Epidemiology of Respiratory Allergies and Asthma

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56.1 Introduction

Asthma has puzzled and confused physicians from the time of Hippocrates to the present day. The word "asthma" comes from a Greek word meaning "panting" (Keeney 1964), but reference to asthma can also be found in ancient Egyptian, Hebrew, and Indian medical writings (Ellul-Micallef 1976; Unger and Harris 1974). There were clear observations of patients experiencing attacks of asthma in the second century and evidence of disordered anatomy in the lung as far back as the seventeenth century (Dring et al. 1689).

More recently, Western countries have experienced an epidemic of respiratory allergy and asthma prevalence (and incidence) that appears to have commenced after the Second World War and has only recently peaked and begun to decline (Pearce et al. 2007). The reasons for the decline remain as mysterious as the reasons for the epidemic itself (Weiland and Pearce 2004). Current WHO estimates suggest that some 300 million persons suffer from asthma, which is the most common chronic disease among children (WHO 2007). In 2010, the annual economic cost of asthma in the United States was estimated to be >$15 billion in direct costs and >$5 billion in indirect costs such as lost productivity (American Lung Association 2010).

Formal epidemiological studies of respiratory allergies and asthma commenced about 50 years ago, and in some respects they have failed to deliver the insight or testable hypotheses that have derived from studies of other common diseases. The roots of this failure lie in the problem of defining asthma, and the consequent difficulty of reproducible and conclusive case ascertainment; in the transient nature of the principal symptoms, the fact that asthma is heterogeneous in its underlying pathophysiology; and in the absence of simple sensitive and specific markers for the condition. However, the epidemiology of asthma and allergy is currently undergoing a rapid expansion and has shifted attention from traditional risk factors which may exacerbate asthma, to protective factors that may prevent respiratory allergies and asthma. This growth of interest is occurring in the context of major concerns about the increasing burden of respiratory allergy and asthma morbidity, and the realization that previous etiological theories based on animal models of asthma and clinical observations do not appear to explain the large global increases in asthma prevalence.

This chapter begins with the definitions and the underlying pathology and physiology of respiratory allergies and asthma, before considering the distinctive features of asthma epidemiology. We subsequently review the global burden of respiratory allergies and asthma and discuss a wide range of potential risk and protective factors. The chapter concludes with a discussion of the role of epidemiology in respiratory allergies and asthma research, and the challenges it is facing, followed by a discussion of the foremost issues for the future of respiratory allergies and asthma epidemiology.

56.2 Definitions of Respiratory Allergies and Asthma

56.2.1 Respiratory Allergy

Allergy can be defined as adverse acute or chronic hypersensitivity reactions resulting from immunologic sensitization with production of immunoglobulin (Ig) E against a specific agent or allergen. Thus, the term "allergy" refers to symptomatic conditions (allergic asthma, rhinitis, etc.), whereas the term "sensitization" refers to an individual's immune status assessed by in vivo or in vitro diagnostic tests (see Sect. 56.4.3). Symptoms can be induced by inhalation of allergens, even at very low concentrations. Individuals that are not sensitized to these allergens will usually not show symptoms even with very high exposure. Symptoms in sensitized subjects are caused by inflammatory reactions initiated by allergen-specific IgE antibodies present in the airways. Only a proportion of sensitized subjects show symptoms and are thus also allergic. It can take weeks to years between the first encounter with an allergen and the development of an allergy.

56.2.2 Atopy

"Atopy" (allergic sensitization) is a common term for IgE-mediated sensitization and/or allergic reactions. In population studies, the term "atopy" is used to indicate the predisposition of individuals to produce increased levels of specific or total IgE after exposure to common allergens such as house dust mite, pet, and various food allergens. It is usually assessed by skin prick tests or specific and/or total serum IgE against common allergens (see Sect. 56.4.3), and it can therefore be defined either in terms of skin prick text positivity or elevated serum IgE levels (Pearce et al. 1999). Depending on the definition, about 20% to 40% of people in affluent countries are atopic. In population studies, atopy is often associated with an increased risk of asthma (Pearce et al. 1999), but the association is stronger in "Westernized" countries than in developing countries (Weinmayr et al. 2007).

56.2.3 Aeroallergens

Many macromolecules (particularly proteins) of non-human origin, including those of animals (e.g., arthropod proteins, animal danders, proteins in excretia), plants (e.g., pollens, latex dust), and microorganisms (e.g., spores of fungi such as *Alternaria, Aspergillus,* and *Penicillium*), can act as allergens by inducing a specific IgE response and provoke allergic reactions in sensitized subjects.

Dust mites produce the predominant inhalant allergens in many parts of the world. The most common mite species that produce allergens are *Dermatophagoides pteronyssinus* and *D. farinae*. The major allergens produced by *D. pteronyssinus* (called Der p 1 and Der p 2) are proteases present in high amounts in fecal pellets. *D. farinae* produces as its major allergen Der f 1. Elevated

levels of these allergens have been detected in house dust, mattress dust, and bedding in damp homes (van Strien et al. 1994).

Other important inhalant allergens include proteins associated with cats and dogs, cockroaches, grass and tree pollens, and fungi such as *Alternaria*. Allergens in the occupational environment can range from cow urinary proteins in farming situations to fungal enzymes in the biotechnology and bakery industry. Low molecular weight chemicals such as diisocyanates (e.g., tolueen diisocyanate, TDI) can also cause occupational allergic asthma, but the specific immunological mechanisms have not yet been resolved.

56.2.4 Asthma

The definition of asthma initially proposed at the Ciba Foundation conference in 1959 (Ciba Foundation Guest Symposium 1959) and endorsed by the American Thoracic Society in 1962 (American Thoracic Society Committee on Diagnostic Standards 1962) is that "asthma is a disease characterized by wide variation over short periods of time in resistance to flow in the airways of the lung." Although these features receive lesser prominence in some current definitions, as the importance of airways inflammation is appropriately recognized, they still form the basis of the recent Global Initiative for Asthma (GINA) description of asthma as:

> . . . a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper-responsiveness 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. (GINA 2006)

These three components, chronic airways inflammation, reversible airflow obstruction, and enhanced bronchial reactivity, form the basis of current definitions of asthma. They also represent the major pathophysiological events leading to the symptoms of wheezing, breathlessness, chest tightness, cough, and sputum by which physicians clinically diagnose this disorder.

56.2.5 Clinical Asthma

There is no single test or pathognomic feature which defines the presence or absence of asthma. Furthermore, the variability of the condition means that evidence of it may or may not be present on the day, or at the time, that someone is assessed. Thus, a diagnosis of asthma is made on the basis of the clinical history, combined with physical examination and respiratory function tests over a period of time. Several studies have found the prevalence of physician-diagnosed asthma to be substantially lower than the prevalence of asthma symptoms in the community (e.g., Asher et al. 1998). This is not surprising since a clinical diagnosis of asthma can only be made if a person presents him or herself to a doctor. This requires an initial self-assessment of the symptoms (in terms of severity and frequency), as well as access to a doctor

Table 56.1 GINA classification of asthma severity

Asthma classification	Criteria
Intermittent	Symptoms less than once a week; brief exacerbations; nocturnal symptoms not more than twice a month; FEV_1 or PEF $\geq$80% predicted; FEV_1 or PEF variability <20%
Mild persistent	Symptoms more than once a week but less than once a day; exacerbations may affect activity and sleep; nocturnal symptoms more than twice a month; FEV_1 or PEF $\geq$80% predicted; FEV_1 or PEF variability 20–30%
Moderate persistent	Symptoms daily; exacerbations may affect activity and sleep; nocturnal symptoms more than once a week; daily use of inhaled short-acting β_2-agonist; FEV_1 or PEF 60–80% predicted; FEV_1 or PEF variability >30%
Severe persistent	Symptoms daily; frequent exacerbations; frequent nocturnal asthma symptoms; limitation of physical activities; FEV_1 or PEF $\leq$60% predicted; FEV_1 or PEF variability >30%

FEV_1 Forced Expiratory Volume in one second, *PEF* Peak Expiratory Flow

once a self-assessment has been made. Several medical consultations may then be required. Thus, diagnosed asthma is dependent not only on morbidity but also on patient perceptions, physician practice, and the availability of health care.

There are a number of tests that may facilitate the diagnosis and monitoring of asthma. Measurements of lung function are the most frequently used and provide important information on airflow limitation including variability, reversibility, and severity. Airflow limitation is most often measured using spirometry or a peak (expiratory) flow (PEF) meter. Spirometry is the preferred method and forced expiratory volume in one second (FEV_1), and peak expiratory flow (PEF) can be derived from this method as indicators for airway obstruction. Pre- and postbronchodilator treatment is important since it will establish whether obstruction is reversible and will distinguish it from chronic obstructive pulmonary disease (COPD) in which obstruction is mostly irreversible. Reversibility of airway obstruction defined as FEV_1 of $\geq$12% and $\geq$200mL from the prebronchodilator value is generally accepted as a valid indication of asthma (GINA 2006). However, due to the highly variable nature of the condition, repeated lung function tests are required. PEF meters are inexpensive and easy to use, but they are less precise than spirometry and may underestimate the degree of airflow limitation (Aggarwal et al. 2006).

In subjects with asthma symptoms but normal lung function, bronchial hyperresponsiveness (BHR) testing is often used as a diagnostic aid. BHR constitutes airway narrowing to non-specific stimuli, such as exercise, cold air, and chemical irritants, and can be measured as airway responsiveness to histamine, methacholine, adenosine-5′-monophosphate (AMP), hypertonic saline, or exercise challenge (de Meer et al. 2004a). However, although BHR is related to asthma, it may occur independently of asthma, and vice versa (Pearce et al. 1998a), which makes this test of limited use for individual asthma-diagnostics (see Sect. 56.4.1).

The degree of asthma severity is commonly classified using GINA criteria (GINA 2006) which subdivide asthma into four categories based on frequency and severity of symptoms and lung function (with the worst feature determining the severity classification) (see Table 56.1). However, as emphasized in the updated

2010 GINA guidelines (GINA 2010), asthma involves both the severity of the disease and its responsiveness to treatment. Therefore, asthma could present with severe symptoms and poor lung function but could become completely controlled with low-dose treatment. Thus, the classification of severity had poor predictive value for what treatment was required and what the response to treatment might be. As a consequence, the 2010 guidelines do no longer include the 2006 asthma severity classification. However, it is still a commonly used classification in many epidemiological studies.

56.2.6 Defining Asthma in Epidemiological Surveys

Defining asthma in population-based epidemiological surveys of asthma prevalence or incidence poses even greater difficulties than defining asthma in individual patients. As a result, comparisons of diagnosed asthma between populations are fraught with difficulty, as the differences in diagnostic practice may be greater in magnitude than the real differences in asthma morbidity.

Thus, asthma prevalence surveys usually focus on self-reported (or parental reported) "asthma symptoms" rather than diagnosed asthma. Standardized questionnaires on asthma symptoms have therefore become the cornerstone of large studies of the incidence or prevalence of asthma (Burney et al. 1994; Asher et al. 1995). This approach allows a large number of participants to be surveyed without great cost, in a short time period. Wheezing, chest tightness, breathlessness, and coughing are all symptoms clinically associated with asthma, but epidemiological studies have shown that wheezing is the most important symptom for the identification of asthma, and the majority of questionnaires used to assess asthma prevalence are based on this symptom (Pearce et al. 1998a) (see Sect. 56.4.1 for more detail).

An alternative approach to symptom questionnaires has been to use more "objective" measures such as bronchial responsiveness testing, either alone or in combination with questionnaires (Toelle et al. 1992). However, some have questioned the validity of BHR for the assessment of asthma (Pearce et al. 1998a) (see Sect. 56.4 for more detail).

