



Worldwide asthma epidemic

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Overall, an increasing trend has been reported in the prevalence of asthma in recent decades; however, large variations in the prevalence of childhood and adult asthma have been reported. Prevalences are generally higher in affluent countries than in poorer countries. Numerous hypotheses have been proposed to explain these trends. These theories most often relate to socioeconomic status, family size, early-childhood infections and hygiene, allergen exposure, diet and obesity, perinatal risk factors, and environmental pollution.

Asthma is a complex syndrome rather than a single entity. Different phenotypes with varying prognosis and determinants have been described, particularly those that occur during the childhood years [1]. Transient early wheezing is characterized by the occurrence of wheezing symptoms in infants up to age 2 to 3 years, after which the symptoms disappear. The main predictor of these wheezing illnesses is premorbid, reduced lung function [2,3]. These impairments in pulmonary function in part are determined by passive smoke exposure in utero [4] and result in symptoms of airway obstruction in infants who are infected with respiratory viruses. Atopy and a family history do not influence the incidence and natural course of this wheezing phenotype.

In contrast, wheeze among school-aged children most often is associated with atopic sensitization, airway hyperresponsiveness, and a familial predisposition for asthma [1]. The severity of symptoms and degree of atopic sensitization and airway responsiveness determine the prognosis of this wheezing phenotype [5]. It seems likely that a third wheezing phenotype exists among preschool children that mostly is related to viral infections [6]. These children have a better prognosis than atopic wheezers, and their symptoms often disappear around school age.

Most epidemiologic studies have been cross-sectional surveys and do not enable examination the different wheezing phenotypes. Only prospective studies

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that follow infants from birth up to school age and adolescence can help identify different wheezing phenotypes and enable the differential analysis of potential risk factors and determinants. These limitations should be recognized when discussing and interpreting findings from cross-sectional surveys. The proportion of different wheezing phenotypes is likely to vary among age groups, and the strength of association between different risk factors and wheeze also is likely to vary across age groups.

Prevalence of childhood asthma

Numerous published studies have assessed the lifetime prevalence of childhood asthma; however, the lack of standardization in disease definition and methodology makes it difficult to compare the findings among diverse population and age groups. Recent standardization of study designs and methods, including questionnaires, has enabled valid comparisons of prevalences among different countries.

Western countries versus developing countries

In general, reported asthma rates are higher in affluent, western countries than in developing countries. The worldwide prevalence of allergic diseases was assessed in the 1990s by the large-scale International Study of Asthma and Allergy in Childhood (ISAAC) [7]. A total of 463,801 children in 155 collaborating centers in 56 countries were studied. Children self-reported, through one-page questionnaires, symptoms of three atopic disorders. Between 20- and 60-fold differences were found between centers in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. The highest 12-month prevalences of asthma symptoms were reported from centers in the UK, Australia, New Zealand, and Ireland. Centers in North, Central, and South America had the next highest prevalences. The lowest prevalences were reported by centers in several Eastern European countries, Indonesia, Greece, China, Taiwan, Uzbekistan, India, and Ethiopia. In general, centers with low asthma rates also showed low levels of other atopic diseases; however, countries with the highest prevalence of allergic rhinitis and atopic eczema were not identical to those with the highest asthma rates.

The European Community Respiratory Health Survey (ECRHS) studied adults aged 20 to 44 [8]. A highly standardized and comprehensive study instrument that included questionnaires, lung function, and allergy testing was used by 48 centers in 22 countries, which predominantly included countries in western Europe, but also included Australia, New Zealand, and the United States. A strong correlation was found between the findings from children as assessed by the ISAAC and the rates in adults as reported by the ECRHS [9]. In the ECRHS data, 64% of the variation at the country level and 74% of the variation at the center level in the prevalence of “wheeze in the last 12 months” was explained

by the variation rates reported for children in the ISAAC. Although there were differences in the absolute prevalences observed in the two surveys, there was overall agreement, which adds support to the validity of both studies.

