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Wheezing in infants and its relation to asthma

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The relation between wheezing lower respiratory illnesses (LRI) occurring in early childhood and the subsequent development of asthma has been the matter of considerable discussion during the last 40 years. In 1953, Boesen (Boesen, 1953) reported the results of the earliest follow-up study of children who had 'asthmatic bronchitis' in early life. He mailed questionnaires to the parents of children from Copenhagen hospitalized with this diagnosis 6-11 years earlier. He observed that only 3% of infants admitted during the first 6 months of life had 'regular attacks of asthma' at follow-up compared with 7% of those admitted between 6 and 11 months, 18% of those admitted between 12 and 35 months and 42% of those admitted after the age of 3. Boesen also reported that, among Copenhagen schoolchildren aged 7-14 years, prevalence of asthma was 0.8% in 1949-1950. This study thus suggested a connection between acute respiratory illnesses requiring hospitalization in early life and the subsequent development of asthma. It also showed that prognosis was better for episodes occurring in the first year of life.

Many subsequent studies have confirmed that children who wheeze during viral infections in early life are at increased risk of developing asthma (reviewed by Samet et al. 1983), but the factors responsible for this connection are not yet entirely understood. Two main approaches to this problem have been proposed (Morgan, 1990). Many investigators consider wheezing a manifestation of a condition, or conditions, that pre-exist the viral infection which usually provokes the illness. Others assume that viral infections may prime the immune system, damage the lungs, and cause a substantial alteration in airway function, all of which may predispose the infant to persistent bronchial responsiveness and to the subsequent development of asthma. Unfortunately, most studies of the outcome of wheezing in early life are based on small numbers of selected subjects or on subjects who were enrolled in the early school years and in whom the history of wheezing during infancy was obtained retrospectively. Only recently have the results of a few prospective studies initiated at birth (Wright et al. 1989) or during infancy (Strope et al. 1991) become available. These studies have considerably changed our understanding of this issue and will be the focus of this chapter.

WHEEZING ILLNESSES IN INFANCY AND LUNG FUNCTION

Several prospective studies have shown that infants with a history of bronchiolitis or wheezing have persistently lower levels of several indices of lung function measured many years later. Sims et al (1978) studied 8-year-old children who had proven respiratory syncytial virus (RSV) bronchiolitis in infancy and found that they had diminished lung function when compared to controls. Pullen and Hey (1982) assessed lung function in 130 children 10 years after hospitalization for RSV-LRI occurring during infancy and found that these children had significantly lower mean values for several indices derived from the maximal expiratory flow-volume curve than controls. Mok and Simpson (1982) followed 200 8-year-old children who had been hospitalized for bronchiolitis during infancy. They found that these children had approximately 5% lower forced expiratory volume in the first second (FEV₁) and 12% lower mean forced expiratory flow between 25% and 75% of vital capacity (FEF₂₅₋₇₅) than children without a history of bronchiolitis.

It is apparent that all these initial studies were performed in children who were hospitalized for LRI in early life. In could be argued that these children may have a more severe expression of the same disease affecting other children who do not require hospitalization. It is also possible that most infants who require hospitalization may have a disease altogether, distinct from that affecting infants with milder illnesses. Strope et al (1991) studied the relation between mild LRI not requiring hospitalization, as documented by the children's paediatricians during the first 6 years of life, and lung function assessed at age 6-18 years in 89 boys and 70 girls. They found that boys who had experienced two or more episodes of wheezing LRI during the preschool years had lower FEV₁ and FEF₂₅₋₇₅ among other lung function parameters, than did boys with one or less wheezing illnesses or who had nonwheezing illnesses. The association between preschool wheezing LRIs and lower subsequent lung function was also present among girls, but did not reach statistical significance probably because of the smaller number of girls involved. The study by Strope et al (1991) thus demonstrated that diminished lung function levels subsequent to wheezing LRIs were not exclusive of subjects with more severe wheezing illnesses requiring hospitalization in early life.

The pathophysiological mechanisms responsible for these diminished levels of lung function have been the matter of considerable debate. It was understood from the beginning that it was unlikely that persistence of symptoms could be the only explanation for these findings, because diminished lung function was also observed among subjects who had been symptom-free after early childhood (Strope et al, 1991). It remained to be elucidated if the lower levels of lung function observed in infants with wheezing LRIs were inborn or were otherwise induced by the viral infections themselves.