56.3 Mechanisms of Respiratory Allergies and Asthma

56.3.1 Asthma Phenotypes

Ten years ago it was widely believed that asthma was an atopic disease caused by allergen exposure. The fundamental etiological mechanism was that allergen exposure, particularly in infancy, produced atopic sensitization, and continued exposure resulted in asthma through the development of eosinophilic airways inflammation, bronchial hyperresponsiveness and reversible airflow obstruction. In recent years, it has become increasingly evident that this picture is, at best, too simplistic (Ronchetti et al. 2007; Weinmayr et al. 2007). A systematic review of population-based studies (Pearce et al. 1999) has shown that the proportion of

asthma cases that are attributable to atopy (defined as skin prick test positivity) is usually less than one-half. Standardized comparisons across populations or time periods also show only weak and inconsistent associations between the prevalence of asthma and the prevalence of atopy. For instance, a comparison of asthma and atopy in 9- to 11-year-olds in Albania and the United Kingdom (Priftanji et al. 2001) showed large differences in the prevalence of current wheeze (4.4% and 9.7%, respectively) and exercise-induced bronchial reactivity (0.8% and 5.4%), but not in skin prick test positivity (15.0% and 17.8%), suggesting that large variations in asthma prevalence can occur without differences in frequency of atopy. This was confirmed by the International Study of Allergies and Asthma in Children (ISAAC; see Sects. 56.5.3 and 56.5.4) which showed that the association between atopy and asthma symptoms differed strongly among populations but increased with the level of economic development (Weinmayr et al. 2007). In this study, the proportion of current wheeze attributable to atopy ranged from 0% in Ankara (Turkey) to 93.8% in Guangzhou (China); the overall proportion of asthma cases that were attributable to atopy was only 41% in affluent countries and 20% in non-affluent countries. This is consistent with a recent study among 3,960 children in Ecuador which found a population attributable fraction of only 2.4% for recent wheeze and atopy (Moncayo et al. 2010). A similar study in Salvador, Brazil suggested the proportion of asthma attributable to atopy to be 24.5% (Souza da Cunha et al. 2010), which, although higher than in Ecuador, is substantially lower than the 50% in most Western countries. The European Community Respiratory Health Survey (see Sects. 56.5.2 and 56.5.4) found that the proportion of asthma attributable to atopy in adults ranged from 4% to 61% between individual study centers with an overall estimate of only 30% for all centers combined (Sunyer et al. 2004). Finally, time trend studies have shown different patterns for atopy and astma in the same geographical areas. For example, a recent study in Sweden in 7- to 8-year-olds showed a significant increase in allergic sensitization over a 10-year period (1996–2006) despite asthma symptoms remaining stable over the same period (Bjerg et al. 2010).

Recent studies using sputum induction and/or bronchoalveolar lavage (BAL) techniques to measure and characterize airways inflammation in asthmatics have also demonstrated that less than 50% of asthma cases are attributable to eosinophilic airway inflammation, the hallmark of allergic asthma (Douwes et al. 2002a; Simpson et al. 2006). Thus, evidence from studies of eosinophilia and asthma is consistent with that from studies of atopy and asthma: in both instances, at most about one-half of asthma cases appears to be due to "allergic" mechanisms. This further adds to the evidence that allergic mechanisms may not be the only, or the most important, underlying mechanism for asthma.

56.3.2 Immunology

56.3.2.1 Allergic Asthma

Allergic asthma is caused by IgE-mediated inflammatory mechanisms in which a large number of cells play a role including mast cells, eosinophils, T lymphocytes, dendritic cells, and macrophages. Briefly, the sensitization process involves the

adaptive (or acquired) immune system whereby allergens interact with dendritic cells in the airway mucosa which migrate to the regional lymph nodes where the allergens are presented to B and T cells. This results (through T-helper-2 (Th_2) responses) in the production of allergen-specific IgE. Once allergic, a subject can develop symptoms minutes after being exposed. This is known as the early phase allergic reaction, and symptoms develop as a result of mast cell degranulation and release of inflammatory mediators through allergen IgE antibody complexes at the surface of the mast cells, causing contraction of bronchial smooth muscle and edema in the airways. Clinically, this results in a decreased lung function and symptoms of wheeze, shortness of breath, chest tightness, and coughing.

During the late phase of the allergic reaction (4 to 8 h after exposure), eosinophil-related inflammatory reactions are particularly important. A critical step in this late phase reaction is the activation of Th_2 cells which release several proinflammatory cytokines including IL-5 resulting in the influx and activation of eosinophils. This reaction is characterized by the development of a non-specific BHR that can continue for several days. Repeated exposures can result in more permanent BHR.

56.3.2.2 Non-Allergic Asthma

As noted above, a substantial proportion of all asthma cases have an underlying pathology that is different from that observed in "classic" allergic asthma (Douwes et al. 2002a; Simpson et al. 2006). Patients may have severe and persistent asthma in the absence of eosinophilic inflammation and may experience an exacerbation of asthma without an increase in eosinophilic inflammation (Turner et al. 1995). Repeated assessments of airway inflammation over time have shown that the non-eosinophilic asthma phenotype is reproducible both in the short (4 weeks) and long term (1 to 5 years) (Simpson et al. 2006). However, the underlying mechanisms of non-eosinophilic/non-allergic asthma are not fully understood. One study in 93 non-smoking adult asthmatics found elevated sputum airway eosinophilia in 41% of all asthma cases, 20% had elevated levels of neutrophils, 8% had a mixed inflammatory profile with both cell types being elevated, and the remainder (31%) had no signs of airway inflammation with eosinophil and neutrophil levels both being within the normal range (Simpson et al. 2006). This suggests that asthma can be categorized into four inflammatory subtypes based on the sputum eosinophil and neutrophil proportions: eosinophilic asthma, neutrophilic asthma, mixed granulocytic asthma, and paucigranulocytic asthma (Simpson et al. 2006).

The common pathophysiological features of neutrophilic asthma involve an IL-8-mediated neutrophil influx, and the subsequent neutrophil activation is a potent stimulus to increased airway hyperresponsiveness (Simpson et al. 2007). Although the stimuli that trigger this response are diverse (endotoxin, ozone, particulates, virus infection), the common features are consistent with activation of innate immune mechanisms (involving Toll-like receptors and CD14) rather than IgE-mediated activation of acquired immunity.

There is also the potential for combined activation of both innate and allergen-specific inflammatory mechanisms in asthma. This may be the case in mixed granulocytic asthma and may explain the ability of ozone and NO2 to potentiate

allergen-induced asthmatic responses (Jenkins et al. 1999). The pathophysiological mechanisms involved in paucigranulocytic asthma are not clear.

Clinically, the eosinophilic and non-eosinophilic phenotypes appear very similar with only small differences in lung function, airway hyperreactivity, corticosteroid use, and β_2 agonist-induced reversibility in FEV_1 (Simpson et al. 2006; Berry et al. 2007). However, there are also distinct differences: non-eosinophilic asthmatics appear to be less atopic, have normal subepithelial layer thickness, and perhaps most importantly, they have a poor short-term response to treatment with inhaled corticosteroids (Berry et al. 2007). Thus, despite clinical similarities they represent distinct pathological phenotypes.

Non-allergic occupational asthma is also very common. For instance, in many occupational environments where workers are exposed to organic dust (e.g., farmers, grain workers), the majority of asthma cases are non-IgE-mediated and are related to chronic exposure to environmental irritants. The underlying inflammatory mechanisms involve innate immune responses which are often directed against constituents of bacteria and fungi (Douwes et al. 2002a, b).

56.4 How to Measure Respiratory Allergies and Asthma in Epidemiological Studies

56.4.1 Measuring Incidence and Prevalence

Ideally, we would wish to measure incidence in epidemiological studies of asthma. However, in practice, asthma incidence is very difficult to measure, both because of the intensive long-term monitoring required and because of the difficulty of establishing the date of onset of the condition. Therefore, most studies involve prevalence rather than incidence. Similar techniques to those described in this section can be used in incidence studies, although incidence studies may involve more intensive monitoring to enable a diagnosis of asthma to be more firmly established. Asthma prevalence reflects both the incidence of asthma and the average duration of the condition. Thus, a population may have a high prevalence of asthma either due to a high exposure to factors (genetic or environmental) which induce asthma or because of high exposure to factors which incite, exacerbate, or prolong asthma symptoms in those who have previously developed the disease (Dolovich and Hargreave 1981).

56.4.1.1 Diagnosed Asthma

Although asthma can be conceptualized either in terms of symptoms such as wheezing or in terms of the underlying bronchial inflammation, the essential feature of asthma (at least in clinical and epidemiological terms) is variable airflow obstruction which can be reversed by treatment or is self-limiting (see Sect. 56.2.4). This poses several problems with the use of "diagnosed asthma" in asthma prevalence studies, since the diagnosis of "variable airflow obstruction" usually requires several medical

consultations over an extended period. It is therefore not surprising that several studies have found the prevalence of physician-diagnosed asthma to be substantially lower than the prevalence of asthma symptoms. For example, Ehrlich et al. (1995), in a survey in school children in Cape Town, found that among children with more than 12 attacks of wheezing in the previous 12 months, only 60% were reported as asthmatic and only 55% as receiving regular treatment.

These problems with using "diagnosed asthma" as an outcome measure in epidemiological studies not only affect prevalence estimates but also affect time trends (Hill et al. 1989) and geographical and social patterns of asthma prevalence. For example, some studies (e.g., Peckham and Butler 1978) have found diagnosed asthma to be more common in upper social class children, possibly because of greater access to health care and therefore greater likelihood of being labeled as asthmatic. The same concerns apply, perhaps to a greater extent, in surveys of use of asthma medication or health services. Although such information may be of value in asthma morbidity studies, it is of very limited use in prevalence studies (Pearce and Beasley 1999).

These issues are of particular concern in geographical prevalence comparisons since there are major international and regional differences in access to health care and labeling of asthma. Thus, some international comparisons have found differences in diagnosed asthma to be much greater than differences in reported asthma symptoms (e.g., Pearce et al. 1993), these differences in diagnosed asthma may partially reflect differences in access to health services and diagnostic practice rather than genuine differences in asthma prevalence. For example, Dodge and Burrows (1980) suggest that "the epidemiology of asthma is a reflection of the diagnostic habits of physicians in the locale, as well as an indicator of the frequency of a specific syndrome."

Such problems of differences in diagnostic practice could be minimized by using a standardized protocol for asthma diagnosis in prevalence studies. However, this is rarely a realistic option since it requires repeated contacts between the study participants and physicians, and this is often not possible or affordable in large-scale epidemiological studies. Although self-reported histories of physician-diagnosed asthma have been found to be relatively valid, this relates to diagnosed asthma rather than true asthma prevalence.

56.4.1.2 Symptoms

Questionnaires on asthma symptoms are the cornerstone of large-scale epidemiological surveys of asthma prevalence. These have the advantage of being inexpensive and simple to administer to large numbers of participants on a single day and will discriminate those with variable airflow obstruction that causes noticeable symptoms. The key issue is that questionnaires should obtain information in a standardized manner on symptoms which are directly related to "variable airflow obstruction." This definition of asthma implies a condition in which symptoms occur from time to time, rather than the presence or absence of symptoms on a particular day. Thus, operational definitions of asthma involve specification of the time period

during which symptoms may have occurred. In particular, "current symptoms" are usually defined as symptoms at any time in the previous 12 months. Although there has been concern that repeated questioning of subjects could increase awareness of respiratory symptoms, a comparison of findings from an intensive longitudinal study and a prevalence study within similar populations found very similar symptom prevalence suggesting that repeated questioning of the longitudinal study population had not biased the prevalence estimates (Sears et al. 1997).

Standard written questionnaires have been the principal instrument for measuring asthma symptom prevalence in community surveys, and in homogeneous populations these have been standardized, validated, and shown to be reproducible (Burney et al. 1989). A number of symptoms including wheezing, chest tightness, breathlessness, and coughing with or without sputum are recognized by physicians as indicative of asthma. Of these the most important symptom for the identification of asthma in epidemiological studies is wheezing, and most questionnaires have focused on this.

Symptoms may be absent despite variable airflow obstruction (asthma), and symptoms may also occur in the absence of asthma. Thus, wheezing is not synonymous with diagnosed asthma; in some instances, wheezing may indicate asthma which has not been diagnosed, but it may also indicate other diseases (particularly chronic bronchitis and emphysema in persons aged 45 years or more) or may be unrelated to other symptoms or disease; conversely, diagnosed asthmatics may not experience or recognize wheeze as a symptom. Nevertheless, wheezing remains the symptom which is most characteristic of asthma, particularly in persons aged 5 to 34 years where asthma is less likely to be confused with bronchitis or emphysema. Thus, most asthma symptom prevalence questionnaires focus on "current wheezing" (defined as wheezing at any time in the previous 12 months), but they usually also include additional questions on the frequency of wheezing and the circumstances in which wheezing occurs (wheezing while at rest, wheezing after exercise, wheezing in the absence of a cold, waking with wheezing), as well as questions on related symptoms (e.g., waking with cough or severe episodes of breathlessness).

A large number of such questions have been used in epidemiological surveys in the last decades. In particular, the questionnaires for the European Community Respiratory Health Survey (ECRHS) in adults (Burney et al. 1994) and the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al. 1995) have now become established as the standard questionnaires for use in prevalence surveys.