Some comparisons of different populations within the ISAAC are informative. In China, the prevalence of asthma and other allergies was assessed in children living in Hong Kong and compared with those of children living in mainland China, Beijing, and Urumqui [10]. Children in Beijing reported significantly more asthma symptoms than did those in Urumqui. Children in Hong Kong had the highest prevalence of asthma and other allergic symptoms. Urumqui, Beijing and Hong Kong are communities that are in the process of westernization, and these results can be interpreted as a reflection of a worldwide trend for the increasing prevalence of allergies as westernization intensifies.

The prevalence of symptoms, diagnosis, and management of asthma in school-aged children in Australia was compared with the prevalence in Nigerian children; this study used another standardized methodology [11]. Wheeze, asthma, and other symptoms of asthma medication use were less prevalent in Nigeria than in Australia. No significant differences were found in the overall prevalence of atopy between the two countries, although atopy was a strong risk factor for asthma in both countries. Dissociations between the prevalence of asthma and atopy have been found in other developing countries. These findings suggest that asthma and atopy are only loosely linked phenotypes and that the strength of association between these phenotypes is dependent on the environment in which the children live.

The timing of exposures to certain environments may have a crucial role in the development of asthma. The relation between the prevalence of respiratory symptoms and time since arrival in Australia was studied in immigrant teenagers living in Melbourne. In subjects born outside Australia, residence for 5 to 9 years in Australia was associated with a two-fold increase in the risk for self-reported wheeze; after 10 to 14 years, this risk increased three-fold. This time–dose effect on the prevalence of symptoms in subjects born outside Australia and living in Melbourne was independent of age and country of birth [12]. These findings suggest that duration of exposure is an important determinant. Alternatively, the results indicate that exposure early in life is more important than exposure thereafter.

East–West gradient across Europe

Another peculiarity in the variation in the prevalence of childhood asthma is the marked East–West gradient across Europe [7]. One study found that, compared with reports from Sweden and Finland, the further east a center was situated in Europe, the lower the prevalence of ever having wheezed and of exercise-induced wheeze [13]. This finding supports previous studies from East and West Germany, Scandinavia, and the Baltic area [14–16]. In 1989, the fall of the Berlin wall in Germany opened a window of opportunity to study the genetically homogeneous populations that had lived under very different eco-

nostic and environmental circumstances in the two separated parts of the country. The reported prevalence of asthma and atopic sensitization was significantly higher in West Germany than in East Germany [17]. Likewise, in a study from the Baltic area, Swedish children showed a higher prevalence of asthma and atopic sensitization than did their peers from Poland and Estonia [15,16].

When a cross-sectional survey of children was repeated in 1996 in East Germany, atopic sensitization measured by skin prick tests had increased significantly, though not enough to attain the prevalence rates of atopy previously reported for children in West Germany [18]. The children from East Germany who participated in this repeat survey were born 3 years before the downfall of communism and were exposed only to Western living conditions after their third birthday. This characteristic may indicate that factors early in life are important for the development of asthma and that, after infancy, environmental factors may influence the development of other allergic disorders. It remains to be seen whether the prevalence of asthma will increase in children of other formerly communist countries in Eastern Europe who are born and raised in a western lifestyle.

There also may be a maternal influence on the temporal trend in asthma prevalence. Maternal transmission of asthma repeatedly has been shown to be stronger than paternal transmission [19], pointing toward independent effects of in utero exposure. If the intrauterine environment must be shifted toward an atopic phenotype to give rise to asthmatic offspring, the environmental factors that influence the temporal rise in asthma prevalence must be determined in the maternal generation that precedes the affected individuals.

Differences between rural and urban populations

In some developing countries, a lower prevalence of childhood asthma has been reported in rural areas than in urban areas. Airway challenges performed in African urban and rural areas documented that airway hyperresponsiveness (AHR) was almost nonexistent in some rural areas in the late 1980s and early 1990s [20]. In turn, among the more affluent urban populations of South Africa and Zimbabwe, AHR reached a prevalence of 3.2% and 5.9%, respectively. Similar results were reported from other African areas. Over the last decade, however, AHR seems to have increased in rural Africa [20]. Similar urban and rural differences were reported from Saudi Arabia [21]. A significantly lower prevalence of allergic symptoms was found in rural children compared with that in urban children.

