

# Childhood asthma

## Introduction



### Key points

- Although childhood asthma has historically been more prevalent in western than eastern Europe, the difference is diminishing as rates in the East rise.
- A British survey reported that 13% of carers of asthmatic children had given up work to care for the child.
- Approximately 60% of school-aged asthmatic children have allergies, particularly to animal dander, house dust mites and moulds, as well as plant pollens.
- Asthma typically begins much earlier in life than other chronic diseases, and consequently imposes a high lifetime burden on individuals, their caregivers and the community.
- Although asthma can usually be controlled, there are currently no proven methods of prevention or cure.

Asthma is the commonest chronic disease in childhood. Due to the various different phenotypes of childhood asthma, it has been difficult to agree on a clear definition of the condition and instead an operational description is used: 'Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment.' (Global Initiative for Asthma, 2012). However, in children <5 years of age, clinical symptoms of asthma are variable and nonspecific, and a symptoms-only approach that defines various wheezing phenotypes has been recommended.

## Epidemiology



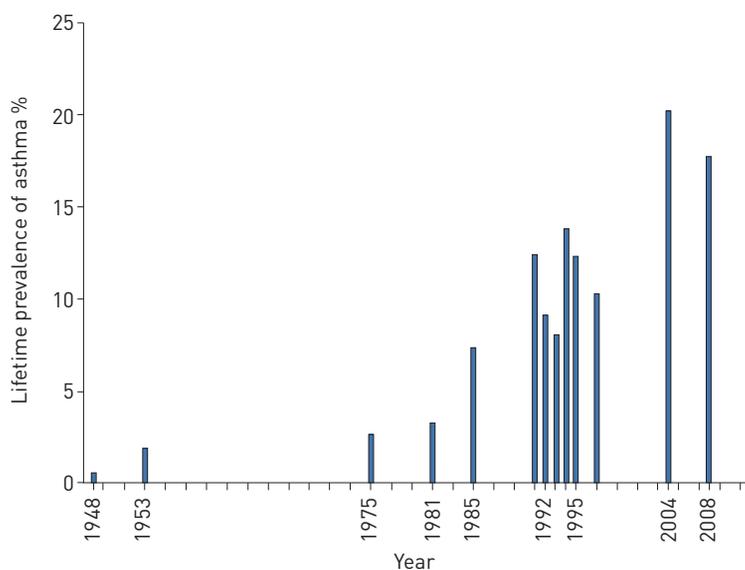
### *Prevalence and incidence, and changing patterns of asthma with age*

The prevalence of childhood asthma increased markedly in Europe in the second half of the 20th century. This is exemplified by published studies of asthma in schoolchildren in Norway, which have