One of the major problems with the use of written questionnaires in international comparisons is with their translation into the different languages of the communities studied. This is particularly problematic for language groups (e.g., German, French, Dutch) which have no colloquial term for "wheezing." To ensure that data regarding the frequency and severity of symptoms is comparable in international comparisons of asthma prevalence, it is important that the questionnaire is translated in a manner that ensures that the terms describing symptoms correspond as closely as possible to the international recommended questions.

56.4.1.3 Physiological Measures

The problems of validity, repeatability, and translation of questionnaires have led to attempts to find more "objective" physiological measures for use in prevalence studies. These measures carry with them their own set of limitations both with regard to their "objectivity" (i.e., they are not unequivocally measures of asthma prevalence) and their practicality in large population-based surveys. Nevertheless, they form a useful complement to symptom questionnaires.

Diminished lung function, besides being used as an outcome measure in prevalence studies, is also a risk factor for the development of wheezing and/or asthma (Martinez et al. 1988). Lung function measurements include forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and peak expiratory flow (PEF). These are all forced expiratory maneuvers undertaken following a maximum inspiratory maneuver. While maximum inspiratory and expiratory maneuvers may lead to small transient changes in airway calibre, the simplicity, standardization, and reproducibility of such maximal expiratory manoeuvres (particularly FEV_1 and FVC) make them the measurements of choice in epidemiological studies (Quanjer et al. 1993), and standardized guidelines are available (American Thoracic Society 1987).

However, such measures may have limited use in prevalence studies, since the airflow obstruction in asthma is reversible over short periods of time and may not be present on the day of assessment. Indeed, one of the characteristic features of reversible airflow obstruction in asthma is its diurnal variation, in that the degree of airflow obstruction is greatest at night or on wakening and least during the day when lung function testing is likely to be undertaken. Thus, a significant proportion of asthmatics may have lung function within normal limits on any one day, and not exhibit the 15% postbronchodilator improvement in FEV_1 or PEF values that is required for a physiological diagnosis of asthma to be made.

A better approach is to undertake repeat measurements of lung function before and after bronchodilator, at different times of the day over a period of time (e.g., two weeks); however, this is difficult and expensive in practice. It is this variation and reversibility of changes in lung function which typifies asthma, and this cannot be captured in a one-off prevalence survey on a particular day. Similarly, a one-off clinical examination with auscultation of the chest to identify the proportion of subjects with wheeze is also of limited value.

Measurements of bronchial hyperresponsiveness (BHR) in epidemiological studies of obstructive respiratory disease have been increasingly used in the past decades, and standard procedures are now well established (James and Ryan 1997). Bronchial hyperresponsiveness (BHR) testing was originally developed in a clinical setting and has conventionally been defined in terms of the dose of agonist producing a 15 or 20% fall in FEV_1. Although BHR is often defined in terms of a dichotomy (e.g., subjects are defined as having BHR if they experience a 15 or 20% fall in FEV_1 at a dose of agonist below a specified level), it can also be regarded as a continuous measure using the dose-response slope (de Meer et al. 2005).

BHR tests are neither wholly sensitive nor specific for asthma (Pekkanen and Pearce 1999), and recent results of the ISAAC Phase II study (see Sect. 56.5.3)

involving BHR testing in 6,826 school children in 16 countries showed that, although BHR and asthma symptoms were associated within individual centers, a poor correlation was found between the level of BHR and wheeze across all participating centers ($\rho = 0.23$, $p = 0.294$) and high prevalences of BHR were not confined to centers with high prevalences of asthma symptoms (Buchele et al. 2010). The same study also showed that BHR (assessed by using hypertonic saline) was more closely associated with atopic asthma with a significant correlation between center-specific mean level of BHR and wheeze in atopic ($\rho = 0.64$, $p = 0.002$), but not in non-atopic children ($\rho = 0.21$, $p = 0.35$). Also, several studies have reported an absence of BHR in a substantial proportion of subjects with asthma, and BHR has also been reported in those without asthma (Josephs et al. 1990). BHR also occurs in chronic bronchitis and in tobacco smokers (Burney et al. 1987).

Perhaps the fundamental problem is that persons with non-specific BHR may have a greater tendency to experience asthma symptoms if they are exposed to the relevant stimulus in the laboratory but whether they do actually experience asthma symptoms in daily life, will depend on whether exposure occurs and at what level. Thus, the severity of airflow obstruction may be determined by the interaction of non-specific reactivity and the strength of a provoking bronchoconstrictor stimulus (Josephs et al. 1990). Furthermore, BHR is only one mechanism contributing to the clinical expression of variable airflow obstruction and may contribute to a greater or lesser extent in different individuals and within the same individual at different times (Josephs et al. 1990).

Thus, although BHR is related to asthma and may be involved in many of the pathways by which variable airflow obstruction may occur, variable airflow obstruction may occur independently of BHR, and vice versa (Pearce et al. 2000a). Also, using BHR to define asthma as has been suggested by some (Toelle et al. 1992), risks not only introducing error but will also bias the asthma sample toward one particular asthma phenotype (i.e., atopic asthma). Thus, asthma and BHR remain separate phenomena which both may involve inflammation of the airways, and which are both worthy of study in their own right.

56.4.2 Measuring Risk Factors

Asthma epidemiology studies typically involve measuring the effect of an exposure (e.g., air pollution) on a particular outcome (e.g., asthma, severe asthma, asthma hospital admission, asthma death) in a population. Strictly speaking, the term *exposure* refers to the presence of a substance (e.g., house dust mite allergen) in the external environment, whereas the term *dose* refers to the amount of substance that reaches susceptible targets within the body, such as the airways. In some situations (e.g., in a coal mine), measurements of external exposures may be strongly correlated with internal dose, whereas in other situations (e.g., indoor exposure to house dust mite allergen), the dose may depend on individual lifestyle and activities and may therefore be only weakly correlated with the environmental exposure levels. However, in this chapter we use the term “exposure” in the very

general sense to denote any attribute or agent which may increase the risk of experiencing the outcome under study. It includes demographic factors (age, sex, ethnicity, social class) and genetic factors as well as environmental risk factors (measured externally and/or internally).

The environmental exposures most commonly associated with asthma (development or exacerbation) in the general population include a wide range of bioaerosols such as non-allergenic microbial agents, including bacterial endotoxin, house dust mite, pet, and cockroach allergens, and allergenic and non-allergenic fungal agents (see Sect. 56.6.1). Also, more than 250 agents have been identified as causes of occupational asthma (see Sect. 56.6.1) with most of these being biological in origin.

Exposure levels can be assessed with regard to the *concentration* of the substance in the environment (e.g., allergen concentration in the air) and the *duration* of time for which exposure occurs. The risk of developing sensitization to an allergen may be much greater if the duration of exposure is long and/or the exposure is high, and the total *cumulative exposure* may therefore be important. However, once a person has become sensitized, then the concentration may be crucial in provoking an acute attack, and such attacks may occur after exposure of a relatively short duration. For protracted etiological processes, the time pattern of exposure may be important, and it is possible to assess this by examining the separate effects of exposures in various time windows prior to the occurrence and recognition of clinical disease (Pearce 1992). For example, several studies have found that exposure to environmental tobacco smoke in the first years of life may be as relevant as current exposures with regard to current asthma symptoms (e.g., Shaw et al. 1994). Similarly, it has been suggested that occupational asthma is most likely to occur after about 1 to 3 years of exposure to a sensitizing agent (Anto et al. 1996).

Epidemiological studies rarely have optimal exposure/dose data and often rely on relatively crude measures of exposure. The key issue is that the exposure data need not be perfect but that it must be of similar quality for the various groups being compared. Provided that this principle is followed, then any bias from misclassification of exposure will be non-differential and will tend to produce "false-negative" findings. Thus, if positive findings do occur, one can be confident that these are not due to inaccuracies in the exposure data; however, if no association (or only a weak association) is found between exposure and disease, then the possibility of non-differential information bias should be considered. In general, the aim of exposure assessment (see also chapter ▸Exposure Assessment of this handbook) is to (1) ensure that the exposure data is of equal quality in the groups being compared and (2) ensure that the data is of the best possible quality given the former restriction.

Methods of exposure measurement include personal interviews or self-administered questionnaires, diaries, observation, routine records, physical or chemical measurements on the environment, or physical or chemical measurements on the person. Measurements on the person can relate either to exogenous exposure (e.g., airborne dust) or internal dose (e.g., plasma cotinine as a biomarker of tobacco smoke); the other measurement options (e.g., questionnaires) all relate to exogenous exposures.

Traditionally, exposure to many non-biological risk factors (e.g., cigarette smoking) has been measured with questionnaires, and this approach has a long history of successful use in epidemiology. Questionnaires may be self-administered (e.g., postal questionnaires) or interviewer-administered (e.g., in telephone or face-to-face interviews) and may be completed by the study subject or by a proxy (e.g., parental completion of questionnaires in a childhood asthma study). The validity of questionnaire data also depends on the structure, format, content, and wording of questionnaires, as well as methods of administration and selection and training of interviewers. Questionnaires may be combined with environmental exposure measurements (e.g., pollen counts, industrial hygiene surveys) to obtain a quantitative estimate of individual exposures. Questionnaires and environmental measurements have good validity and reproducibility with regard to current exposures and are likely to be superior to biological markers with respect to historical exposures (as described in the following).

Exposure can also be measured using molecular markers of internal dose. However, there are a number of major limitations of many available biomarkers of exposure (Armstrong et al. 1992), particularly with regard to historical exposures (Pearce et al. 1995) with even the best markers of exposures usually reflecting only the last few weeks or months of exposure. Thus, if the aim is to measure historical exposures, then historical information on exposure surrogates may be more valid than direct measurements of current exposure or dose levels. This situation has long been recognized in occupational epidemiology, where the use of work history records in combination with a job-exposure matrix (based on historical exposure measurements of work areas rather than individuals) is usually considered to be more valid than current exposure measurements (whether based on environmental measurements or biomarkers) if the aim is to estimate historical exposure levels (Checkoway et al. 2004). However, some biomarkers have potential value in validation of questionnaires which can then be used to estimate historical exposures. Furthermore, biomarkers of internal dose may have relatively good validity in studies involving an acute effect of exposure such as the triggering of specific asthma attacks.

A more fundamental problem of measuring internal dose with a biomarker is that it is not always clear whether one is measuring the exposure, the biological effect, or some stage of the disease process itself. Thus the findings may be uninterpretable in terms of the causal association between exposure and disease.

A further major problem with the use of biomarkers is that the resulting expense and complexity may drastically reduce the study size, even in a case-control study, and therefore greatly reduce the statistical power for detecting an association between exposure and disease.

Thus, questionnaires and environmental measurements will continue to play a major role in exposure assessment in asthma epidemiology, but biomarkers may be expected to become increasingly useful over time, as new techniques are developed. The emphasis should be on using "appropriate technology" to obtain the most practical and valid estimate of the etiologically relevant exposure.

The appropriate approach (questionnaires, environmental measurements, or biological measurements) will vary from study to study and from exposure to exposure within the same study (or within the same complex chemical mixture, e.g., in tobacco smoke).

56.4.3 Measuring Causal Mechanisms

The causal mechanisms of asthma are still poorly understood. The focus, until recently, was on atopic immune responses, and epidemiological studies therefore often involved measuring atopy. With the introduction of new techniques such as exhaled NO measurements, sputum induction testing, and exhaled breath condensate measurements, epidemiologists now have a wider range of tools available allowing both atopic and non-atopic immunological mechanisms to be studied more fully in population surveys (rather than in laboratory animals as has traditionally been the case).

56.4.3.1 Atopy

Atopy (as defined above) is both an associated condition and a risk factor for developing *allergic* asthma. In the latter context, atopy can often also be considered as an intermediate factor in the causal pathway leading from allergen exposure to allergic asthma. For example, it might be considered inappropriate to control for atopy in a study of dust mite allergen exposure in infancy and asthma at age 5 years, since the development of atopic sensitization might be considered to be an intermediate stage of the causal process leading from dust mite allergen exposure to asthma symptoms. However, atopy may also modify the effect of dust mite allergen exposure, that is, non-asthmatic atopic persons may be more likely to develop asthma symptoms than non-atopic persons at the same level of dust mite exposure. Also, atopics may be more sensitive to irritant exposures causing non-allergic asthma. Thus atopy may be an intermediate factor and/or a modifier of the effects of other exposures.

A positive response to the application of a specific allergen in skin prick testing reflects the production of specific IgE antibodies to the allergen. Skin prick testing therefore provides a convenient test for atopy in epidemiological studies. Although asthma and atopy are often strongly associated, they also occur independently of each other, and "only" one half of all asthma is attributable to atopy (see Sect. 56.3.1) (Pearce et al. 1999). Serum IgE measurements are another well-accepted and widely used measure to assess atopy or atopic sensitization and have the advantage that a larger panel of allergens can be tested. However, they require venipuncture, which may reduce response proportions. Both skin prick tests and serum IgE measurements provide additional information about the potential immunological mechanisms (atopic versus non-atopic), and in case of atopic asthma, they may provide an indication of the potential causal allergen involved.