Three studies contributed to clarify this issue, at least in part (Martinez et al, 1991; Tager et al, 1993; Young et al, 1994). Investigators in Tucson

and Boston in the U.S., and in Perth in Australia took advantage of the development of new techniques to assess lung function in infancy (Taussig et al, 1982), and obtained data for maximal expiratory flows at end-tidal expiration (\dot{V}_{max} FRC) during the first 6 months of life and before any LRI developed. There has been considerable debate about what aspect of lung function \dot{V}_{max} FRC represents, but studies using bronchodilators and histamine have demonstrated a pattern of responses that suggest that \dot{V}_{max} FRC reflects the size of the intrathoracic airways (Prendiville et al, 1987). The studies by Martinez et al (1991), Tager et al (1993) and Young et al (1994) showed convincingly that infants who would subsequently develop wheezing illnesses had, as a group, lower mean \dot{V}_{max} FRC before any such illness developed.

These studies gave rise to the hypothesis that, in many if not most instances, infant wheezing could be a mechanical phenomenon, associated with a critically smaller airway diameter (Martinez et al, 1988). Briefly stated this hypothesis suggests that both genetic and intrauterine factors determine the size of the intrapulmonary bronchi at birth. This size is a function of the size of the lung, of the thickness of the airway wall, and of the forces that keep airways void of cartilage open (Martinez et al, 1991). Wheezing is the vibration induced by the passage of air through an airway after a critical resistance to airflow in the lumen of that airway has been reached. Because resistance is a function of the fourth power of the radius, reductions in airway diameter due to oedema, mucus, and intraluminal fluid may result in markedly higher increases in resistance in airways with diminished initial intraluminal diameters.

This hypothesis offered a plausible explanation for the changes in the incidence of wheezing illnesses with age: this incidence is highest in the first months of life and decreases markedly after 6 months of age (Martinez, in press). Morgan and Martinez (unpublished observations) recently showed that maximal flows grow faster than lung volumes during the first 6 years of life and it is thus likely that the critical resistance for the development of wheezing may not be reached as easily in older children as it is in infants.

WHEEZING IN INFANCY AND BRONCHIAL HYPERRESPONSIVENESS

In spite of these advances in our understanding of the risk factors for infant wheezing, several issues remained to be elucidated. The finding of diminished lung function prior to any LRI in children who subsequently developed wheezing LRIs did not clarify what causes these diminished airway function levels and, specifically, if bronchial hyperresponsiveness (BHR) and/or increased airway tone are involved in it. Indeed, it has been suggested that BHR may be a risk factor for wheezing LRIs in early life (Wilson et al, 1992). Several studies had found that children hospitalized with bronchiolitis in infancy had both higher prevalence of BHR and lower levels of lung function than children without such a history (Gurwitz et al, 1981; Sims et al, 1981; Pullen and Hey, 1982). More recently, three groups

of researchers studied bronchial responsiveness to histamine or methacholine in infants with a history of bronchiolitis (Tepper et al, 1992) or who had wheezing episodes during the first months of life (Stick et al, 1991; Clarke et al, 1992). Tepper et al (1992) studied 18 infants with acute bronchiolitis, nine of whom were hospitalized for their disease, and 24 controls. They found that approximately 4 months after their illness, infants with bronchiolitis had significantly diminished percent predicted $\dot{V}_{max}FRC$ but bronchial responsiveness was not increased when compared to that of controls. Ten months after the acute episode, children with a history of bronchiolitis still had significantly diminished $\dot{V}_{max}FRC$ levels, but now their bronchial responsiveness was also significantly increased compared to controls. The authors proposed the hypothesis that most infants are born with BHR and become hyporesponsive with age, but in those who develop bronchiolitis, BHR may be more likely to persist. Both Stick et al (1991) and Clarke et al (1992) studied infants with a history of recurrent wheezing, and Stick et al specifically excluded infants with a diagnosis of RSV infection. Both groups reported lower $\dot{V}_{max}FRC$ levels in wheezy infants than in controls, but found no difference in level of bronchial responsiveness between the two groups. These results were in agreement with those reported by Voter et al (1988). These researchers studied lung function (using flow-volume curves) and methacholine responsiveness in 57 males between the ages of 11 and 22. These subjects belonged to the same paediatric practice in North Carolina on which Strope et al (1991) based their previously quoted study, and LRI history had been documented in the children's charts. Practically all LRIs were managed on an out-patient basis. The authors found no relation between preschool wheezing illness experience and methacholine sensitivity in these adolescent subjects, but they confirmed in this smaller subgroup of subjects that spirometric performance was significantly lower in children with two or more wheezing illnesses in early life.