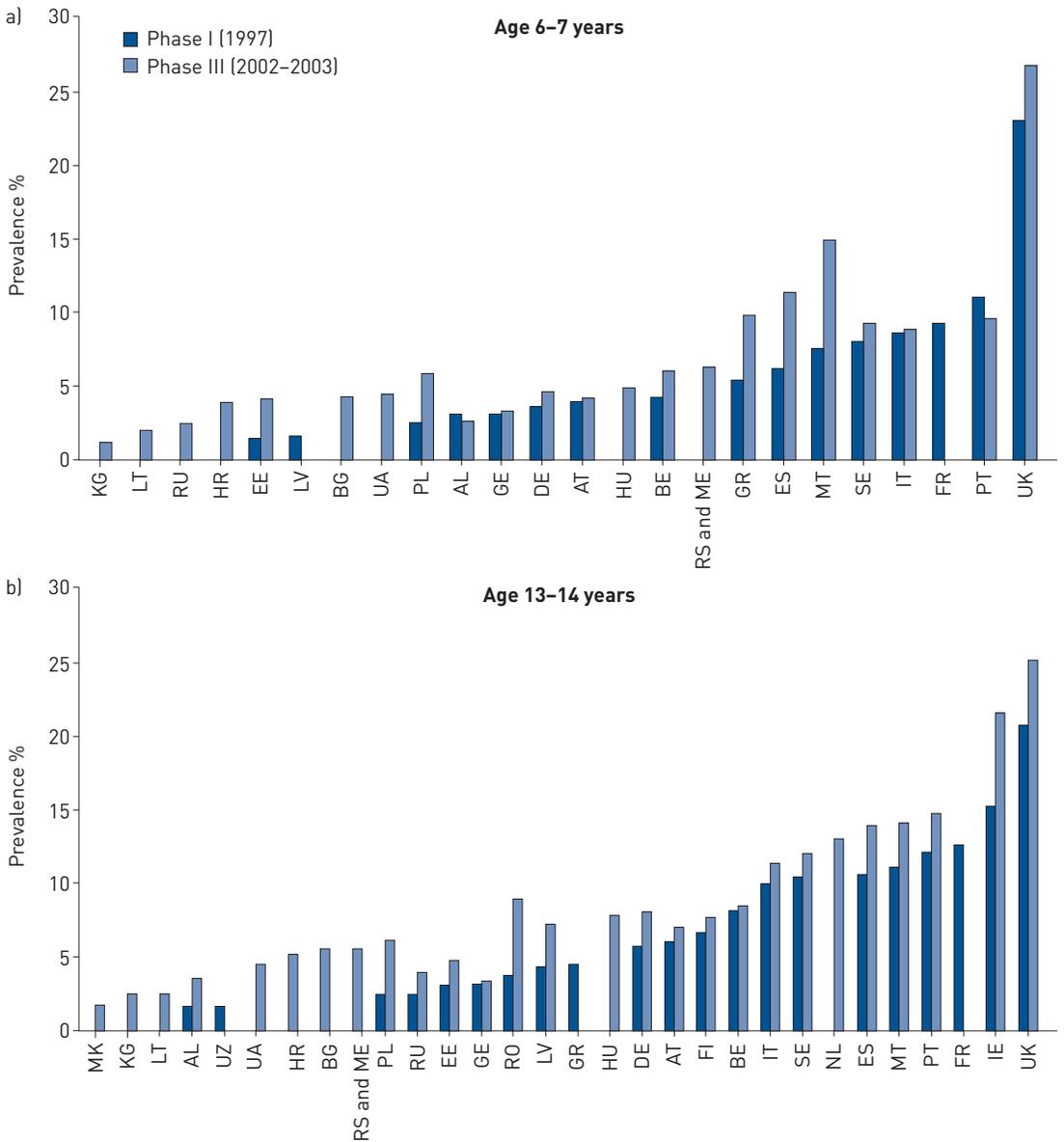
“ *Asthma mortality in children is low and over recent years it has decreased in most European countries* ”

reported an increase in prevalence from 0.4% in 1948 to 12.3 % in the mid-1990s and 20% in a study performed in 2004, although the most recent study, in 2008, reported a levelling off to 17.6% (figure 1). The increase was initially most marked in western Europe. The questionnaires developed for the International Study of Asthma and Allergy in Childhood (ISAAC) have provided a common tool for assessing the prevalence of asthma and wheezing disorders in children. In the ISAAC study performed in 1997, the highest prevalence of childhood asthma in Europe was found in the British Isles, with the prevalence of ‘asthma ever’ (lifetime prevalence of asthma) ranging from 1.6% in Albania to 20.7% in the UK for 13–14-year-old children, and from 1.4% in Estonia to 22.9% in the UK among 6–7-year-olds, with markedly increasing rates across Europe from East to West (figure 2). This East-to-West difference has diminished over recent years with a relative increase in lifetime prevalence in eastern Europe compared with the West; this may be related to simultaneous changes in lifestyle in eastern Europe. Figure 3 shows the prevalence rates of current wheezing in the ISAAC study phase III (data collected 2002–2003) in various centres in Europe.