56.4.3.2 Exhaled NO

Airway inflammation is often considered a hallmark of asthma, but it is difficult to measure, particularly on the scale required for large population studies. Bronchial biopsy, bronchoalveolar lavage, and induced sputum (see below) can be used, but these methodologies are invasive (with exception of suptum induction), time-consuming, and require highly specialized staff. The measurement of the fraction of nitric oxide in exhaled air (FE_{NO}) has been increasingly recognized as a convenient and cost-effective means of non-invasively assessing atopic airway inflammation in asthma, and several instruments are now available utilizing either chemiluminescent or electrochemical NO measurement technologies.

Increased FE_{NO} has been shown to be associated with disease severity, atopy, airway eosinophilia, and bronchial hyperresponsiveness in asthmatics (Alving et al. 1993; Jatakanon et al. 1998; Berry et al. 2005), and corticosteroid therapy has been shown to decrease FE_{NO} (Kharitonov et al. 1996). More recently, it has been suggested that FE_{NO} measurements can be used to optimize corticosteroid dose without negatively impacting upon asthma control (Pijnenburg et al. 2005). Although measuring FE_{NO} shows promise in the diagnosis and management of asthma, other factors not directly related to asthma such as smoking, atopy, height, and sex affect FE_{NO} levels (Kharitonov et al. 1995; Olin et al. 2006; Taylor et al. 2007; Dressel et al. 2008). Furthermore, increased FE_{NO} levels may only be associated with atopic or eosinophilic asthma, as patients with non-atopic or non-eosinophilic asthma appear to have normal FE_{NO} levels, regardless of disease severity (Porsbjerg et al. 2009). Thus, despite FE_{NO} being used in large population studies, it is a poor single diagnostic marker of asthma as has been demonstrated in community-based population studies (Travers et al. 2007). Nonetheless, FE_{NO} may be used to assess allergic or atopic airway inflammation and may therefore provide additional information on the mechanism underlying asthma.

56.4.3.3 Sputum Induction Testing and Exhaled Breath Condensate

Objective monitoring of a wide range of inflammation markers and mediators in asthmatic subjects can provide important information with regard to underlying mechanisms causing asthma symptoms. Exhaled NO (see above) measures only one aspect of airway inflammation which therefore does not provide a complete picture of the inflammatory responses underlying respiratory allergies and asthma. Initial studies on airway inflammation in asthmatics have relied upon bronchoalveolar lavage taken during bronchoscopy, but this technique is invasive and unsuitable for large-scale epidemiological studies. Sputum induction testing and exhaled breath condensate testing are methods involving non-invasive procedures that have the potential to be used in population-based studies.

Sputum induction involves subjects inhaling a 4.5% saline solution at increasing intervals typically starting at 30s to a total of up to 10 to 12 min (Gibson et al. 2000; Simpson et al. 2006). Lung function is measured in between each inhalation period and subjects given inhaled β_2-beta agonist if their FEV_1 drops below 15 to 20% of baseline. The subjects are asked to cough up any sputum after each dose of

hypertonic saline and samples will be used to analyze cell types and inflammatory markers and mediators (e.g., IL4, IL5, IL8, ECP). These tests can be done in children from age 8 to 10 years and adults but given the laborious procedures involved the population sample size will necessarily be limited. An increasing number of population-based studies are being conducted using sputum induction testing, and these and previous studies have clearly shown that asthma consists of at least two inflammatory phenotypes (see Sect. 56.3.1). Further studies are currently in progress to assess the clinical and epidemiological importance of these findings.

Exhaled breath condensate (EBC) sampling is a technique that has been used to identify inflammatory markers and mediators in a number of respiratory conditions, including asthma, COPD, acute respiratory distress syndrome (ARDS), and cystic fibrosis (Hoffmeyer et al. 2009). EBC collection involves normal tidal breathing into a tube that is cooled by ice, the breath condensing against the tube's inner surface forming a condensate which can then be poured into vials and frozen for future analysis. Breath condensate volume is mainly determined by duration of ventilation, and it takes up to 10 to 20min to obtain 1 to 3mL of condensate which is sufficient for most analyses.

Most of the condensate consists of water vapor, including a number of volatiles that may serve as markers of airway inflammation. In addition, non-volatile substances (i.e., proteins including a number of cytokines) in the lower respiratory tract can be transported in the form of aerosols in exhaled breath. Successful collection of EBC has been reported using a variety of devices including teflon-lined tubing in an ice bath and specially designed double-wall glass condenser systems (Hoffmeyer et al. 2009). EBC has been shown to contain a range of inflammatory markers and mediators, including nitric oxide, hydrogen peroxide, nitrites, eicosanoids, and various cytokines (Kharitonov and Barnes 2006; Hoffmeyer et al. 2009). The significance of breath condensate analyses is that this technique is straightforward, non-invasive, and completely safe and could be widely used in population-based surveys of asthma (including young children in whom more invasive procedures are not possible). However, EBC results have been highly variable between and within laboratories, and further validation work is therefore required before the technique can "routinely" be used in epidemiological studies of respiratory allergies and asthma (Czebe et al. 2008).

56.5 The Global Burden of Respiratory Allergies and Asthma

56.5.1 Time Trends

It has long been suspected that the prevalence of asthma has been increasing not only in industrialized countries but also in developing countries (Pearce et al. 2000b). However, this has been a particularly difficult issue to resolve because of the lack of systematic standardized studies measuring changes in asthma prevalence over time, and some reviewers have argued that the increases in reported prevalence are largely due to increased awareness, labeling and diagnosis of asthma

symptoms (Magnus and Jaakkola 1997). Nevertheless, most studies, which have determined the prevalence of asthma symptoms using the same methodology in the same community at different times, have reported that asthma prevalence has increased in recent decades and that the magnitude of the increase has in some cases been substantial (Table 56.2). Although methodological differences in these studies make it difficult to compare the magnitude of the differences in asthma prevalence between countries, the trend of increasing prevalence among populations in countries of widely differing lifestyles, and ethnic groups is generally consistent.

One of the most informative studies to date is that of Haahtela et al. (1990) who analyzed the medical examination reports of approximately 900,000 conscripts to the Finnish defence forces during 1966–1989, and a proportion of those examined in 1926–1961. During 1926–1961, the prevalence of asthma recorded at call up examinations was in the range of 0.02–0.08%. However, asthma prevalence increased from 0.29% in 1966 to 1.79% in 1989. The authors concluded that the increase was unlikely to be due to improved diagnostic methods and that much of the increase was likely to be real. This conclusion was strengthened by a concomitant rise (from 0.12% in 1966 to 0.75% in 1989) in exemptions and discharges due to asthma. This study is consistent with other evidence that the increases in asthma prevalence in industrialized countries appear to have commenced after the Second World War, particularly in the 1960s and 1970s.

Thus, until recently, most studies had reported that asthma prevalence has increased in recent decades and that the magnitude of the increase had in some cases been substantial.

However, several recent studies have reported either no increase or even a decrease in asthma prevalence over the last ten years. For instance, Bollag et al. (2005) examined time trends in consultations for asthma in primary care in Switzerland and found that overall consultation rates for asthma increased from 1989 to 1994, then stabilized and have declined since 2000. The observation that asthma incidence might be falling is in agreement with several other studies that showed similar time trends for asthma and hay fever (Pearce and Douwes 2005). The best indication of what is currently happening globally is provided by the Phase III of the International Study on Asthma and Allergies in Children (ISAAC); the results of which are discussed below.

The causes of the international time trends in the prevalence of asthma are unclear and are currently a major focus for asthma epidemiology worldwide. An important component of this research process involves standardized international prevalence comparisons (Pearce et al. 1998a). The key problem is to gain information on large numbers of people in random samples collected in a comparable manner across social groups, regions, and countries. Thus, comparisons of asthma prevalence are increasingly being based on a simple comparison of symptom prevalence in a questionnaire survey in a large number of people, followed by more intensive testing of factors related to asthma (e.g., BHR) and risk factors for asthma (skin prick test positivity, serum IgE, and environmental exposures) in a subsample, and a repeat of the prevalence survey over time. This approach has been used in the international

Table 56.2 Changes in asthma prevalence in children and young adults

		Asthma prevalence		
Country	Period	1st study	2nd study	Reference
Australia	1964–1990	19.1%	46.0%	Robertson et al. (1991)
	1982–1992	10.4%	28.6%	Robertson et al. (2004)
	1992–2002	28.6%	23.7%	
	1987–1992	5.6%	9.3%	Campbell et al. (1992)
	1992–1995	9.3%	11.4%	Adams et al. (1997)
	1993–2002	27.2%	20.2%	Robertson et al. (2004)
Canada	1980–1983	3.8%	6.5%	Infante-Rivard et al. (1987)
	1980–1990[c]	140/10,000	256/10,000[a]	Manfreda et al. (1993)
		125/10,000	254/10,000[b]	
England	1956–1975	1.8%	6.3%	Morrison Smith (1976)
	1966–1990	18.3%	21.8%	Whincup et al. (1993)
	1973–1986	2.4%	3.6%	Burney et al. (1990)
	1978–1991	11.1%	12.8%	Anderson et al. (1994)
England and Wales	1970–1981	11.6%	20.5%[a]	Fleming and Crombie (1987)
		8.8%	15.9%[b]	
Finland	1961–1986	0.1%	1.8%	Haahtela et al. (1990)
France	1968–1982	3.3%	5.4%	Perdrizet et al. (1987)
Germany	1991/2–1995/6	3.7%	4.1%	von Mutius et al. (1998)
Israel	1986–1990	7.9%	9.6%	Auerbach et al. (1993)
Italy	1983–1993/5	2.9%	4.4%	Ciprandi et al. (1996)
Japan	1982–1992	3.3%	4.6%	Nishima (1993)
Netherlands	1989–1993	13.4%	13.3%	Mommers et al. (2005)
	1993–1997	13.3%	11.9%	
	1997–2001	11.9%	9.1%	
New Zealand	1969–1982	7.1%	13.5%	Mitchell (1983)
	1975–1989	26.2%	34.0%	Shaw et al. (1990)
Papua New Guinea	1973–1984	0.0%	0.6%	Dowse et al. (1985)
Scotland	1964–1989	10.4%	19.8%	Ninan and Russell (1992)
	1989–1994	19.8%	25.4%	Omran and Russell (1996)
Spain	1994–2003	9.3%	9.3%	Garcia-Marcos et al. (2004)
Sweden	1971–1981	1.9%	2.8%	Aberg (1989)
	1979–1999	2.5%	5.7%	Aberg (1989)
Tahiti	1979–1984	11.5%	14.3%	Liard et al. (1988)
Taiwan	1974–1985	1.3%	5.1%	Hsieh and Shen (1991)
United Kingdom	1991–1998	33.9%	27.5%	Anderson et al. (2004)
USA	1964–1983[d]	183/100,000	284/100,000	Yunginger et al. (1992)
	1971–1976	4.8%	7.6%	Gergen et al. (1988)
	1981–1988	3.1%	4.3%	Weitzman et al. (1992)
	1983–1992	9.2%	15.9%	Farber et al. (1997)
Wales	1973–1988	4.0%	9.0%	Burr et al. (1989)

[a]Men
[b]Women
[c]Prevalence per 10,000 subjects
[d]Incidence rates per 100,000 subjects

survey of asthma prevalence in adults (Burney et al. 1994) and in the International Study of Asthma and Allergies in Childhood (Pearce et al. 1993; Asher et al. 1995; Ellwood et al. 2005).

56.5.2 The European Community Respiratory Health Survey (ECRHS)

In the European Community Respiratory Health Survey (ECRHS), a representative sample of 3,000 adults in each center, aged 20 to 44 years, completed a Phase I screening questionnaire seeking information on asthma symptoms and medication use (Burney et al. 1994). Individuals answering "yes" to waking with an attack of shortness of breath, an attack of asthma, or current asthma medications were defined as "asthmatic." A random subsample of 600 subjects and an additional sample of up to 150 "asthmatic" individuals in each center were then studied in more detail in Phase II, with measurements of skin prick tests to common allergens, serum total, and specific IgE and bronchial responsiveness to inhaled methacholine, as well as an additional questionnaire on asthma symptoms and medical history, occupation and social status, smoking, the home environment, and the use of medications and medical services. The Phase I results (Burney et al. 1996) included data from 48 centers, predominantly in Western Europe, with only 9 centers from 6 countries (Algeria, Iceland, India, New Zealand, Australia, USA) being from outside of Europe. Phase II was conducted in 37 centers in 16 countries (Burney et al. 1996).