Urban and rural differences in childhood asthma are less pronounced in western countries. In a large British study, only marginal differences were observed in the prevalence of childhood asthma between rural and urban areas [22]; however, in Scotland, children from rural areas showed a lower prevalence of severe asthma compared with other more urbanized areas in the UK [23]. Data from Sweden indicated a higher prevalence of atopic sensitization to aeroallergens in children from urban centers compared with that in children from rural areas, but no information was available for childhood asthma [15]. Findings from

Austria [24], Finland [25], Canada [26], Southern Germany [27], and Switzerland [28] suggested that the lower prevalences of atopic diseases in rural populations may be attributable to the presence of unspecified protective factors in a farm environment rather than to the absence of urban risk factors.

Several authors have investigated rural populations and have shown that growing up on a farm confers significant protection against the development of asthma and atopy [24–26,28]. This protective effect was not detected in children who were raised in a rural environment by nonfarming parents. Several investigators observed that frequent contact with livestock seems to indicate that the protection is associated with farm life. A dose-response relation between exposure to farm animals and the prevalence of atopic disease was reported among farmers' children in Bavaria [27]. It also was shown that the protective effect ascribed to exposure to livestock was not limited to children growing up in farms. Frequent contact with farm animals also conferred significant protection from developing atopy in children who did not live on farms but who regularly were exposed to the farm animals in the barns [24]. The effects were most pronounced when exposure to stables and (unpasteurized) farm milk occurred in the first year of life [29]. The prevalence of asthma was reduced to 1.4% if infants were exposed to stables and farm milk in the first year of life as compared with 11.8% in the nonexposed group [29]. This finding supports the importance of timing with respect to the impact of environmental exposures on the subsequent development of disease.

Time trends in asthma prevalence

Numerous studies have investigated the trends in the occurrence of childhood asthma [30]. Data collected over the last 40 years in industrialized countries indicate a significant increase in asthma prevalence. A wide array of disease definitions, sample populations, and age groups has been used by different investigators, making direct comparisons among studies difficult. The investigators, however, have undertaken repeated, cross-sectional surveys using identical questionnaires in similar population samples at different times. These studies are reliable indicators of changes in prevalence over time. Most studies lack objective measurements, such as airway responsiveness and atopic sensitization. Parental questionnaires, however, are subject to bias, because the perception of childhood asthma may have changed over time as public awareness of allergic conditions increased. Nevertheless, the consistent and strong increase in the prevalence of undiagnosed wheeze indicates that the increase in the prevalence is legitimate.

In some studies, the prevalence of diagnosed asthma increased more rapidly than did the prevalence of wheezing [31]. This finding suggests that there was a broadening of the definition of asthma or were improvements in its detection. Alternatively, it may indicate an increase in the severity of asthmatic symptoms, leading to more easily recognizable disease. This finding was reported in a survey of English schoolchildren [32], in which exercise-induced AHR was assessed

jointly with questionnaire-derived information over 15 years. The results of bronchial challenge tests suggested an increase in the prevalence and severity of exercise-induced symptoms that matched the increase of asthma reported by parents. Other surveys, however, did not document increases in the severity of asthmatic symptoms as assessed by speech-limiting episodes, school absenteeism, and activity impairments [33].

A well-documented study from Australia that used airway histamine challenges, skin prick tests, and questionnaires reported that the prevalence of AHR almost doubled between 1982 and 1992 [34,35]. The prevalence of current wheeze (assessed as wheezing in the last 12 months) also doubled during the same period in the study population of 8- to 10-year-old school children. These findings corroborate by objective measure the increasing trend in the prevalence of asthma.