The prevalence, causes and clinical presentation of asthma all vary with age. Many children first develop symptoms during infancy, but many cease wheezing in early

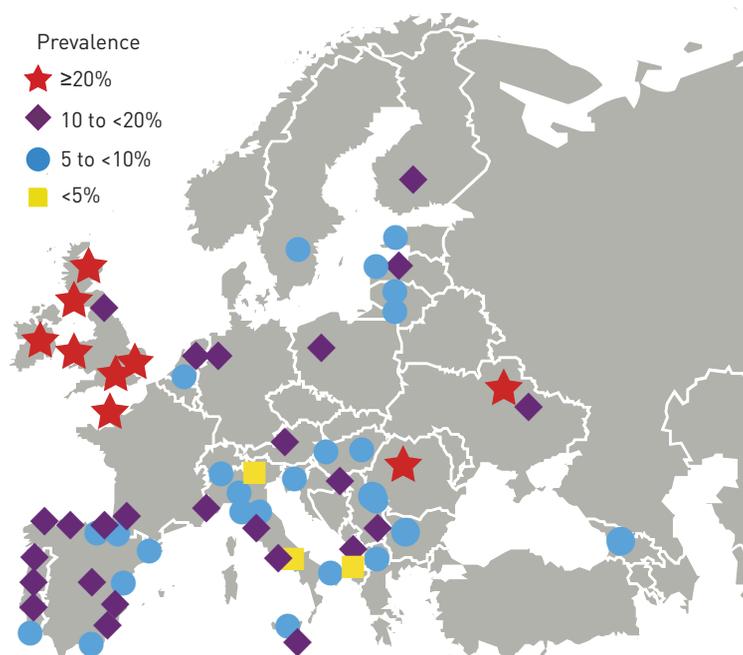


**Figure 1** - Lifetime prevalence of asthma among Norwegian schoolchildren, 1948–2008.



**Figure 2** – Lifetime prevalence of asthma in a) 6-7-year-old and b) 13-14-year-old children in 1997 and 2002-2003. Source: International Study of Asthma and Allergy in Childhood phases I and III.

childhood. Asthma can appear *de novo* throughout life, but it starts most commonly in early childhood, as illustrated in figure 4. This Canadian study reported that asthma affected approximately one-third of the population at some time between the ages of 4 and 80 years, much like diabetes or malignant disease. However, asthma starts much earlier in life than other disorders and thus has a lifelong impact on quality of life and health costs. The economic consequences of asthma are therefore particularly high due to its frequent early onset.



**Figure 3** – Prevalence of current wheezing in children in centres across Europe. Reproduced and modified from LAI *et al.*, 2009, with permission from the publisher.

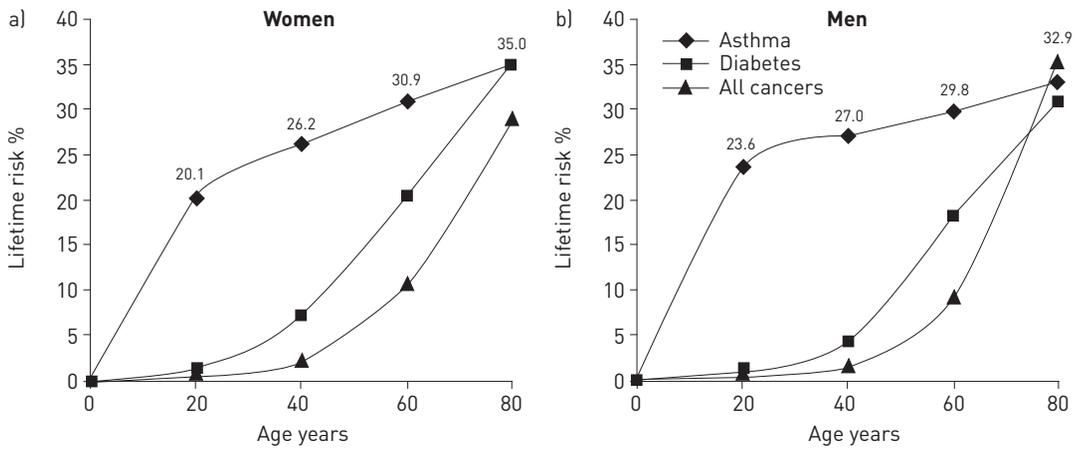
## Mortality

Asthma mortality in children is low and over recent years it has decreased in most European countries. Historically, mortality was highest among the youngest children, lower during school age, and then increased from puberty to adulthood.