56.5.3 The International Study of Asthma and Allergies in Childhood (ISAAC)

The International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al. 1995; Ellwood et al. 2005) had a similar study design compared to that of the ECRHS study, with a simple Phase I survey and a more in-depth Phase II survey. However, in order to obtain the maximum possible participation across the world, Phase I (which was conducted in 155 centers in 56 countries) was separated from Phase II (which was conducted in a smaller number of centers), and the Phase I questionnaire modules were designed to be simple and inexpensive to administer. In addition, a video presentation of clinical signs and symptoms of asthma was developed (Shaw et al. 1995) in order to minimize translation problems. The population of interest was school children aged 6 to 7 years and 13 to 14 years within specified geographical areas. The Phase I findings, involving more than 700,000 children, showed striking international differences in asthma symptom prevalence (Asher et al. 1998; Beasley et al. 1998). Figure 56.1 shows the international patterns of 12-month period prevalence of wheezing in 13 to 14-year-olds (based on the question "have you had wheezing or whistling in the chest *in the last 12 months*?").

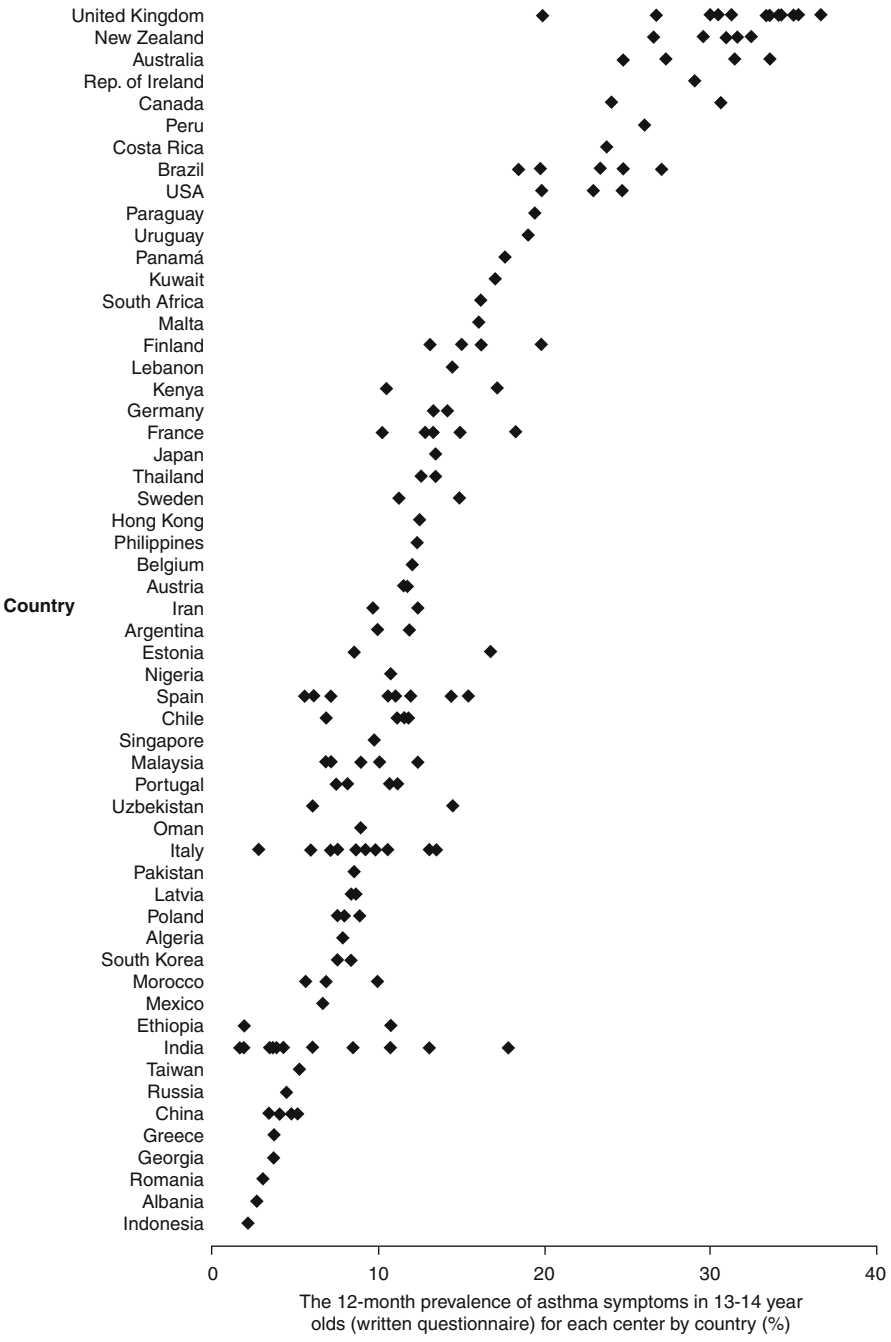

Fig. 56.1 Wheeze in the previous 12 months for each center by country ordered according to the mean prevalence for all centers in the country (Source: Beasley et al. 1998)

ISAAC Phase II was conducted in 30 centers in 22 countries and involved parental questionnaires ($n = 54{,}439$), skin prick tests ($n = 31{,}759$), and serum IgE measurements ($n = 8{,}951$). House dust samples to measure indoor allergens were also collected (Weinmayr et al. 2007).

Phase III involved a repeat of the Phase I survey after 5 to 10 years in 106 centers in 56 countries in children aged 13 to 14 years ($n = 304{,}679$) and in 66 centers in 37 countries in children aged 6 to 7 years ($n = 193{,}404$) (Asher et al. 2006; Pearce et al. 2007).

56.5.4 What Do the ECRHS and ISAAC Studies Show?

The ISAAC and ECRHS studies provide, for the first time, a picture of global patterns of asthma prevalence and identify the key phenomena which future research must address and attempt to explain.

Firstly, both studies show a particularly high prevalence of reported asthma symptoms in English-speaking countries (Fig. 56.1), that is, the British Isles, New Zealand, Australia, the United States, and Canada (Burney et al. 1996; Asher et al. 1998). This appears to be unlikely to be entirely due to translation problems, since the same pattern was observed with the ISAAC video questionnaire (Asher et al. 1998).

Secondly, the ISAAC survey showed that centers in Latin America also had particularly high symptom prevalence (Fig. 56.1). This finding is of particular interest in that the Spanish-speaking centers of Latin America showed higher prevalences than Spain itself, in contrast to the general tendency for more affluent countries to have higher prevalence.

Thirdly, among the non-English-speaking European countries, both studies show high asthma prevalence in Western Europe, with lower prevalences in Eastern and Southern Europe. For example, in the ISAAC survey, there is a clear northwest-southeast gradient within Europe, with the highest prevalence in the world being in the United Kingdom and some of the lowest prevalences in Albania and Greece (Asher et al. 1998). The west-east gradient was particularly strong; in particular, there was a significantly lower prevalence in the former East Germany than in the former West Germany.

Fourthly, Africa and Asia generally showed relatively low asthma prevalence (Fig. 56.1). In particular, prevalence was low in developing countries such as China and Indonesia, whereas more affluent Asian countries such as Singapore and Japan showed relatively high asthma prevalence. Perhaps the most striking contrast is between Hong Kong and Guangzhou which are close geographically and involve the same language and predominant ethnic group; Hong Kong (the more affluent city) had a 12-month period prevalence of wheeze of 10.1%, compared with 2.0% in Guangzhou (the less affluent city).

Fifthly, in contrast to the asthma findings, the highest prevalences of rhinitis symptoms were reported from centers scattered throughout most regions of the world, including Western Europe, Africa, North America, and Southeast Asia; the

highest prevalences of eczema were generally in centers of high latitude, including Scandinavia and New Zealand, although there were some notable exceptions including some centers in South America and Africa (Ethiopia). Thus, although the prevalences of these conditions were correlated, the association was not particularly strong, and there were numerous centers which had high prevalence for asthma but not for rhinitis and/or eczema, and vice versa, suggesting that the major risk factors are different for these related disorders or that they involve different latency periods and time trends.

Sixthly, the ISAAC Phase II study showed that the link between atopic sensitization and asthma symptoms differed strongly between populations and increased with economic development (Weinmayr et al. 2007); the association between atopy and flexural eczema was also weak and positively linked to gross national income (Flohr et al. 2008).

Finally, asthma prevalence has peaked or even begun to decline in many affluent countries, whereas asthma symptom prevalence continues to rise in less affluent countries. In particular, ISAAC Phase III showed that international differences in asthma symptom prevalence have reduced, particularly in 13- to 14-year-olds, with decreases in prevalence in English-speaking countries and Western Europe and increases in prevalence in regions where prevalence was previously low including Africa, Latin America, and parts of Asia (Fig. 56.2) (Asher et al. 2006; Pearce et al. 2007). Similarly, Phase II of the European Respiratory Health Survey (ECRHS) found no further increase in current or severe asthma symptoms (Chinn et al. 2004). Nonetheless, a significant increase in diagnosed asthma was observed which most likely reflects changes in diagnostic labeling and/or medical treatment for mild and/or moderate asthma (Weiland and Pearce 2004). The asthma symptom prevalence increases in Africa, Latin America, and parts of Asia indicating that the global burden of asthma is continuing to rise, but the global prevalence differences are lessening.

56.6 Causes of Respiratory Allergies and Asthma

56.6.1 Risk Factors

56.6.1.1 Genetic Factors

Asthma is multifactorial in origin and influenced by multiple genes and environmental factors. Thus, it is not inherited in the simple Mendelian fashion that is characteristic of single-gene disorders. A particular genetic factor may affect one or more aspects of the complex etiological processes potentially involved in asthma including atopic sensitization, bronchial hyperresponsiveness (BHR), airway inflammation, innate immunity, etc. Whether this genetic potential is expressed will depend on various factors, including whether sufficient exposure to environmental factors occurs. Investigating possible genes for the individual etiological factors is also fraught with difficulties, since control of these factors (e.g., IgE production and BHR) are also multifactorial (Zamel et al. 1996).

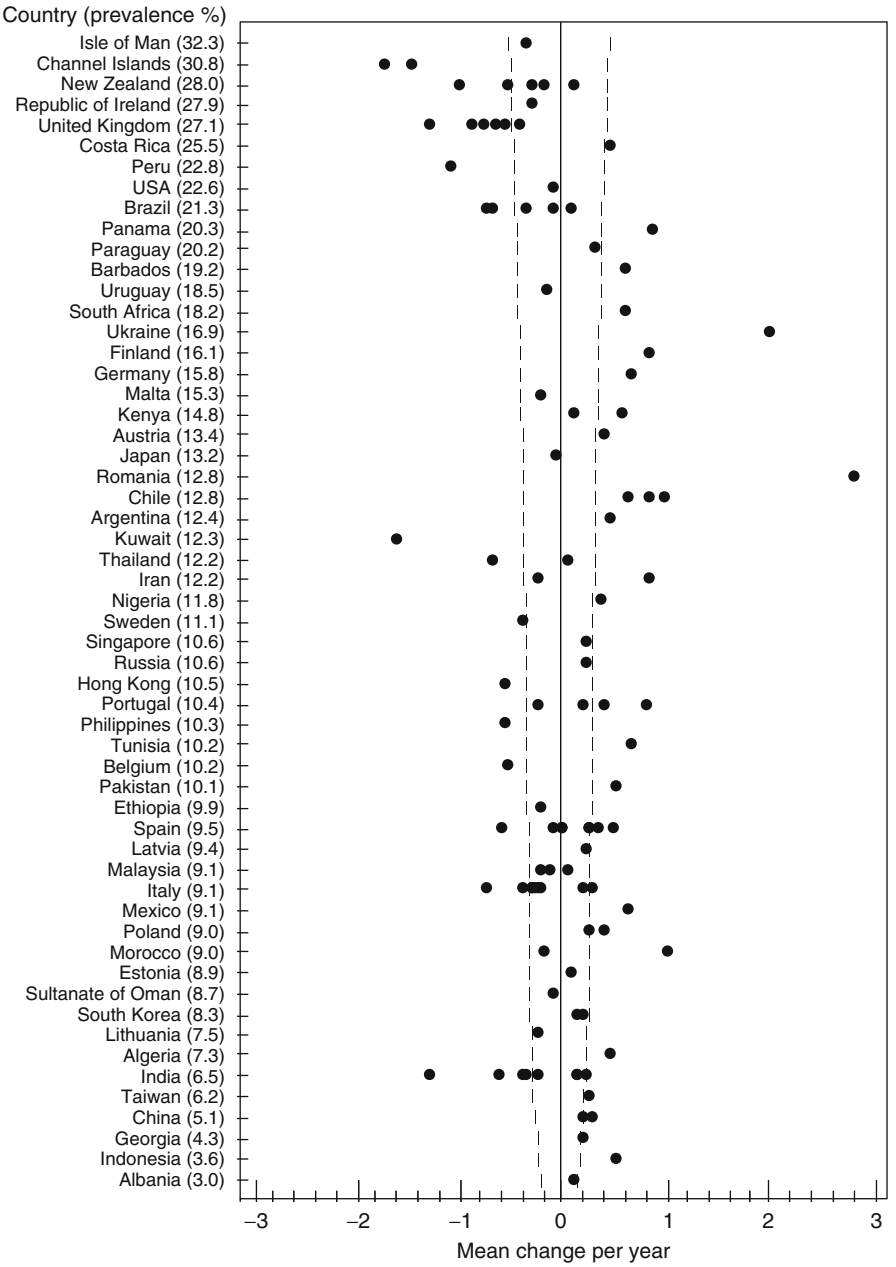

Fig. 56.2 Ranking plot showing the change per year in prevalence of current wheeze (wheeze in the last 12 months) in 13- to 14-year-old children for each center by country, with countries ordered by their average prevalence (for all centers combined) across Phase I and Phase III [the plot also shows the confidence interval about zero change for a given level of prevalence (i.e., the average prevalence across Phase I and Phase III) given a sample size of 3,000 and no cluster-sampling effect] (Source: Pearce et al. 2007)

Also, as noted earlier, asthma is an extremely heterogeneous disease including a variety of phenotypical and clinical manifestations which are likely to be associated with different (combinations of) genes. Another potential source of phenotypic variability is that asthma development, exacerbations, and progression may involve different environmental triggers and genetic factors.