It thus appears that, when studies are limited to subjects with mild diseases not requiring hospitalization, a consistent pattern of diminished levels of lung function but prevalence of BHR within normal ranges was observed, whether lung function tests or tests of bronchial responsiveness were performed months or years after the initial episode. Subjects with more severe symptoms requiring hospitalization also showed diminished average lung function parameters, but in several studies they showed increased prevalence of BHR as well. It remained to be elucidated if in these children, persistent BHR represented a hereditary developmental pattern attributable to an asthmatic predisposition or if it was the result of the viral insult itself. In a study of 63 normal infants without a history of LRI, Young et al (1991) assessed bronchial responsiveness to histamine at a mean age of 4.5 weeks, and thus before LRIs had occurred. They found that subjects with a family history of asthma had similar baseline $\dot{V}_{max}FRC$ but significantly higher prevalence of BHR than subjects without such a family history. There was no relation between cord serum IgE level and bronchial responsiveness. These results suggested that children with a genetic predisposition to develop asthma are at increased risk of having

BHR but not of having lower levels of lung function shortly after birth and before they developed any symptoms.

WHEEZING PHENOTYPES IN EARLY LIFE

The picture emerging from these data indicate the existence of a group of infants whose respiratory system may have a congenital form of limitation to airflow, and this developmental pattern becomes clinically important during infancy, that is, at a time when specific airflow conductance (i.e. the functional size of the airways relative to the size of the lungs) may be lower than that of older children. Infants belonging to this group are at increased risk of presenting with wheezing during viral respiratory infections, but they do not seem to have increased prevalence of BHR. The data suggest that this group of infants constitute the majority of subjects who wheeze in early life, and are more frequently represented among children with milder symptoms. Until recently, little was known, however, about the prognosis of these infants and about the factors associated with persistence of symptoms beyond the preschool years. In fact, many studies had suggested that most children with asthma start wheezing during infancy (Godfrey, 1984). Therefore, an important proportion of wheezing infants will go on to develop asthma, but it is not known if wheezing in infancy is the first manifestation of asthma in these children. The study by Tepper et al (1992) quoted earlier suggested that in subjects with a diagnosis of bronchiolitis, among whom hospitalization and thus more severe symptoms are more frequent, BHR is more prevalent than in control infants, and Young et al's (1991) data suggested that BHR may perhaps preexist bronchiolitis and be associated with a family history of asthma. The relation between this predisposition to asthma and the lower levels of lung function observed prior to any LRI (Martinez et al, 1991; Fager et al, 1993; Young et al, 1994) remained to be elucidated, but the results reported by Young et al also implied that a family history of asthma was not associated with lower $\dot{V}_{max}FRC$ levels during the first months of life.

INFANT WHEEZING AND ALLERGIC SENSITIZATION

Allergic sensitization and higher IgE levels are significantly more common in schoolchildren with asthma than in children without this diagnosis (Burrows et al, 1989). The same does not hold true for wheezing in early life: there is now good evidence indicating that, as a group, children with a history of bronchiolitis or wheezing in infancy do not have increased IgE levels in cord blood (Hakonen et al, 1992) nor are they more likely to be skin-test positive to aeroallergens later in life (Pullen and Hey, 1982). It is still possible, however, that a minority of wheezing infants whose symptoms may well be the first manifestation of asthma could coexist with the majority of infants who wheeze for mechanical reasons unrelated to an allergic inflammatory reaction occurring in the airways.