In Denmark, a significant upward trend in asthma mortality was seen between 1973 and 1987. This was due solely to increasing mortality in the 15–19-year-old age group. From 1988 to 1994, the mortality rate among children aged less than 19 years decreased in general. In Norway, mortality among children  $\geq 5$  years of age has been consistently low since 1960, while in children  $< 5$  years of age the mortality rate decreased until 1990 and was then as low as in the older age-groups. In contrast, in Russia an increasing mortality rate among children  $< 5$  years of age was reported, from 0.06 per 100 000 in 1980 to 0.11 per 100 000 in 1989; there was, however, no increase among 5–34-year-old asthmatic subjects.

In the Netherlands, asthma mortality declined among 5–34-year-olds between 1980 and 1994, remaining stable among other age groups, whereas in England there was no change in asthma mortality among children aged 0–14 years from 1980 (0.389 per 100 000) to 1990 (0.387 per 100 000) compared to a 24% reduction in mortality for all causes. A further reduction in asthma mortality was seen in five European countries (France, Germany, Italy, Spain and the UK) between 1994 and 2005 among children and young adults (aged 5–34 years). Nevertheless, in 2004, there still remained 6700 possibly preventable deaths at all ages in these five countries.

In Sweden, the rate of asthma deaths among children and young adults (aged 1–34 years) decreased between 1994 and 2003. It was, however, remarkable that nine of the 12 deaths in the population aged  $< 19$  years were due to anaphylaxis, with asthma caused by food allergy.



**Figure 4** – Lifetime risk of developing chronic diseases from birth in a) women and b) men. Reproduced from To *et al.*, 2010, with permission from the publisher.



When comparing childhood asthma mortality between countries, there are noteworthy correlations between the prevalence of asthma symptoms and asthma mortality as well as hospital admissions for asthma. Any reduction in prevalence may therefore have an impact upon asthma mortality. The decreasing mortality rate of asthma during childhood seen in most countries over the past two decades is probably due to the more widespread use of inhaled corticosteroids (which, even in low doses, have been shown to decrease mortality), together with improved treatment of acute asthma attacks.

Recent data (2004–2010, from the World Health Organization (WHO)) for children aged 0–14 years show that mortality is generally very low in Europe, with little difference between countries, implying better control of the condition with improvements in treatment.

### **Morbidity**

Asthma morbidity is a major burden for the child, his/her family and the community. Asthma attacks are very frightening for the child and due to the resulting disruption of life and reduced physical ability there is an emotional, as well as economic, impact of the disease. The social burden of asthma is considerable, not only on the sick child but also on parents, siblings and the household in general. In England, 69% of parents or partners of parents of asthmatic children reported taking time off from work because of the child's asthma, while 13% had given up their jobs completely. In assessing quality of life in asthmatic children, it is important also to assess the quality of life of the caregivers.

Severe problematic asthma that is poorly responsive to the common asthma treatments has been reported in approximately 4.5% of children with current asthma.

Direct healthcare costs for childhood asthma arise from consultations in both primary and secondary care, as well as hospital admissions (figure 5) and treatment costs. In some, but not all, countries, hospital admissions have fallen in recent years (see above), but greater use of both inhaled and oral agents has increased the expenditure on asthma drugs. A number of new drugs have recently been introduced, thereby increasing the drug-related cost. In particular, the use of inhaled steroids has increased markedly in recent years.

