8

Asthma
and Wheezing in the First Years of Life

A guide for health professionals

Asthma
and Wheezing in the First Years of Life

An information paper for health professionals

The aim of this paper is to provide an up-to-date evidence-based summary of the issues around asthma and wheezing in the first years of life. A consumer brochure on this topic is also available. These documents were produced by the Australian Government Department of Health and Ageing.

Technical writers

Jenny Zangger and Elizabeth Hall

Contents

Disclaimer

Australian Government
Department of Health and Ageing

NATIONAL ASTHMA COUNCIL AUSTRALIA

Key messages (Level of evidence III-2)

Wheezing in infancy and childhood is not a single disorder and is just as likely to be due to causes other than asthma.

In more than half of the children who wheeze within their first three years, the wheezing is transient and does not increase the risk of later asthma.

Wheezing that persists and is likely to develop into asthma can have an early or late onset.

Children with persistent wheezing are more likely than those with transient wheezing to have features of atopy and reduced lung function by the age of six years.

The earlier asthma symptoms such as persistent wheezing appear, the more severe the disease in later life and the greater the damage to the airways.

There is a clear association between parental asthma or atopy, persistent wheezing and asthma.

Exposure to tobacco smoke significantly increases the risk of wheezing in the first three years of life but not in later childhood.

Maternal smoking during pregnancy is a risk factor for transient wheezing and affects lung development.

There is a strong association between atopy, persistent wheezing and asthma, but the role of allergic sensitisation in the development of asthma is not yet clear.

Environmental conditions that increase the rate of bacterial and viral infections are risk factors for transient wheezing but may protect against persistent wheezing and asthma.

Children with frequent simple colds and other common childhood infections in infancy are less likely to develop persistent wheezing in later childhood.

Asthma and wheezing – is prevention possible?

Asthma is a complex, heterogeneous disease involving both the airways and the immune system. Inflammatory responses, usually associated with atopy, lead to respiratory symptoms such as airway hyper-responsiveness, wheeze, cough and breathlessness.

Generally, asthma is identified by the presence of these symptoms, together with features of atopy or a family history of atopy or asthma, and impaired lung function.[1] However, asthma is not easy to define and diagnose, especially in the first years of life. Wheeze, cough and breathlessness are common in young children and can all be symptoms of conditions other than asthma.[1]

The prevalence of asthma, atopy and wheezing is on the rise all over the world.[1] Intense research efforts are underway to identify what might be causing this increase – and to understand more about the early natural history of asthma. There is increasing evidence that asthma originates in the first years of life and involves a complex interaction between genetic and environmental factors.[2]

Many studies are investigating the relationship between wheezing and asthma to see whether wheezing can be used as a predictor of asthma. So far there has been considerable progress in defining different wheezing disorders in childhood and identifying factors predictive of persistent wheeze and asthma. However, on current evidence it is not yet possible to develop interventions to address likely causative factors.

Primary preventive measures target a population that is still healthy but at risk of a disease, mostly using a range of interventions. However, it remains uncertain whether manipulating factors that may be associated with asthma can reduce its prevalence or delay onset.

Quality of the evidence

This paper is based on review of the recent literature as outlined below. Most evidence in this area is from observational cohort studies, and would therefore be ascribed a level of evidence of III-2.

Sources of evidence

Observational, prospective, birth cohort or other longitudinal studies, either of whole population or of high risk groups, that identify factors associated with persistent wheezing and subsequent development of asthma.

Reviews and other studies exploring the aetiology and prevention of wheezing and asthma.

While there is increasing interest in preventing asthma in those genetically at risk,[3] there remain a number of limitations to the available evidence.

Limitations of existing evidence

- There are difficulties in assessing lung function in children aged under five using standard tests such as spirometry.
- The fact that many of the studies are so recent means that there has been limited time for follow-up.
- Many studies focus on infants at high risk of atopy or asthma (usually on the basis of family history) so findings cannot always be applied to the general population.