Despite the use of different methods and definitions of asthma, most studies from industrialized countries suggest an overall increase in the prevalence of asthma and concurrent wheezing symptoms between 1960 and 1990. Most studies have been performed among children, and little is known about time trends among adults. Twenty-year trends of the prevalence of treated asthma among pediatric and adult members of a large US health maintenance organization were reported [36]. From 1967 to 1987, the treated prevalence of asthma increased significantly in all age-sex categories, except in men aged 65 and older. In the United States, the greatest increase was detected among children and young adults living in inner cities [37]. Likewise, the prevalence of asthma increased in children and adults from 1981 to 1990 in the province of Saskatchewan, Canada [38].

Studies suggest that, in some areas, this trend continues unabated. Kuehni and colleagues from the United Kingdom reported that among preschool children, all types of wheezing increased in prevalence from 1990 to 1998 [39]. In contrast, studies from Italy showed that among school children surveyed in 1974, 1992, and 1998 the prevalence of asthma had increased significantly during 1974 to 1992; in contrast, it has remained stable over the last 4 years [40]. Further observations are needed to document population morbidity over the years to come.

The costs of asthma were assessed in a large, two-period (1985 and 1994) US study [41]. Cost estimates were based on US population and health care survey data available from the National Center for Health Statistics. The total US costs of asthma for 1994 were \$10.7 billion. On the basis of 1985 estimates adjusted to 1994 dollars, total asthma costs increased by 54%, and direct medical expenditures increased by 20% during the indicated 10-year period [41,42].

Trends in hospital admission rates for childhood asthma

The increase in prevalence of childhood asthma has been accompanied by an increase in hospital admissions; however, the association between these two observations is not necessarily straightforward. When interpreting hospitalization data, additional factors must be considered.

Since the 1960s, a striking increase has been reported in hospital asthma admissions of children between 14 years old or younger in New Zealand, England, Wales, the United States, Canada, and Australia [43]. Hospital-admission data in the form of the international classification of disease (ICD-9) was available for analysis in these countries, except for the United States, where disease data was obtained at hospital discharge. In this international comparison, hospital admission showed a 10-fold increase in New Zealand between the mid-1960s and the early 1980s, and rates in England and Wales rose by six fold. In the United States, a three-fold increase was observed, and in Australia, the increase varied between three and eight fold. This increase was strongest in children 4 years old and younger, but rates in children 5 to 14 years old have more than doubled since the early 1970s. There are indications, however, that the increasing trend in hospitalization stopped in the late 1980s. A decrease in admission rates has been reported for some countries in the 1990s [44].

In many countries, the rate of hospitalization rose much faster than did the prevalence of asthma. There is, however, little evidence to suggest that severe asthma requiring hospital admission has increased as dramatically as did hospitalization rates since the 1960s. Changes in coding of respiratory conditions may have contributed to the observed trends. The diagnosis of bronchitis seems to overlap with the classification of asthma. Although a US study suggested a sudden 40% shift from the diagnosis of bronchitis to that of asthma as a consequence of changes in the ICD coding that occurred in 1979, no similar diagnostic shifts are evident in New Zealand, England, Wales [45], and Australia [46]. In western Australia, however, a significant shift from the diagnosis of bronchitis to asthma was reported over a 17-year period. This finding likely contributed, in part, to increases in hospital admissions over the last decades [46].

In the United States, the prevalence of childhood asthma and respiratory symptoms was assessed in 1981 and 1988 [47]. These assessments noted a significant increase in asthma symptoms, with no accompanying evidence of an increase in disease severity or hospitalization because of asthma. Canadian data from the Provincial Health Insurance plan also were available for examination of changes in the prevalence of physician-diagnosed asthma [47]. These data indicate an increase in asthma prevalence in all age groups between 1980 and 1990. The increase was highest in 5- to 14-year-old children. Potential changes in asthma severity between 1983 and 1988 were assessed in another study using the same database [48]. Although the previously reported increase of asthma prevalence was confirmed in this study, declines in hospitalization and emergency department visits also were noted. Whether this finding indicates a decline in severe asthma cases, the effectiveness of preventive treatment, or changes in health care policies is not clear.