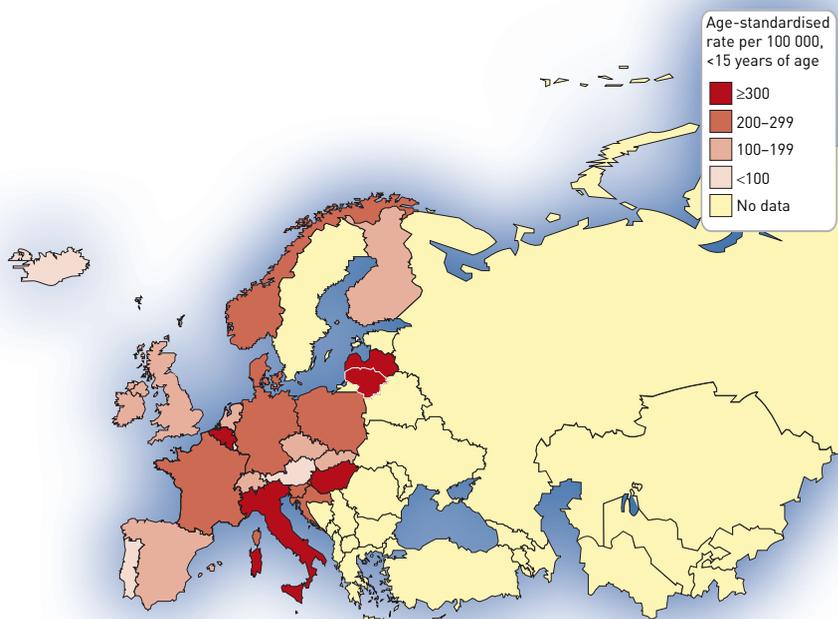
Although loss of working days is not directly applicable to children, absence from school is a comparable consequence. Good European studies are difficult to find, but one US study reported 10.1 million days' absence from schools due to asthma in 1 year, extrapolated from a study of 17 000 families.

## Causes/pathogenesis



### Environmental

Asthma results from an interaction between different environmental and genetic factors. The environmental influences begin during pregnancy: allergic sensitisation has been described before birth, and several studies have demonstrated reduced lung function in newborn infants of smoking mothers compared to those of nonsmoking mothers. Smoking increases the risk of both asthma and poorer lung function



**Figure 5** – Hospital admission rate for asthma in children. Data from World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update.



throughout childhood. All children should have the right to an environment free from tobacco smoke products both before and after birth.

Lifestyle changes have been linked to the increased prevalence of asthma, and especially allergic asthma. Studies from Russian and Finnish Karelen show a much higher prevalence of asthma and allergic diseases in the Finnish population compared with the Russian.

Respiratory virus infections are the major cause of acute bronchiolitis in infancy and of acute asthma attacks among older asthmatic children (more on childhood viral infections can be found in chapter 16). 1.5–2% of all children are hospitalised due to respiratory syncytial virus (RSV) bronchiolitis during the first 2 years of life, and approximately 60% of these children later develop asthma. At 13 years of age, more than 40% of children hospitalised in infancy with acute RSV bronchiolitis still have symptoms and bronchial hyperresponsiveness. From 2 years of age, rhinovirus infections are the most frequent precipitators of acute asthma. With modern techniques of virus diagnosis (e.g. those based on PCR), approximately 65% of all asthma attacks in schoolchildren have been reported to be due to rhinovirus infection, and when all types of virus infections are included it has been estimated that 85% of acute asthma attacks are precipitated by respiratory virus infections.

From 2 years of age and especially during school years, inhalant allergy becomes increasingly important for childhood asthma. Approximately 60% of all school-aged asthmatic children are allergic. The most important allergens vary according to climate, but in all European countries animal dander is among the most frequent allergens in asthma. In a warm and humid climate, house dust mites and moulds are also of major importance, and, depending upon climate, the seasonal allergens (birch, grass and mugwort pollen) play a role. Allergen exposure may cause acute asthma exacerbations, and even in the absence of an exacerbation, may increase airway inflammation and bronchial hyperresponsiveness.

Allergens may be encountered both outdoors and indoors, and house dust mites and animal dander are particularly important perennial indoor allergens. Occupational agents play a minor role during childhood, but several types of allergy may influence the choice of education in relationship to later working life. Kindergartens and schools are the working environment of children, and the need for a healthy indoor environment in such institutions should be emphasised. Special consideration should be given to the increased risk of respiratory infections, especially in kindergartens. In schools, precautions may be taken to reduce allergen exposure for

allergic asthmatic children. Emphasis should also be put upon mastering exercise-induced asthma in gymnastic lessons and physical training.

## *Genetic*

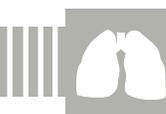
Asthma, and one of its major causes, allergy, have strong hereditary traits. During recent years, much effort has been put into genetic family studies in order to identify genetic markers. A large number of markers with possible relationships to asthma and airway inflammation have already been identified, but these vary between populations. There has also been increased focus upon epigenetics: the finding that environmental influences may cause DNA methylation and histone formation, and thus change and inactivate the influence of specific genes, has given insight into how the environment may interact with genes, and has shown that this interaction may even be transferred from mother to child.