Wheezing in childhood

Wheezing is a non-specific symptom that results from obstruction of the lower airways. In westernised countries, wheezing affects about one-third of babies in their first year.[1]

Wheezing-associated respiratory illnesses in children are often described as asthma.[4] But while most children with asthma wheeze, not all wheezing is related to asthma. Wheezing in infancy and childhood is not a single disorder[4] and is just as likely to be due to causes other than asthma.[5]

Understanding the different wheezing disorders may help to identify young children whose wheezing is likely to be related to development of asthma[5] and to avoid inappropriate treatment of children with non-asthma related wheeze.[6]

During this process it is important to remember that:

- evaluating wheezing is part of the overall process of diagnosing asthma and other respiratory conditions, and it remains difficult to distinguish young children with atopic asthma from the larger group with wheezing;[7] and
- minor respiratory illnesses are common in childhood and are needed to build up a child's immunity. They generally do not require medical treatment and in many cases are not an indication that a child will develop asthma.[8]

Wheeze unlikely to be related to asthma

More than half of the children who wheeze during their first three years have:[1]

- congenital or acquired structural abnormalities that reduce the size of the airways;
- cystic fibrosis causing excess production of thick mucus in the airways;
- bronchiolitis not requiring hospitalisation; or
- viral-induced transient early wheezing.

Specific conditions such as structural abnormalities and cystic fibrosis that lead to lower airway obstruction and wheezing can generally be identified.[1]

Bronchiolitis that causes wheezing in the first years of life is usually associated with reduced rates of airflow that will continue into later childhood but does not increase the risk of asthma.[1]

Transient early wheezing is caused by transient conditions (generally lower respiratory infections) associated with small airway calibre in infancy. In this group of children, lower respiratory illness is not associated with allergy, and the wheezing and other respiratory symptoms tend to resolve as the child grows and the airways widen,[7] usually by the age of three.[5]

Transient wheezing does not increase the risk of asthma or allergy later in life.[5]

Wheeze likely to be related to asthma

Persistent wheezing is wheezing that continues and may develop into asthma.[5] This is more likely if there are other risk factors such as a family history of asthma or atopy[1] (see *factors associated with wheezing* below). Bronchiolitis or wheezy bronchitis requiring hospitalisation is also likely to be related to later onset of asthma.[1,9]

Persistent wheezing may have an early or late onset:[5]

- *early onset* – children who begin wheezing during their first three years and continue to wheeze up to school age.[4,5]
- *late onset* – children who do not wheeze in the first three years of life but begin wheezing around the age of six years.[4,5]

Regardless of when symptoms occur, children with persistent wheezing are more likely to have developed atopy than children with transient early wheezing.[4] They already have raised serum IgE levels and diminished airway function within their first year and have reduced lung function by the age of six.[5]

The reduced lung function seen in young adults with asthma can be traced back to the impact that the disease process has on the growth and maturation of the lungs and airways in the first six years of life.[10,11] There appears to be little further change in lung function after this age.[12] The lungs grow more rapidly during this time than at any other, allowing the disease process to have its greatest impact.[12,13]

The earlier asthma symptoms appear, the more severe the disease in later life and the greater the damage to the airways.[14]

Factors associated with wheezing

It is likely that there is a different contribution of risk factors to the various types of wheezing disorders in childhood.[4]

Family history

The link between family history, wheezing and asthma is clear. A family history of atopy or asthma (or other lower airways disease) is a risk factor for all types of wheezing, but significantly more of a risk for persistent wheezing.[4] Maternal atopy and asthma in particular increase the risk of persistent wheezing.[5]

Family studies have demonstrated the genetic contribution to atopy, persistent wheezing and asthma.[4] The familial contribution to transient early wheezing is likely to take the form of congenitally small airways.[4]

All types of wheezing are significantly more frequent in boys than girls[4] and boys tend to have lower airway function than girls during infancy and childhood.[15]

Environmental tobacco smoke

Maternal smoking in pregnancy is a risk factor for all types of wheezing but not for asthma itself. It increases the risk of transient early wheezing and impaired lung function in infancy, but not in later childhood.[14] It appears to affect lung development, resulting in reduced lung capacity and smaller airways, as well as prematurity and low birth weight.[4]