Nonetheless, it is well established that people with a family history of asthma are more likely to develop asthma themselves, and parental asthma is a stronger predictor of asthma in the offspring than parental atopy. However, this association is not necessarily due only to genetic factors but could also reflect similar lifestyles and exposures in family members (Sandford et al. 1996).

Some indication of the possible contribution of genetic factors in asthma is given by studies of twins. For example, Edfors-Lubs (1971) analyzed data on 7,000 twin pairs from the Swedish Twin Registry and found that concordance of asthma in monozygotic twins was greater than in dizygotic twins. However, the concordance was still only 19%, and even this may in part be due to similar environmental exposures in monozygotic twins, including a common intrauterine environment (Godfrey et al. 1994). Other large population studies have yielded similar findings, but this may be because these studies have determined asthma on the basis of questionnaires or hospital and pharmacy records, whereas smaller studies with more intensive diagnostic methods have generally yielded higher concordance (Sandford et al. 1996).

Recent genome-wide association studies (GWAS) including two meta-analyses (GABRIEL and EVE consortia; Moffatt et al. 2010; Ober and Yao 2011) have shown a number of loci that were consistently associated with asthma. However, these associations were relatively weak and the genetic variants very common. As a result, despite these associations being highly statistically significant, the sensitivity and specificity for identifying asthmatics based on these genetic variants was poor (Ober and Yao 2011). Also, many "asthma genes" previously indentified in candidate gene association studies (using a hypothesis-driven approach) were not replicated in these large GWAS meta-analyses. This may be because GWAS studies are not able to detect some of the rarer variants (Michel et al. 2010), or, alternatively, the previously indentified candidates may be false-positive results. Whatever the reason, it is clear that our knowledge of the genetics of asthma is currently still very limited, but future GWAS for asthma on well-defined asthma phenotypes may shed some more light on the importance of genetics in the development of asthma.

56.6.1.2 Demographic Factors

There are a variety of demographic factors which are associated with asthma including age (Anderson et al. 1992), sex (Anderson et al. 1992), and ethnicity (Pattemore et al. 2004). Age is the demographic factor which is most strongly related to asthma symptom prevalence, with symptoms usually declining at or before the onset of puberty (Kimbell-Dunn et al. 1999).

Asthma incidence and prevalence are consistently lower in females than in males before age 12 years, whereas during adolescence and adulthood there is evidence

of higher incidence and prevalence in females (Kimbell-Dunn et al. 1999). One possible explanation is that the average age of onset in childhood and adolescence may be later in females. Levels of cord blood IgE are lower at birth in girls than in boys (Weeke 1992), indicating a lower risk of the subsequent development of asthma. Some authors have noted that boys have smaller airways than girls, relative to lung size, and that this may explain the greater frequency and severity of lower respiratory tract illness in boys, even though infection rates are similar for both sexes (Martinez et al. 1988). Alternatively, it is possible that boys have more exposure to factors that increase asthma incidence or duration. The relatively higher prevalence (or smaller reduction in prevalence) in females than in males after puberty could be due to hormonal influences on allergic predisposition, airway size, inflammation, and smooth muscle vascular functions (Redline and Gold 1994). Premenstrual asthma may be especially relevant to the hormonal involvement of asthma since it may not only cause asthma exacerbations but may thereby affect the frequency and duration of asthma symptoms, resulting in an increase in the prevalence of "current asthma."

Studies in the 1960s and 1970s suggested that asthma is more common in children in the higher social classes. There has been less evidence of social class differences as the diagnosis of asthma has become more widespread (Littlejohns and Macdonald 1993), even though diagnostic labeling of wheezing in adults differs by social class (Littlejohns et al. 1989). However, severe asthma appears to be more common in children in the lower social classes (Stewart et al. 2001) and in some disadvantaged ethnic groups (Pattemore et al. 2004), and low socioeconomic status is associated with hospital admissions for asthma (Watson et al. 1996) and with reduced lung function in adults. This could represent either a greater prevalence of asthma in disadvantaged groups, or increased severity due to environmental factors (e.g., environmental tobacco smoke, nutrition, occupational exposures) (Eagan et al. 2002; Ellison-Loschmann et al. 2007), or inadequate disease management and poor access to health care (Ellison-Loschmann and Pearce 2006).

56.6.1.3 Obesity

The specific mechanisms linking body weight and asthma are unclear, but several have been proposed including (1) common etiologies, (2) comorbidities, (3) mechanical factors, and (4) adipokines, that is, cytokines secreted by adipose tissue (Shore 2007). Like asthma, the prevalence of overweight and obesity has increased dramatically in the past few decades in many regions of the world (Burney 2002). Studies have shown associations between body weight and asthma in both adults (Braback et al. 2005) and children (von Mutius et al. 2001). Prospective studies of children suggest that obesity precedes asthma signaling a causal link (Gilliland et al. 2003; Gold et al. 2003), as do studies showing associations between asthma and both weight gain and weight loss in adults (Hakala et al. 2000). Nonetheless, some studies have failed to show an association (Brenner et al. 2001), while others showed an association only in one sex (Mannino et al. 2006). Several reported an association only with respiratory symptoms (e.g., wheeze), but not BHR (Bustos et al. 2005), although this may merely indicate that obesity increases asthma risk

through mechanisms other than BHR. Obesity may also increase severity in subjects with preexisting asthma (Akerman et al. 2004).

56.6.1.4 Diet

Many studies have investigated the effects of breast-feeding on allergies and asthma with some studies showing protective effects, some showing no effect, and others suggesting that breast-feeding is a risk factor (Friedman and Zeiger 2005). A recent longitudinal study found that exclusive breast-feeding was associated with a slightly reduced risk of asthma and atopy at age 7, but an increased risk at age 14 and 44 (Matheson et al. 2007). Another infant cohort study showed that breast-feeding did not protect against atopy and asthma but even increased the risk at age 9 to 26 years (Sears et al. 2002). A cluster randomized trial reported similar findings for allergies and asthma at age 6.5 years (Kramer et al. 2007).

Other nutritional factors may also play a role in the etiology of asthma. In particular, it has been speculated that the increase in asthma prevalence may be due to a change in dietary patterns in the past few decades, that is, as cultures have become more "westernized," they have shifted from a tradition of growing and consuming locally grown foods to consuming more processed foods with an overall increase in the intake of refined sugars, fats, and additives, as well as a reduction in the intake of fresh fruits, vegetables, and fish. Several observational studies have shown protective effects of fruit and vegetables, whole grain products, and fish (Devereux 2007), and these findings are consistent with an ecological analysis of the ISAAC Phase I survey (Ellwood et al. 2001). Fruit, vegetables, and wholegrain products are rich in antioxidants and may reduce airway inflammation by protecting the airways against both endogenous and exogenous oxidants (Devereux 2007). Fish oils are rich in n-3 polyunsaturated fatty acids which may also protect against airway inflammation and subsequent symptoms of asthma (Devereux 2007). However, dietary supplement studies focusing on antioxidants and n-3 fatty acids have not shown convincing evidence of a protective effect on allergies and asthma (Reisman et al. 2006; Almqvist et al. 2007).

56.6.1.5 Outdoor Air Pollution

The role of outdoor air pollutants (particulate matter, ozone, nitrogen dioxide, and sulfur dioxide) in asthma and other diseases has been extensively studied and debated. An association between measures of distance to major roads or traffic density and asthma symptoms has been found in a number of European countries (WHO 2005). Also, a large number of studies have reported associations between direct measurements of air pollution levels and exacerbation of preexisting asthma, both in children and adults (Boezen et al. 1999; WHO 2005). Some studies, including a recent birth cohort study (Brauer et al. 2007), have also suggested that air pollution may cause *new onset* of asthma and allergic disease. In particular, several large prospective studies have suggested a role for ozone (McDonnell et al. 1999; McConnell et al. 2002), although significant associations with some asthma outcomes were also shown for PM2.5, soot, and NO_2 (Brauer et al. 2007). Nonetheless, although it is clear that air pollution can provoke exacerbations in

preexisting asthma and a positive association between outdoor air pollution and asthma prevalence at the population level has been shown (Asher et al. 1998), the weight of evidence does not currently support a *major* role for outdoor air pollution as a cause of the initial development of asthma.

56.6.1.6 Indoor Air Pollution

Little is currently known about the contribution of indoor air pollutants (other than environmental tobacco smoke) to the incidence and prevalence of asthma. The range of potential pollutants is large, the determinants of ambient levels involve a complex interaction of lifestyle and building factors, and precise measurement of airborne concentrations is difficult. Nitrogen dioxide from burning fossil fuels has received by far the most attention, while sulfur dioxide from burning sulfur-containing coal or gas, mosquito coil smoke, and formaldehyde from wood preparation have also been considered. Particulates from open or closed wood and coal burning fires have received less attention in developed countries but have been studied in developing countries where very high indoor levels have been encountered.

Damp indoor environments and indoor fungal exposure may also play a role as demonstrated in a large number of studies conducted across many geographical regions (Douwes and Pearce 2003). However, although it has been concluded that the evidence for a causal association between dampness and respiratory morbidity is strong, it is not clear whether indoor dampness *causes* or "only" *exacerbates* preexisting respiratory conditions such as asthma (Douwes and Pearce 2003).

56.6.1.7 Tobacco

Similarly, the evidence for a role of tobacco smoke in asthma is strongest for increases in severity in children who already have asthma, whereas the evidence for the initial occurrence of asthma (incidence) is less conclusive. In particular, several recent reviews and meta-analyses differ in their conclusions about the role of second-hand tobacco smoke (SHS). The US Environmental Protection Agency (EPA) and Californian EPA concluded that SHS was causally associated with the development of asthma in children (EPA 1992; OEHHA 1997). The 2006 Surgeon General's report on "health effects from involuntary exposure to tobacco smoke" (DHHS 2006) concluded that the evidence was suggestive, but not sufficient to infer a causal relationship. This analysis was based on a previous meta-analysis conducted by Strachan and Cook (1998) and did not include the most recent epidemiological studies. However, the more recent meta-analysis including studies published between 1970 and 2005 concluded that household SHS exposure was positively and consistently associated with the incidence or new onset asthma (Vork et al. 2007) not only in younger but also older children.

The evidence on active smoking as a risk factor is also conflicting with some studies reporting only exacerbations (Siroux et al. 2000), whereas others have also documented a dose-related risk of new-onset asthma in adolescents and adults (Eagan et al. 2002). Overall, it therefore appears that environmental tobacco smoke

is a cause of asthma exacerbations and that in addition it may also be involved in the development of asthma itself.