Furthermore, hereditary traits have been found to influence the response to asthmatic drugs. Examples include  $\beta_2$ -receptor sensitivity and responsiveness to inhibitors of leukotriene synthesis.

## *Exercise*

Throughout childhood, but increasingly during school age, exercise is an important cause of asthma exacerbations (exercise-induced asthma). It has been reported that 30% of all asthmatic children suffer from restriction of physical activity and it is very important to teach asthmatic children to master exercise, by education, advice related to 'warming up' and medical treatment.

## *Clinical manifestations and consequences*



## *Phenotypes*

As previously discussed, asthma often starts in early childhood with acute attacks or exacerbations provoked by respiratory viral infections. Attention has focused on different asthma phenotypes especially during infancy and pre-school age, with diagnostic labels such as early wheeze, transient wheeze and late-onset wheeze, describing the longitudinal outcome of wheezing during early childhood. However, such retrospective labelling is not useful in predicting the prognosis. Recurrent wheezing during pre-school years often improves during school years and puberty. However, longitudinal cohort studies show that respiratory symptoms and bronchial obstruction often recur after the age of 16–20 years.

Most cases of asthma during childhood are mild or moderate and can be optimally controlled with treatment. However, a proportion have severe problematic asthma even during childhood, with lack of response to treatment with inhaled corticosteroids.

Exercise-induced asthma is particularly common in children and, if untreated, it may reduce activity and impair fitness. A major goal of all international guidelines for treating childhood asthma is to master exercise-induced asthma.

## Prevention



Several efforts have been made to prevent the development of asthma. These can be divided into: primary prevention, the aim of preventing symptoms and signs of allergy and asthma from occurring at all; and secondary prevention of asthma in a predisposed child who has, for example, atopic dermatitis. Tertiary prevention is the prevention of symptoms in an affected child. Prolonged feeding with breast milk may prevent respiratory infections but probably not asthma.

It is important to avoid exposure to tobacco smoke products. Since lung function is decreased in the newborn children of smoking mothers, it is especially important for such children to avoid worsening the impairment by taking up smoking in adolescence and young adulthood. In high-risk children, trials have been performed to reduce exposure to allergens, especially house dust mites and animal dander, but the efficacy of such measures remains to be proven. Although allergic sensitisation is related to early allergen exposure, low exposure to animal dander and house dust mite do not seem to reduce the occurrence of bronchial asthma in the general population.

Trials of pharmacological prevention have been performed using antihistamines, but so far the effect seems limited. It has been proposed that early introduction of anti-inflammatory drugs like inhaled steroids may influence the long-term development of asthma, but this remains to be proven.

Asthma education and asthma schools are important tools for educating patients, enabling them to take proper precautions before taking part in different activities.

## Management



Modern guidelines for treating childhood asthma distinguish between controlling and relieving treatment. Among the controlling treatments, inhaled corticosteroids are the most important drugs and enable most children and adolescents with asthma to lead a normal life. In most cases, inhaled corticosteroids also control exercise-induced asthma, allowing participation in physical activity and sports. High doses of inhaled steroids may impair growth but only to a small extent (1–2 cm in height at most), and usually in the early phase of treatment. Adrenal suppression can occur with high doses, and hypoglycaemic convulsions have been reported. Recently, an inhaled corticosteroid has been introduced as a pro-drug,

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*Physical activity is of prime importance in childhood asthma, and should be encouraged*  
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which depends for its effect on enzymatic activation in the respiratory epithelium. The lack of systemic side-effects makes such agents particularly suitable for childhood asthma.