While smoking does not increase the likelihood of later asthma,[7] exposure to maternal smoking in utero has been associated with long-term deficits in lung function that, together with the lung impairment produced by asthma, may increase the risk of chronic respiratory diseases later in life.[16]

As well as improving overall health, evidence suggests that reducing maternal smoking would decrease wheezing illnesses in young children and reduce the long-term effects of tobacco smoke on children with asthma.[16]

Allergic sensitisation

Allergic responses such as allergic rhinitis and eczema are associated with persistent wheezing but not transient wheezing.[4] There is also a direct relationship between risk of persistent wheezing and serum IgE level during the first year of life, just as there is a link between asthma and IgE level in older children and adults.[5]

Despite the strong association between atopy, persistent wheezing and asthma, the role of sensitisation in the development of asthma is far from clear. There have been conflicting results from studies examining the effects of common allergens such as house dust mite and pets on the development of asthma.[17]

A growing body of research indicates that the prevalence of asthma is independent of allergen exposure in early life.[17] Interventions to reduce exposure to allergens (such as house dust mite) can reduce wheezing in babies but do not appear to alter the development of wheezing or asthma in later childhood.[18]

Allergen sensitisation may not be a direct risk factor for persistent wheezing and asthma. There may be other, as yet unknown, factors responsible for both allergen sensitisation and the onset of persistent wheezing and asthma.[18]

Infections and the hygiene hypothesis

Environmental conditions that increase the rate of bacterial and viral infections, such as larger family size and attending a day care centre, have been found to both cause and protect against wheezing and asthma.

- Both are risk factors for transient wheezing and early onset persistent wheezing, probably related to the effect of viral infections in smaller airways.[4]
- Conversely, these same factors are protective against late onset wheezing, possibly because early infections may down-regulate the immune system against allergic responses to environmental antigens (see below).[4]

Children with frequent simple colds and other common childhood infections in infancy (without associated wheeze) are less likely to develop persistent wheezing in later childhood.[19]

The proposed protective effect of childhood infections is called the 'hygiene hypothesis'. Infections are said to promote normal maturation away from the foetal type 2 immune response that increases susceptibility to allergic disease, towards the adult type 1 response which is more effective in eliminating viruses and other infections.[20]

It is still not clear exactly which viruses protect against and which cause wheezing and asthma, and how to reproduce the protective effects of some infections while reducing the burden of other more serious infections.[20]

Predicting whether wheeze is due to asthma

Despite growing evidence about different wheezing phenotypes, it remains difficult to exclude or diagnose asthma in young children presenting with their first episode of wheeze.[1] A particular challenge is to distinguish children with transient wheezing from children whose wheezing persists and who later develop asthma.[7]

Airway tissue inflammation leading to airway remodelling occurs at an early age and is fundamental to the development of asthma. While characteristic features of inflammation such as increased eosinophil levels (eosinophilia) can be used to distinguish asthma-related wheezing from wheezing caused by viral infections, these markers can also occur in other allergic conditions not related to asthma.[21] Until unique markers for distinguishing asthma from other respiratory conditions are identified,[21] predicting whether wheeze is due to asthma will depend on the integration of different types of information gathered over time.[8]

Evidence from different longitudinal studies has been used to develop indices to assist health care professionals in determining whether episodes of wheeze in young children are due to asthma.[22,23]

One such set of indices suggests that nearly 60 per cent of children with any wheeze and close to 80 per cent of children with frequent wheeze are likely to develop asthma if their wheezing is associated with the following risk factors:

- parents with asthma or eczema; and
- two out of the following three features of atopy – eosinophilia, wheezing without colds or allergic rhinitis.