56.6.1.8 Occupational Exposures

Occupational asthma (OA) is the most common occupational respiratory disease in developed countries. For example, asthma accounted for 28% of cases reported to the United Kingdom surveillance of work-related and occupational respiratory diseases (SWORD) project (Meredith et al. 1991). Estimates of the total proportion of adult asthma which is thought to be occupational in origin range from 2 to 15% in the United States (Chan-Yeung and Malo 1994), 15% in Japan (Chan-Yeung and Malo 1994), 5% in Spain (Kogevinas et al. 1996), 2% to 3% in New Zealand (Fishwick et al. 1997), and 2% to 6% in the United Kingdom (Meredith and Nordman 1996). However, much higher estimates have also been reported. For example, a study of the entire employed population of Finland from 1986 to 1998 estimated the attributable fraction of adult-onset asthma due to occupation to be 29% for men and 17% for women (Karjalainen et al. 2001). More than 250 agents have been identified as causes of OA (Department of Health and Senior Services, State of New Jersey 2006). Some of the most common occupational asthmagens include flour/grain dusts, wood dusts, latex allergens, and isocyanates.

56.6.1.9 Respiratory Viruses

Viral infections are common causes of exacerbations of asthma (Johnston et al. 1995). In fact, respiratory viral infections are detected in the majority of asthma exacerbations (80% to 85% in children and 75% to 80% in adults); of these, about 60% are rhinoviruses (Johnston 2007). There is also a strong association between viral infections and hospital admission for asthma in both children and adults.

Viral infections may also be involved in the development of asthma, but the evidence is less clear. Several long-term longitudinal studies have shown that respiratory syncytial virus (RSV) infections increase the risk of subsequent recurrent wheezing and asthma in early childhood (Stein et al. 1999; Sigurs et al. 2005). However, this risk may progressively decrease with increasing age (Stein et al. 1999). Other viruses have also been associated with asthma development including human rhinovirus (HRV) which may in fact be a more important risk factor than RSV (Lemanske et al. 2005). The mechanisms of viral-induced asthma are poorly understood, but it has been speculated that impaired innate immune responses may play a crucial role (Johnston 2007).

56.6.1.10 Medications

Antibiotics The "hygiene hypothesis" postulates that growing up in a more hygienic environment with less microbial exposure may increase the risk of allergies and allergic asthma (see Sect. 56.6.3). A corollary of the hygiene hypothesis is that antibiotic use may increase the risk of asthma by reducing the protective effect of bacterial infections and/or disruption of the normal gut bacterial flora (Farooqi and Hopkin 1998; Mendall and Kumar 1998). However, the epidemiological evidence

of an association between exposure to antibiotics (as well as infection) and the development of asthma has been conflicting (Celedon et al. 2002; Cohet et al. 2004; Kummeling et al. 2007).

One of the first reports was that of Farooqi and Hopkin (1998) who found significant associations between treatment with oral antibiotics in the first two years of life and subsequent asthma, hay fever, and eczema at age 12 to 20 years in Oxfordshire. The association was stronger for infections treated with broad-spectrum antibiotics and increased with the number of antibiotic courses received. McKeever et al. (2002a) found that antibiotic exposure in early life was associated with an increased risk of asthma diagnosis, but the association was reduced when the data were adjusted for consulting behavior. They also reported that exposure to antibiotics in utero was associated with a dose-related increase in the child's risk of asthma, hay fever, and eczema (McKeever et al. 2002b). However, Celedon et al. (2004) found no significant association between antibiotic use in the first year of life and the subsequent development of asthma, allergic rhinitis, or eczema at age 5 years. Wjst et al. (2001) found a dose-dependent association of antibiotic use with asthma diagnosis in children aged 5 to 14 years. However, the authors suggested that their findings may be due to reverse causation.

More recently, Foliaki et al. (2009) analyzed the ISAAC Phase III data (see Sects. 56.5.3 and 56.5.4) and found that the reported use of antibiotics in the first year of life was associated with parental-reported symptoms of asthma in 6 to 7-year-old children, following adjustment for other asthma risk factors. The association was present in all major regions of the world (with the possible exception of Africa). Similar associations were observed between the use of antibiotics in the first year of life and the risk of severe asthma symptoms and "asthma ever." Weaker (but still statistically significant) associations were also observed for symptoms of rhinoconjunctivitis and eczema.

Paracetamol It has been reported that prenatal paracetamol (or acetaminophen) use during pregnancy was a risk factor for asthma, wheezing, and total IgE in the offspring at 6 to 7 years of age (Shaheen et al. 2002, 2005) which was unlikely to be confounded by unmeasured behavioral factors linked to paracetamol use (Shaheen et al. 2010). Similarly, several cross-sectional and longitudinal studies have reported that paracetamol use was associated in a dose-dependent manner with an increase in asthma in children and adults and also new-onset asthma in adults (Shaheen et al. 2000, 2008; Barr et al. 2004). Furthermore, national per capita consumption of acetaminophen was ecologically associated with the prevalence of wheeze, diagnosed asthma, and bronchial hyperresponsiveness in Western Europe (Newson et al. 2000).

In the ISAAC Phase III data (see Sects. 56.5.3 and 56.5.4), the reported use of paracetamol for fever in the first year of life was associated with an increased risk of current asthma symptoms (Beasley et al. 2008). There was a dose-dependent increased risk of current asthma symptoms. However, the association was weaker than that observed for antibiotic use in the same data set (see above; Foliaki et al. 2009), and the association reduced (from 1.77 to 1.46) when adjusted for antibiotic use and

other asthma risk factors, indicating that the elevated risk was, at least in part, due to confounding. In particular, it has been suggested that the observed association is due to confounding by indication or reverse causation (Lowe et al. 2009).

However, confounding by indication or reverse causation are unlikely to fully explain the positive associations in birth cohort studies (Shaheen et al. 2002, 2005, 2010), and longitudinal studies in adults that focused on new-onset asthma (Barr et al. 2004). The underlying mechanisms are unclear, but it has been suggested that paracetamol decreases glutathione levels in the lung, which may predispose to oxidative injury, bronchospasm, and an increased Th_2 response (Shaheen et al. 2002). Interestingly the use of paracetamol has increased considerably (replacing aspirin) in the 1970s and 1980s (Varner et al. 1998) suggesting that the increased use of paracetamol may account for some of the increasing prevalence of childhood asthma.

56.6.1.11 Allergens

Indoor allergens, particularly house dust mite allergens, are perhaps the group of possible asthma risk factors that have received the greatest attention. It is well established that in sensitized asthmatics, allergen exposure can trigger asthma attacks and that prolonged exposure can lead to the prolongation and exacerbation of symptoms. However, most studies in children show only weak associations between allergen exposure and current asthma, even when the analyses are restricted to atopic patients and allergen avoidance has been accounted for (Pearce et al. 2000c). Also, secondary intervention trials have had mixed results (Gotzsche et al. 1998).

In fact, although there is good evidence for asthma exacerbations, the evidence for new onset asthma is much weaker (Pearce et al. 2000c). The key study linking allergen exposure in infancy to the subsequent development of asthma is that of Sporik et al. (1990) who followed 67 children with a family history of atopy. They found an association between dust mite allergen levels and mite sensitization and an association between exposure to more than 10ug/g in the first year of life and a history of wheezing, although this association was not statistically significant (odds ratio (OR) = 2.3, p = 0.17). There were non-significant associations of dust mite levels with "active wheezing and BHR" ($p = 0.08$) and with "receiving medication" ($p = 0.10$).

More recent longitudinal birth cohort studies have found little or no association between early dust mite allergen exposure and asthma later in childhood (Burr et al. 1993; Corver et al. 2006; Tepas et al. 2006). For example, Burr et al. (1993) conducted a longitudinal study among 453 infants in South Wales with a family history of allergic diseases. Doctor diagnosed asthma and wheezing at age 7 years was neither associated with mite allergen exposure as determined in the first 12 months nor with dust mite levels measured at 7 years of age (odds ratios were not given). Similarly, in the German Multicentre Allergy Study, levels of mite and cat allergens in early life remained strongly related to specific sensitization at age 3 to 7 years, but no dose-response relationship between allergen exposure and any measure of asthma/wheeze at 7 years of age was found (Lau et al. 2000, 2002). Dust mite allergens are therefore unlikely to play a major role in the initial development of asthma.

There are several other indoor and outdoor allergens that have been suggested to be associated with the development of asthma including cat, dog, cockroach, and *Alternaria* allergens. However, the evidence for a causal relationship is even weaker than for house dust mite allergens (Pearce et al. 2000c). In fact, several studies have even reported that having a pet early in life protects against the development of asthma (see Sect. 56.6.3).

56.6.1.12 Emotional Stress

Until the second half of the twentieth century, the predominant view was that asthma was a psychosomatic disorder in which emotional stress was the key factor in its etiology; the condition was therefore commonly referred to as "asthma nervosa" (Salter 1860). With the recognition of causal environmental exposures such as pollen (Blackley 1873) and house dust (Osler 1892) in the latter half of the nineteenth century and the increased understanding of the inflammatory mechanisms underlying asthma in the second half of the twentieth century (Holgate 2004), the notion that asthma was caused by emotional stress slowly lost support. Thus, many asthma researchers currently regard emotional stress as predominantly a consequence of the disease or as an external factor which may trigger exacerbations in those with preexisting asthma. Associations between stress/anxiety and asthma in (cross-sectional) epidemiological studies are therefore generally dismissed as examples of reverse causation. However, several prospective studies in young children and adults suggest that this assumption may not be justified (Douwes et al. 2010, 2011).

A recent birth cohort in 5,810 children aged 7.5 years showed a strong association between prenatal maternal anxiety symptoms (as an indicator of stress during fetal life) and asthma prevalence at 7.5 years (Cookson et al. 2009). Children of mothers in the highest quartile of anxiety scores were 64% more likely to have asthma compared with those in the lowest quartile ($OR = 1.64$, 95% confidence interval (CI) = 1.25–2.17). Postnatal anxiety was not associated with asthma when adjusted for prenatal anxiety, suggesting that the prenatal period may be particularly critical.

The effects of stress/anxiety may not be limited only to early life events. For example, a 13-year follow-up study which assessed the associations between war-related stressors and new onset asthma in 2,066 elderly (50 to 69 years) Kuwaiti civilians following the Iraqi invasion in 1990 and the subsequent 7-month occupation found a dose-response relationship with asthma incidence (assessed as a self-reported doctor diagnosis of asthma), after adjusting for potential confounders including air pollution related to burning oil fires (Wright et al. 2010). The highest stress level more than doubled the risk of new onset asthma ($OR = 2.3$, 95% CI = 1.3–3.9).

The mechanisms underlying the association between stress and asthma remain far from clear. Several studies have suggested that stress acts principally through altered regulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenomedullary (SAM) nervous system (Vig et al. 2006). The subsequent change in levels of neurohormones (and in particular endogenous

glucocorticoids) has considerable immunomodulatory effects, including an atopy (or Th_2)-biased response favoring allergic outcomes (von Hertzen 2002). In addition to neuroimmunomodulatory effects, it is plausible that direct neurogenic mechanisms may underlie at least part of the association between stress and asthma (Miller et al. 2009).

56.6.2 Can the Traditional Risk Factors Explain the International Patterns and Time Trends?

Although there is substantial evidence that various environmental risk factors can increase the risk of developing asthma, there is little evidence that the traditional risk factors can account for the global prevalence increases or the international prevalence patterns that have been observed. The increases in asthma prevalence cannot be due to genetic factors, since they are occurring too rapidly, and the rapidity of the increases indicates that genetic factors alone are unlikely to account for a substantial proportion of asthma cases (Douwes and Pearce 2002), although genetic susceptibility to changing environmental exposures may play an important role.

The global patterns of asthma prevalence are also inconsistent with the hypothesis that air pollution is a major risk factor for the development of asthma (Asher et al. 1998, 2006; Beasley et al. 1998). Regions such as China and Eastern Europe where there are some of the highest levels of traditional air pollution such as particulate matter and SO_2 generally have lower asthma prevalence than the countries of Western Europe, North America, Australia, and New Zealand which have lower levels of pollution. It also appears very unlikely that the international prevalence patterns can be explained by differences in smoking (Mitchell et al. 2002) or in occupational exposures.

Allergen exposure is the risk factor that has perhaps received the most attention as a possible cause of the global increases in prevalence of asthma and allergies. In particular, it has been suggested that increases in indoor allergen exposures, through changes in lifestyle such as wall-to-wall carpeting, cold water washing, greater time spent indoors watching television, etc., could account for the global increases in asthma prevalence (Sporik et al. 1990). However, the only study of English homes at two time points (1979 and 1989) did not find any change in house dust mite allergen levels (Butland et al. 1997), although marked increases have been observed in Australian studies (Peat et al. 1996).