Data supporting this hypothesis was provided by Henderson et al (1992). These authors studied lung function and allergic sensitization in the group of 159 North Carolina school-age children whose history of wheezing episodes had been documented from early infancy and until age 6 by their paediatricians (Strope et al, 1991). As they had reported earlier, boys with two or more wheezing episodes during the first 6 years of life had lower levels of spirometric function. However, the authors now found that, in children with a history of recurrent wheezing in early life, increasingly more intense level of allergic sensitization to housedust mites (as assessed by radioimmunosorbent test, RAST) was correlated with progressively lower mean levels of small airway function. No such correlation was observed for boys without a history of recurrent wheezing in early life. It was not possible to determine from these data if prognosis of children with a history of recurrent wheezing in the first 6 years of life was modified by subsequent allergic sensitization. The authors speculated, however, that wheezing infants who subsequently were shown to be sensitized to housedust mites may have been sensitized very early in life; that wheezing during infancy was 'associated' with this early sensitization; and that this association could explain the linkage between mite allergy and lower levels of lung function reported in their study. Henderson et al (1992) also found that mite sensitization was associated with increased BHR in both subjects with and without a history of recurrent wheezing in early life. The authors again speculated that only early mite sensitization was associated with lower levels of lung function, whereas both early and late sensitization would be associated with increased BHR.

Further evidence in favour of a possible role of early allergic sensitization to housedust mites in the development of early wheezing was provided by Sporik et al (1990). These authors found that the age of onset of wheezing in 11-year-old asthmatic children was inversely correlated with the concentration of housedust mites as measured in the children's homes around the age of 2 years. Sporik et al speculated that exposure to the antigens of housedust mites in early life was a risk factor for both early allergic sensitization and for early onset of asthmatic symptoms. However, because all subjects had a diagnosis of asthma by age 11, it was not possible to assess with this study the relation between the allergic sensitization and prognosis of wheezing in early life.

ASTHMA AND WHEEZING IN THE FIRST 6 YEARS OF LIFE

Our group recently reported the results of a longitudinal study of 826 children followed from birth and in whom most LRIs occurring during the first 3 years of life were ascertained by their paediatricians (Martinez et al, 1995). Serum IgE levels measured at a mean age of 9 months were available for most subjects, whereas results of pulmonary function tests (\dot{V}_{max} FRC) performed during infancy were available for 121 children. At a median age of 6 years, parents reported on wheezing episodes occurring during the

previous year, and serum IgE levels, lung function tests, and skin-test reactivity to aeroallergens were also ascertained. Subjects were divided into four groups: those who had no wheezing LRIs during the first 3 years of life and who had no parental reports of wheezing episodes for the previous year at age 6 (never wheezers, 51%); those with one or more wheezing LRIs before age 3 but no current wheezing at age 6 (transient early wheezers, 20%); those with no wheezing LRIs in early life who had at least one episode of wheezing reported for the previous year at age 6 (late onset wheezers, 15%); and those who had one or more wheezing LRIs before age 3 and who were current wheezers at age 6 (persistent wheezers, 14%). It is important to stress that in this study, wheezing was ascertained in most cases at physical examination by the physician during the first 3 years of life, whereas parental reports were used to assess wheezing status at age 6. This discrepancy is almost inevitable: parents are much more likely to take their infant or toddler to the paediatrician for their wheezing than they are to take school-age children to the paediatrician for the same reason. Nevertheless, it is unlikely that biases in parental reporting at age 6 may explain the findings.

A first important feature is the very high cumulative incidence of wheezing episodes in this age group: by age 3, one third of all children had at least one wheezing LRI, and almost half had one or more wheezing episodes by age 6. Of all infants who had at least one wheezing LRI in the first 3 years of life, almost 60% had no wheezing episodes during the previous year at age 6.

Transient early wheezers were not more likely to be males, to have a maternal or paternal history of asthma, or to have eczema during the first year of life than never wheezers. Their mean serum IgE levels measured at birth, at a mean age of 9 months, and at age 6 were also not significantly different from those of never wheezers, as was a prevalence of positive skin test reactivity to allergens at age 6. However, transient early wheezers had markedly and significantly reduced length-adjusted \dot{V}_{max} FRC during the first year of life when compared to never wheezers, late onset wheezers, and persistent wheezers. Height-adjusted \dot{V}_{max} FRC at age 6 was still significantly lower in transient early wheezers than in never wheezers, in spite of the fact that the former were not actively wheezing at that age.

Persistent wheezers, on the other hand, had lung function values assessed shortly after birth that were not significantly different from those of never wheezers. However, by age 6, they had \dot{V}_{max} FRC levels that were markedly lower than those of never wheezers. Their serum IgE levels were not increased in cord blood, but were already higher than those of all other groups at a mean age of 9 months and also at 6 years, at which time they were also significantly more likely to have a positive skin test to aeroallergens. Almost two-thirds of persistent wheezers were males, and they were almost four times more likely to have an asthmatic parent than never wheezers, and twice as likely to have eczema during the first year of life. They also had more frequent wheezing symptoms than transient early wheezers and parents reported that they noticed wheezing apart from colds more often in infants who would later become persistent wheezers than in transient early wheezers.