Significantly, 95 per cent of children without these risk factors are not likely to develop asthma.[22]

Another predictive model, this time in children at higher risk of asthma due to family history, combined age at presentation and concentration in the blood serum of soluble interleukin-2 receptor (an indicator of eosinophilia) and found that wheeze was more likely to be persistent in older atopic children with two atopic parents. The model was around 70 per cent accurate in predicting clinical outcome and had over 90 per cent chance of predicting children who were destined to become asymptomatic.[23]

While the negative predictive value of these indices is much greater than their positive predictive value, they can still be used to indicate subsequent development of asthma with reasonable accuracy and a low risk of including asymptomatic children.[22,23] Further research will continue to improve the clinical usefulness of predictive models.

The box below summarises stages in confirming a diagnosis of asthma that highlights some important predictors of asthma.[1]

Stages in confirming a diagnosis of asthma[1]

- **If the first episode of wheeze is in the first year of life, the child has a 50 per cent chance of developing asthma**
- **If the first episode of wheeze occurs when the child is older, there is a greater probability that asthma is the cause**
- **If the child develops recurrent or persistent wheeze, the likelihood that the child has asthma is 80 per cent**
- **If the child has: any feature of atopy such as eczema or hay fever; positive allergen skin prick test; or elevated IgE antibodies, the probability of asthma rises to more than 95 per cent**
- **Evidence of altered lung function or inflammation confirms the diagnosis of asthma**

Early life origins of asthma

In order to identify children at risk of developing asthma, we need to better understand the early natural history of the disease. There is growing evidence that both genetic and environmental factors have significant effects on airway development and function in early life and influence both the onset and course of asthma.[24]

At-risk children have compromised airways from birth, plus skewed immune responses and raised IgE levels during the first years of life. A prospective birth cohort study in the UK found that atopic and non-atopic children who had never wheezed, but had atopic parents, had lower lung function than children without a family history of atopy or asthma.[6] This suggests that their airways could be pre-modelled, possibly in utero, putting them at increased risk of developing respiratory diseases such as asthma.[6]

The identification of 'asthma genes' related to IgE synthesis and allergic inflammation indicates that a genetic susceptibility to develop asthma is present from conception. It may be that clinical expression of asthma then depends on environmental factors[2] that operate differently in susceptible individuals, interacting with the developing immune system to cause disease.[18] Recent evidence suggests that environmental factors mediate the onset of persistent wheezing in genetically predisposed children, so avoiding allergens and other associated factors may delay but not prevent the onset of childhood asthma.[25]

Is it possible to prevent wheezing and asthma in a young child with a genetic predisposition?

On current evidence it is still not possible to answer this question. Decades of research have shed light on many aspects of asthma but because of its complexity it remains difficult to identify causative factors and develop interventions to address them. For this to occur, we need to know much more, including:

- the environmental factors that interact with 'asthma genes' in the development of persistent wheezing and asthma
- which tools can be used to distinguish young children who are at high risk of developing asthma from the larger group with transient wheezing
- which strategies can prevent deficits in lung function in very young children in whom the disease process is beginning
- the nature of the population at risk, so we can develop interventions that are effective in preventing different types of childhood asthma
- the time frame in which to intervene with various approaches.

Further information

Representatives from the National Asthma Council, Asthma Australia and Australian Government Department of Health and Ageing were involved in the editorial process for this paper.

National Asthma Council (NAC)
The NAC website contains information on asthma and has links to other asthma sites.
www.NationalAsthma.org.au

Australian Government Department of Health and Ageing
Information on the Australian Government's Asthma Management Program and copies of resources for health professionals and consumers can be found on the Department of Health and Ageing's websites:
www.health.gov.au/pq/asthma
www.healthinsite.gov.au

Asthma Australia
Patients can contact their local Asthma Foundation on **1800 645 130** or visit their websites:

www.asthma.org.au
www.asthmansw.org.au
www.asthmasa.org.au
www.asthmawa.org.au
www.asthmatas.org.au
www.asthmant.org.au
www.asthmaqld.org.au
www.asthmaaustralia.org.au

This series on Asthma Topics for Health Professionals comprises eight separate titles:

1 Asthma and Allergy
2 Asthma and Lung Function Tests
3 Asthma and Pain Relievers
4 Asthma and Air Pollution
5 Asthma and Complementary Therapies
6 Asthma and Infant Bedding
7 Asthma and Diet in Early Childhood
8 Asthma and Wheezing in the First Years of Life

To access these documents log on to:
www.NationalAsthma.org.au or contact the Department of Health and Ageing on **1800 500 053**.