Inhaled  $\beta_2$ -agonists are important reliever medication, for both acute and chronic asthma. Combination treatment consisting of an inhaled corticosteroid and an inhaled long-acting  $\beta_2$ -agonist has proved to be very effective in adult asthma care, but in childhood asthma and especially in pre-school children, the treatment response has not been as good. Children should be monitored carefully to assess the response to treatment, and treatment that proves to be ineffective should be stopped. This also applies to leukotriene antagonists, which are remarkably effective in some patients, both as controller and reliever treatment, but there is a high percentage of non-responders. Anticholinergic therapy, in particular ipratropium bromide, is also effective as a bronchodilator in children and may have an additive effect to inhaled  $\beta_2$ -agonists. Anticholinergic treatment seems to have a special place as pre-medication before exercise in children with exercise-induced asthma and in treatment of asthmatic adolescents with an athletic career. The anti-immunoglobulin (Ig)E monoclonal antibody omalizumab has proved effective for some patients with severe allergic asthma, but, again, some fail to respond, emphasising the need for careful follow-up. Other novel treatments are currently being investigated.

Asthma care involves much more than just pharmacological treatment, although this is a very important part of the treatment plan. Participation in physical activity is of prime importance in childhood asthma and should be encouraged.

## Prognosis



Childhood asthma most often starts before school age. During puberty, many children – especially boys – experience improvement, but later in life the symptoms of asthma often recur. During early life, boys more frequently have asthma; after 10 years of age, however, girls more frequently develop asthma, often with greater severity. However, with modern asthma treatment and care, most asthmatic individuals are able to lead a normal, healthy life. The lifetime risk of asthma is approximately 35%, with most cases occurring early in life, and many requiring lifelong medical follow-up and medication, and thus having an impact on health costs. Early childhood asthma and, in particular, severe childhood asthma increase the risk of chronic airway obstruction in adult life.

## Future developments



Based on the current situation, a further increase in the prevalence of asthma is anticipated, particularly in eastern European countries where acquisition of a Western lifestyle has already been shown to increase the prevalence of childhood asthma to as much as 20%. Furthermore, as there appears to be a cohort effect on the increased prevalence of asthma in childhood, an increase is likely among adults (especially young adults) in the near future. Greater use of anti-inflammatory drugs, and the possible development of more effective drugs, may reduce the acute morbidity of asthma and the need for acute hospital admissions. New drugs targeting pathways in the inflammatory processes may improve therapy, but this remains to be shown. However, there will be

an increasing need for specialist diagnosis and monitoring of asthmatic patients especially at an early stage of the disease, with the aim of reducing its long-lasting effects.

## Research needs



Further research is needed on all aspects of childhood asthma, including clinical as well as basic and genetic research. In particular, more data are needed on the environmental and genetic causes of childhood asthma in order for society to be able to take preventive measures.

Asthma cannot be cured with current treatment, but we can reduce morbidity and improve our mastery over the illness. There is a need for research into new treatment approaches, especially in young children. In many countries in Europe the resources for independent research in this area are limited, and cooperation between centres, with the creation of networks of centres of excellence, should be encouraged.

### Summary of research needs

- Cohort studies: follow-up studies from birth to adulthood of entire cohorts, taking into consideration:
  - Environmental factors: including outdoor and indoor pollution, the influence of infections and allergen exposure in early childhood and the long-term effects of anti-inflammatory treatment;
  - Genetic factors of importance for asthma and airway inflammation: repeated sampling over time of DNA in birth cohorts enabling longitudinal studies on epigenetics as well as long-term tracking from birth to adulthood of lung function, bronchial responsiveness and markers of airway inflammation.
- Basic research into the aetiology and pathogenesis of asthma, allergy, airway inflammation, bronchial hyperresponsiveness and exercise-induced asthma.
- Intervention studies to evaluate primary and secondary preventive measures, including attempts to prevent/reduce respiratory epithelial barrier damage.
- Epidemiological studies to enable more comprehensive Europe-wide monitoring of asthma prevalence, morbidity and hospitalisation.
- Clinical studies to develop new treatment modalities.
- International studies comparing quality of asthma care and health economics in order to optimise the quality of asthma care throughout Europe.

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*Several studies have demonstrated reduced lung function in newborn infants of smoking mothers*  
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### General

- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2012. [www.ginasthma.org/uploads/users/files/GINA\\_Report\\_2012\\_Feb09.pdf](http://www.ginasthma.org/uploads/users/files/GINA_Report_2012_Feb09.pdf)

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