These results thus suggested that, for the majority of wheezing infants, their illness is a transitory phenomenon associated with diminished lung function in early life. These infants with a good prognosis are not, as a group, more genetically predisposed to develop asthma or allergies than the general population and they usually run out of their symptoms by age 6, perhaps because of the relatively faster growth of their airways compared with their lungs. Persistent wheezers, on the other hand, have increased prevalence of the same risk factors that are characteristic of older children with asthma: they have high serum IgE levels already during the first year of life, increased prevalence of allergic sensitization as infants, are more likely to be males, and are genetically predisposed to develop asthma. All the evidence thus suggests that many of these infants have a form of very early onset asthma.

Three characteristics of persistent wheezers in our data merit attention. First, these infants are probably born with lung function parameters that are not significantly lower than those of never wheezers. By age 6, however, they have significant deficits in mean \dot{V}_{max} FRC values. This deterioration in lung function may be similar to that observed by Henderson et al (1992) among children with a history of recurrent wheezing before age 6 and who were sensitized to house dust mites: chronic allergic inflammation of the airways may be responsible for these changes. Second, cord serum IgE levels were not increased in persistent wheezers, but by 9 months of age, serum IgE levels were significantly higher in this group compared to never wheezers. This suggests that early allergic sensitization may indeed have occurred in these infants and that this may be associated with a worse prognosis. Finally, persistent wheezers had apparently more frequent and more severe symptoms in early life. This may explain why subjects with a diagnosis of bronchiolitis (Tepper et al, 1992) or who are hospitalized for wheezing LRI in infancy seem to have a worse prognosis and are often found to have higher prevalence of BHR than wheezing infants with milder symptoms: early onset asthma may be over represented in this group.

SUMMARY

There is now little doubt that at least two groups of wheezing infants, whose symptoms have very different pathogenesis and prognosis, coexist in early life. Respiratory noises among transient early wheezers are probably the result of enhanced airway obstruction by mucus and oedema caused by respiratory infections in infants with congenitally narrower airway passages. In these children, lung function tracks with age and therefore, their lung function remains persistently lower than that of infants with no history of wheeze, even after symptoms have subsided. A smaller group of wheezing infants have early onset asthma, and in these subjects the airways are genetically predisposed to respond to viral and allergic inflammation, as is the case for older children with asthma. If these infants become sensitized to aeroallergens, recurrent episodes of airway obstruction will persist beyond the early years of life, and BHR that does

not subside after infancy and deterioration of lung function will ensue. Identifying infants who will go on to develop persistent wheezing, and determining if inhaled anti-inflammatory drugs (Bisgaard et al, 1990) or other therapeutic approaches (Holt, 1994) can block the seemingly irreversible process leading to chronic asthma, is perhaps the most important challenge in the prevention of this common and invalidating condition.