References

1 Landau LI. 2002. Definitions and early natural history *MJA* 177: S38-39.

2 Gern JE, Lemanske RF, Busse WW. 1999. Early life origins of asthma. *J Clin Invest* 104: 837-43.

3 Mellis CM. 2002. Is asthma prevention possible with dietary manipulation? *MJA* 177(Suppl): S78-S80.

4 Rusconi F, Galassi C, Corbo GM et al. 1999. Risk factors for early, persistent and late onset wheezing in young children. *Am J Respir Crit Care Med* 160: 1617-22.

5 Martinez FD, Wright AL, Taussig LM et al. 1995. Asthma and wheezing in the first six years of life. *N Engl J Med* 332: 133-38.

6 Lowe L, Murray CS, Custovic A, Simpson BM. 2002. Specific airway resistance in 3-year old children: a prospective cohort study. *The Lancet* 359: 1904-09.

7 Helms PJ & Christie G. 1999. Prospects for preventing asthma. *Arch Dis Child* 80: 401-03.

8 Keeley DJ & Silverman M. 1999. Are we too ready to diagnose asthma in children? *Thorax* 54: 625-28.

9 Saga R, Mochizuki H, Tokuyama K et al. 2001. Relationship between bronchial hyperresponsiveness and development of asthma in wheezy infants. *Chest* 119: 685-90.

10 Sears MR, Greene JM, Willan AR et al. 2003. A longitudinal, population-based, cohort study of childhood asthma followed into adulthood. *New Engl J Med* 349: 1414-22.

11 von Mutius E. 2002. Childhood experiences take away your breath as a young adult. *Am J Respir Crit Care Med* 165: 1467-68.

12 Martinez FD. 2003. Toward asthma prevention – does all that really matters happen before we learn to read? *N Engl J Med* 349: 1473-75.

13 McKay KO & Hogg JC. 2002. The contribution of airway structure to early childhood asthma. *MJA* 177: S45-47.

14 Strachan DP, Butland BK, Anderson HR. 1996. Incidence and prognosis of asthma and wheezing illness form early childhood to age 33 in a national British cohort. *BMJ* 312: 1195-99.

15 Dezateux C, Stocks J, Dundas I, Fletcher ME. 1999. Impaired airway function and wheezing in infancy. Am J Respir Crit Care Med 159: 403-10.

16 Gilliland FD, Berhane K, Li Y-F et al. 2003. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 167: 917-25.

17 Kemp AS. 2002. Do allergens play a role in early childhood asthma? *MJA* 177: S52-54.

18 Tang MLK. 2002. Is prevention of asthma possible? Allergens, infection and animals. *MJA* 177: S75-77.

19 Illi S, von Mutius E, Lau S et al. 2001. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 322: 390-95.

20 Johnston SL & Openshaw PJM. 2001. The protective effect of childhood infections. *BMJ* 322: 376-77.

21 Lemanske RF. 2002. Inflammation in childhood asthma and other wheezing disorders. *Pediatrics* 109: 368-73.

22 Castro-Rodriguez JA, Holberg CJ, Wright AL et al. 2000. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 162: 1403-06.

23 Clough JB, Keeping KA, Edwards LC. 1999. Can we predict which wheezy infants will continue to wheeze. *Am J Respir Crit Care Med* 160: 1473-80.

24 Klinnert MD, Nelson HS, Price MR et al. 2001. Onset and persistence of childhood asthma: predictors from infancy. *Pediatrics* 108: E69.

25 Kurukulaaratchy RJ, Matthews S, Hasan Arshad S. 2004. Does environment mediate earlier onset of the persistent childhood asthma phenotype? *Pediatrics* 113: 345-51.