood asthma is more controversial, with some studies finding a protective effect, whereas others find no relation. There was no significant relationship between asthma by age 13 and duration of exclusive breastfeeding in the CRS. However, the association between feeding and asthma was altered by maternal asthma status and atopy in the child (51). Among children with nonasthmatic mothers, the percent with asthma by age 13 was unrelated to duration of breastfeeding. In contrast, among children with a maternal history of asthma, there was a direct relation between duration of breastfeeding and asthma. Further, this relation was limited to those children who were themselves atopic at age 6. Asthma showed no relation to infant feeding for children who lacked maternal asthma, or who were themselves nonatopic. These findings are consistent with the hygiene hypothesis because breastfed infants are both protected against many infectious organisms, and have lower levels of Gram-negative bacteria in their gut flora.

Finally, although early-life exposures influence the subsequent development of asthma and wheeze, there also appear to be factors that increase risk for asthma that do not occur until late in childhood. Specifically, increasing body mass index (BMI) appears to be associated with the development of asthma in middle to late childhood (52,53). Using percentiles for BMI standardized for age and gender, CRS children were classified at both age 6 and 11 in two groups: normal (BMI <85th percentile), and overweight/obese ("OW," BMI $\geq$ 85). There was no association between BMI at age 6 and prevalence of wheezing at any age. Females, but not males, who were OW at age 11 yr were more likely to have current wheezing at ages 11 and 13, but not at age 6 or 8. Females who became overweight or obese between 6 and 11 yr were significantly more likely to develop new asthma symptoms at age 11 or 13 than those who did not. OW females at yr 11 were more likely to have increased bronchodilator responsiveness and increased variability of peak flow at age 11 (18.4% vs 8.3%, $p = 0.038$), but were no more likely to be atopic than females who did not become overweight/obese. Males did not show these associations.

Summary/Conclusions

To summarize, wheeze is common throughout childhood, although it decreases as children age. However, the characteristics of wheeze, its relations with asthma, and its risk factors all change with

age. Longitudinal studies have shown that "transient early wheezing" predominates during the first years of life. The principal risks for this type of wheezing are largely mechanical, relating to small airways, and infectious, relating to the risk of becoming infected with respiratory viruses. Associated with passive exposure to cigarette smoke, exposure to other children, and not being breastfed, this form of wheezing was unrelated to increased airway liability or atopy in the child. For the majority of children, particularly those with low lung function at birth, wheezing with early LRIs is a benign condition, not associated with subsequent wheeze or risk for asthma.

During the middle part of the first decade of life, wheezing appears to reflect a mix of infectious and allergic wheezing. By 6 yr of age, some children have already wheezed persistently. This group is more likely to have high total IgE levels, to be skin-test positive, and to be given a diagnosis of asthma. Further, their immunologic response to their early LRIs was consistent with a Th2 bias: persistent wheezers produced high levels of IgE, and did not demonstrate the normal pattern of decreased eosinophils. Nevertheless, the children who wheeze in middle childhood are a mixed group, with some being less allergic. Thus, although markers of allergy become increasingly important predictors of wheezing for the group as a whole, wheezing in middle childhood is not associated with later methacholine hyperresponsiveness (42).

Finally, persistent allergic wheezing, usually associated with a diagnosis of asthma, predominates by the end of the first decade of life. Wheezing at this age is associated with methacholine responsiveness, peak-flow variability, and markers of atopy, such as total IgE and allergy skin-test response. Although children who wheezed early in life are more likely to wheeze later, early wheeze does not increase the risk of atopy, suggesting that early LRIs are markers of increased risk rather than causes. The gender differences in wheeze disappear, with boys becoming less likely to wheeze and to have asthma, whereas both conditions appear to increase in girls. Finally, some of the risk factors for early LRIs, such as exposure to other children in infancy, appear to be associated with protection from later allergic wheezing.

Clearly, asthma and wheeze during childhood are complex entities, presenting with different characteristics at different ages, and implicating varied and changing causes. Genetic factors are important determinants of the intermediate phenotypes. However, environmental factors operating at different developmental stages also appear to influence the development of asthma. Additional research regarding these relationships is essential, both to elucidate possible causal mechanisms and to provide insight into the primary prevention of asthma.

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