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REFERENCES

- Bisgaard H, Munck SL, Nielsen JP et al (1990) Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 336: 649-651.
- Roessig I (1953) Asthmatic bronchitis in children. Prognosis for 162 cases, observed 6-11 years. *Acta Paediatrica* 42: 87-96.
- Burrows B, Martinez FD, Halonen M (1989) Association of asthma with serum IgE levels and skin-test reactivity to allergens. *New England Journal of Medicine* 320: 271-277.
- Clarke JR, Reese A & Silverman M (1992) Bronchial responsiveness and lung function in infants with lower respiratory tract illness over the first six months of life. *Archives of Disease in Childhood* 67: 1454-1458.
- Godfrey S (1984) The wheezy infant. In Meadow R (ed.) *Recent Advances in Paediatrics* 7: 137-153.
- Guirwitz D, Mindorff C & Levison H (1981) Increased incidence of bronchial reactivity in children with a history of bronchiolitis. *Journal of Pediatrics* 98: 551-555.
- Halonen M, Stern D, Taussig LM et al (1992) The predictive relationship between serum IgE levels at birth and subsequent incidences of lower respiratory tract illnesses and eczema in infants. *American Review of Respiratory Disease* 146: 866-870.
- Henderson FW, Stewart JW, Burchinal MR et al (1992) Respiratory allergy and the relationship between early childhood lower respiratory illness and subsequent lung function. *American Review of Respiratory Disease* 145: 283-290.
- Holt PG (1994) A potential vaccine strategy for asthma and allied atopic diseases during early childhood. *Lancet* 344: 456-458.
- Martinez FD, Morgan WJ, Wright AL et al (1988) Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. *New England Journal of Medicine* 319: 1112-1117.
- Martinez FD (1991) Sudden infant death syndrome and small airway occlusion: facts and a hypothesis. *Pediatrics* 87: 190-198.
- Martinez FD (ed.) *Childhood Asthma and Other Wheezing Disorders*. London: Chapman and Hall.
- Viral infection in early life. In Silverman M (in press).
- Martinez FD, Morgan WJ, Wright AL et al (1991) Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. *American Review of Respiratory Disease* 143: 312-316.
- Martinez FD, Wright AL, Taussig LM et al (1995) Asthma and wheezing during the first 6 years of life. *New England Journal of Medicine* 332: 133-138.
- Mok JYQ & Simpson H (1982) Outcome of acute lower respiratory tract infections in infants: preliminary report of seven year follow-up study. *British Medical Journal* 285: 333-337.
- Morgan WJ (1990) Viral respiratory infection in infancy: provocation or propagation? *Seminars in Respiratory Medicine* 11: 306-313.
- Prenzlville A, Green S & Silverman M (1987) Airway responsiveness in wheezy infants: evidence for functional beta adrenergic receptors. *Thorax* 42: 100-104.
- Pullen CR & Hey EN (1982) Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *British Medical Journal* 84: 1665-1669.

- Sarnet JM, Tager IB & Speizer FE (1983) The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. *American Review of Respiratory Disease* 127: 508-523.
- Sims DG, Downham MAPS, Gardner PS et al (1978) Study of 8 year old children with a history of respiratory syncytial virus bronchiolitis in infancy. *British Medical Journal* 1: 11-14.
- Sims DG, Gardner PS, Weightman D et al (1981) Atopy does not predispose to RSV bronchiolitis or postbronchiolitic wheezing. *British Medical Journal* 282: 2086-2088.
- Sporik R, Holgate ST, Plants-Mills TAE et al (1990) Exposure to house-dust mite allergen (Der p 1) and the development of childhood asthma: a prospective study. *New England Journal of Medicine* 323: 502-507.
- Stick SM, Arnott J, Turner DJ et al (1991) Bronchial responsiveness and lung function in recurrent wheezy infants. *American Review of Respiratory Disease* 144: 1012-1015.
- Strope GL, Stewart PW, Henderson FW et al (1991) Lung function in school-age children who had mild lower respiratory illnesses in early childhood. *American Review of Respiratory Disease* 144: 655-662.
- Tager IB, Hanrahan JP, Tosteson TD et al (1993) Lung function, prenatal and postnatal smoke exposure, and wheezing in the first year of life. *American Review of Respiratory Disease* 147: 811-817.
- Taussig LM, Landau LI, Godfrey S et al (1982) Determinants of forced expiratory flows in newborn infants. *Journal of Applied Physiology* 53: 1220-1227.
- Tepper RS, Rosenberg D & Eigen H (1992) Airway responsiveness in infants following bronchiolitis. *Pediatric Pulmonology* 13: 6-10.
- Voter KZ, Henry MM, Stewart PW et al (1988) Lower respiratory illness in early childhood and lung function and bronchial reactivity in adolescent males. *American Review of Respiratory Disease* 137: 302-307.
- Wilson NM, Phagoo SB & Silverman M (1992) Atopy, bronchial responsiveness and symptoms in wheezy 3-year olds. *Archives of Disease in Childhood* 67: 491-495.
- Wright AL, Taussig LM, Ray CG et al (1989) The Tucson Children's Respiratory Study. II. Lower respiratory tract illnesses in the first year of life. *American Journal of Epidemiology* 129: 1232-1246.
- Young S, Le Souef PN, Geelhoed GC et al (1991) Influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *New England Journal of Medicine* 324: 1168-1173.
- Young S, Arnott J, Le Souef PN et al (1994) Flow limitation during tidal expiration in symptom-free infants and the subsequent development of asthma. *Journal of Pediatrics* 124: 681-688.

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