Factors other than changes in disease coding also may have contributed to the increased rate of hospitalization for asthma between the 1960s and 1980s. Apparent changes in the accessibility of hospital care compared with that of primary care may have a role. A five-fold increase of self-referrals for asthma attacks in children was observed in a British study [45]. This finding reflects the

increasing tendency of parents to take their children directly to emergency departments in the event of an asthma attack instead of first consulting a primary care physician [49]. A lack of accessible primary care facilities also may be a reason why children of minority backgrounds, such as black children in the United States or Polynesian children in New Zealand, show higher admission rates for asthma than do their white peers. The availability of appropriate health care for children is linked to the economic status of families. When controlling for family income, black and white children of similar poverty levels showed nearly identical rates of hospitalization for asthma in the United States [50].

Asthma treatment in ambulatory care settings also may influence the rate of hospital admissions. A Swedish study demonstrated a drastic reduction between 1985 and 1993 in the total number of hospital days and hospital admissions for childhood asthma. These reductions coincided with the Swedish introduction of inhaled steroids as an anti-inflammatory treatment in this age group. These findings were confirmed by a second Swedish study that correlated a decrease in hospitalization for childhood asthma with increased regional sales of inhaled corticosteroids [51]. An alternative explanation for a recent report of decreases in US hospitalization rates was suggested by a study that investigated asthma severity by measuring oxygen saturation levels within the first 24 hours of admission [52]. A three-fold increase was observed in severe asthma admissions between 1991 and 1995 with an overall constant hospitalization rate. This finding may indicate a heightened threshold for asthma admissions to keep hospitalization rates low during the 1990s.

Trends in childhood asthma mortality

Asthma is a rare cause of childhood deaths, and mortality rates caused by asthma remained fairly low in the second half of the 20th century in most developed countries. Two major epidemics of asthma deaths may have occurred in children and young adults in the 1960s and late 1970s. Both epidemics were linked to the overuse of certain high-dose bronchodilators, but this evidence was not conclusive. After, these drugs were removed from the market, death rates decreased [30,53].

Mortality trends differ greatly among countries. An increase in childhood asthma-related deaths between the mid-1970s and mid-1980s was observed in the United Kingdom, Australia, and Germany. In the United States, the rate of childhood asthma mortality almost doubled between 1978 and 1987. Asthma mortality in nonwhite American children was found to be three times higher than that in white children. Other countries, such as Japan, Switzerland, and France, experienced little variation in mortality rates over the same period of time. More recent studies from the United Kingdom have shown decreases in asthma mortality beginning in the late 1980s [54]. Death rates remained stable in the 1990s, approximately less than 1 per 100,000 in 15- to 24-year-olds and less than 3 per 100,000 in children aged 14 years and younger [55,56]. In the United

States, a further increase in asthma mortality was reported as recently as 1994. Asthma mortality among children and young adults at that time was similar to that in England. This increase was observed despite increased sales and use of anti-inflammatory drugs.

Data on asthma mortality are sparse in developing countries. A survey from Mauritius reported an overall dramatic decline of asthma deaths in children [57]. Between 1982 and 1991, asthma mortality dropped steadily from 20 to 5 per 100,000 in children aged 4 years and younger and from 2.6 to 1.0 per 100,000 in 5- to 34-year-olds. The major drop in asthma mortality in this short time most likely reflected improvements in general health care and better availability of treatment. At the beginning of the 1990s, no significant difference in childhood asthma mortality was seen between Mauritius and other, more industrialized countries.

Summary

Large variations in the prevalence of childhood and adult asthma have been reported. Prevalences are generally higher in affluent countries than in poorer countries. Lower levels are seen in some rural areas in Africa, Saudi Arabia, China, and among farmers' children in Europe. Overall, an increasing trend has been reported in the prevalence of asthma in recent decades. Numerous hypotheses have been proposed to explain these trends. These theories most often relate to socioeconomic status, family size, early-childhood infections and hygiene, allergen exposure, diet and obesity, perinatal risk factors, and environmental pollution. Future evaluations have to consider genetic factors and the importance of gene–environment interactions to explain the spatial and temporal variations and trends in the prevalence of asthma and related conditions.

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