The ISAAC (Asher et al. 1998) and ECRHS studies (Burney et al. 1996) have consistently found uniformly high levels of asthma prevalence in centers in English-speaking countries, even though there is a wide variation in house dust mite levels across these countries (Martinez 1997). In geographical areas in which dust mite exposure is very low or absent, including desert regions and mountainous regions, the prevalence of asthma is as high or even higher than that in other areas where house dust mite exposure is high (Martinez 1997).

Other available evidence on the association between allergen exposure and the subsequent risk of asthma at the population level is also less than persuasive. For example, Leung et al. (1997) reported that asthma prevalence was high in

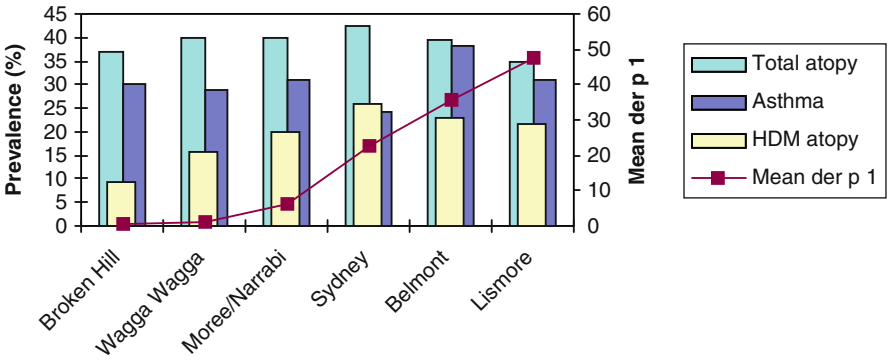

Fig. 56.3 Mean Der p 1 levels and prevalence (%) of house dust mite atopy, total atopy, and asthma in six areas of Australia

Hong Kong (6.6% for asthma ever) and low in San Bu, China (1.6%), but exposures to house dust mite allergen were similar in Hong Kong and San Bu. Similarly, Fig. 56.3 shows data from seven Australian surveys in centers with widely differing levels of mite allergen exposure; the overall prevalences of sensitization and asthma were both unrelated to the levels of house dust mite allergen (Der p 1) exposure in the six centers. The dominant allergen varied between regions, but there was little overall difference in the prevalence of sensitization or of asthma despite the major differences in mite allergen levels. Similarly, von Mutius et al. (1994) found that asthma was significantly higher in Munich, West Germany (5.9%) than in Leipzig, East Germany (3.9%), and this paralleled the pattern of skin prick test positivity (19.2% and 7.3%). However, house dust mite allergen levels were similar in the east and the west (Hirsch et al. 1998).

The other asthma risk factors (e.g., diet, obesity, paracetamol, emotional stress) may significantly contribute to the observed time trends and international patterns of asthma prevalence, but there is little evidence for this currently.

56.6.3 Protective Factors

Recent research has shifted attention from allergens that may cause sensitization and/or provoke asthma attacks, to factors that may "program" the initial susceptibility to asthma, through allergic or non-allergic mechanisms. This also in part involves a shift of attention from risk factors for asthma to protective factors and the possible role of the loss of protective factors in the global increases in asthma prevalence.

56.6.3.1 The Hygiene Hypothesis

The "hygiene hypothesis" postulates that growing up in a more microbiologically hygienic environment may increase the risk of developing respiratory allergies

and has been prompted by evidence that overcrowding and unhygienic conditions were associated with a lower prevalence of atopy, eczema, hay fever, and asthma (Strachan 1989). Having a large number of siblings (especially older siblings) and attendance at day care centers were determined to be particularly protective (Ball et al. 2000). An increase in infections has been proposed as an explanation for these findings and several studies have in fact shown a direct association between infections (e.g., Hepatitis A, measles) or immunization with BCG (Bacillus Calmette-Guérin) against tuberculosis and a lower prevalence of atopy and allergies (Shaheen et al. 1996; Matricardi et al. 1997). However, the results for airborne viruses (measles, mumps, rubella, and chickenpox) and BCG vaccination were inconsistent (Alm et al. 1998; Matricardi et al. 2000).

Exposure to specific microbial agents with strong proinflammatory properties, such as bacterial endotoxin, has also been suggested to be protective (Douwes et al. 2002a). Studies in both rural and non-rural environments have reported a significant inverse association between indoor endotoxin levels and atopic sensitization (Gehring et al. 2001), hay fever, and atopic asthma (Braun-Fahrlander et al. 2002). In contrast, a birth cohort study conducted by the same researchers found that early endotoxin exposure was associated with an *increased* risk of atopy at the age of 2 years (Bolte et al. 2003). However, two similar birth cohort studies found a protective effect on atopy in 2-year-olds (Bottcher et al. 2003) and asthma symptoms in 4-year-olds (Douwes et al. 2006).

Thus, the evidence is currently mixed as to whether endotoxin exposures may protect against atopy and allergic asthma. If there is a causal association, most of the evidence points toward endotoxin, but other pathogen-associated molecular patterns (PAMPs) may be equally (or more) important. There is evidence that exposure to peptidoglycans, CpG-containing DNA, and certain viruses may also reduce the risk of atopic disease (Douwes et al. 2004). The evidence for these PAMPs is, however, scarce.

Although the specific immune mechanisms are not clear, it is believed that microbial exposure may affect T lymphocytes which have an important function in controlling immune responses, including help for B cell production of antibodies (IgE, IgG, IgA, IgM). T-helper-2 (Th_2) cells stimulate B cells to produce IgE upon allergen stimulation, whereas T-helper-1 cells (Th_1) inhibit this process. The initial interpretation was that growing up in a more hygienic environment with less microbial exposure may enhance atopic (Th_2) immune responses, whereas microbial pressure would drive the response of the immune system – which is known to be skewed in an atopic Th_2 direction during fetal and perinatal life – into a Th_1 direction and away from its tendency to develop atopic immune responses. More recently, an alternative interpretation has been offered which involves inadequate immunoregulation by T regulatory cells wich control both Th_1 and Th_2 immune responses. Active regulation through T regulatory cells is believed to be critical in maintaining tolerance to allergens through a balanced Th_1/Th_2 immune response. The hypothesis is that a lack of microbial exposure may result in reduced immune suppression of T regulatory cells allowing upregulation of both Th_1 and Th_2 immunity, thus rendering subjects more susceptible to developing allergies (as well as Th_1

conditions including autoimmune disease which has also increased in prevalence in the past few decades). However, the immunological mechanisms underlying the observed epidemiological associations remain largely unclear (Romagnani 2004).

56.6.3.2 Animal Contact

Several studies have shown that the presence of pets in the home early in life is inversely associated with atopy in children (Hesselmar et al. 1999). Other studies have also shown a protective effect of pet ownership and asthma, for example, de Meer et al. (2004b) showed that having had a cat before the age of 18 protected against atopy to outdoor allergens, airway hyperreactivity, current wheeze, and current asthma. These results should, however, be interpreted with caution, since avoidance behavior (removal of pets in the families with sensitized and/or symptomatic children) may have contributed to this inverse association. However, in a longitudinal study in which subjects with childhood asthma at enrolment were excluded from the analyses, the protective effects actually increased (de Meer et al. 2004b), whereas a decrease would be expected if selective avoidance was a major issue. There are also studies that have found no association, or a positive association, between pet exposure and asthma, despite showing an inverse association with atopy (Apelberg et al. 2001; Kerkhof et al. 2009). In other parts of the world (Guinea-Bissau and Nepal), it has been shown that pigs and cattle in the home are associated with less atopy (Shaheen et al. 1996; Melsom et al. 2001). Thus, although the evidence for a protective effect on atopy is reasonably consistent, currently, it is unclear whether pets can also protect against asthma.

At present it is not clear which specific exposures and immunological mechanisms underlie the observed protective effects on atopy of animal contact, but increased microbial exposure may play a role, which would be consistent with the hygiene hypothesis (see above).

56.6.3.3 Farming

A number of studies have found consistently low prevalences of allergies and asthma in farmers' children, both in high-income countries such as Canada, the US, Australia, New Zealand, and Europe (Braun-Fahrlander et al. 1999; Ernst and Cormier 2000; Riedler et al. 2000, 2001; von Ehrenstein et al. 2000; Downs et al. 2001; Klintberg et al. 2001; Horak et al. 2002; Remes et al. 2002, 2003; Wickens et al. 2002; Chrischilles et al. 2004; Alfven et al. 2006; Dimich-Ward et al. 2006; Perkin and Strachan 2006; Midodzi et al. 2007; Douwes et al. 2008), and in low-income countries including Mongolia and Southern Africa (Weinberg 2000; Viinanen et al. 2007). These protective effects for allergies and asthma have also been observed in adult farmers (Leynaert et al. 2001; Kauffmann et al. 2002; Kilpelainen et al. 2002; Portengen et al. 2002, 2005; Braback et al. 2004; Eduard et al. 2004a, b; Koskela et al. 2005; Radon et al. 2006; Chen et al. 2007; Douwes et al. 2007; Smit et al. 2007, 2008) despite the increased risks of other respiratory conditions such as COPD, reduced lung function, and farmers' lung (Schenker et al. 1998). The fact that similar effects are found in low-income countries

(Weinberg 2000; Viinanen et al. 2007), where people have less opportunity to move away from farming because of allergies and asthma, further suggests that selection effects are unlikely to explain the often substantial lower risk in farming communities (Douwes et al. 2009).

The observed protective effects of farming on allergies and asthma have been particularly strong for animal contact (Riedler et al. 2000; von Ehrenstein et al. 2000; Downs et al. 2001; Remes et al. 2002, 2003; Douwes et al. 2008). Farm animals are associated with high exposures to microorganisms, in particular bacterial endotoxin (Douwes et al. 2002b). Also, an upregulation of several innate immune receptors specific for microbial products (TLRs and CD14) has been shown in farmers' children (Ege et al. 2006) suggesting that microorganisms and microbial products may be involved. In fact, a recent study showed that exposure to a wide variety of environmental microorganisms as well as exposures to specific fungal and bacterial species explained a substantial fraction of the inverse association between farm upbringing and asthma (Ege et al. 2011). Exposures early in life including the prenatal period appear particularly protective, although continued exposure may be required to maintain optimal protection (Douwes et al. 2007).

Consumption of unpasteurized farm milk in farmers' and non-farmers' children has also been shown to be protective in several of the farmers studies (Riedler et al. 2000; Barnes et al. 2001; Wickens et al. 2002; Perkin and Strachan 2006; Waser et al. 2007). The etiological mechanisms are unclear, but probiotic bacteria or other currently unidentified non-microbial components in farm milk may play a role. Evidence from other populations with anthroposophic lifestyles which are characterized by (among other things) diets rich in (probiotic) microbes (Alm et al. 1999) suggests that this protective effect may not be limited only to the farming environment, although the findings of these studies have not always been consistent (Alfven et al. 2006). These observations are also consistent with the hygiene hypothesis.

56.6.4 Can Protective Factors Explain the International Patterns and Time Trends?

As noted above, the hygiene hypothesis, if it is correct, would explain an increase in atopic/allergic asthma. However, since about one-half of asthma cases involve non-atopic/allergic mechanisms (Pearce et al. 1999), it is questionable whether the hygiene hypothesis on its own can explain the large increases observed over the last decades or the global prevalence patterns, particularly since there is some evidence that non-atopic asthma may have increased more than atopic asthma (Thomsen et al. 2004). Also, although housing conditions are unlikely to have become more hygienic in United States inner city populations, asthma prevalence has increased significantly in those populations, particularly among African Americans living in poverty (Crater et al. 2001). Finally, the hygiene hypothesis is unlikely to explain why asthma prevalence is now apparently falling in affluent countries, as exposures to factors that have previously been identified as being "protective" (family size,

endotoxin exposure, infectious diseases, pets) are likely to have decreased in more recent times rather than increased. These findings thus further emphasize the potential limitations of the current hygiene hypothesis (Douwes and Pearce 2008). Nevertheless, whatever mechanism is involved, it is becoming increasingly clear that the "package" of changes associated with westernization may be contributing to the global increases in asthma susceptibility and prevalence.

56.7 The Role of Epidemiology in Respiratory Allergy and Asthma Research

In this final section, we will make some more general observations on the role of epidemiology in respiratory allergy and asthma research. Until fairly recently and with some notable exceptions, most asthma epidemiology was done by clinicians rather than professional epidemiologists, and epidemiology was largely regarded as a means of "confirming" clinically based observations and theories (e.g., that allergens can cause asthma exacerbations and therefore "must" also cause asthma itself) (Pearce and Douwes 2009). The field was perhaps comparable to the situation in cardiovascular disease and cancer in the 1950s. For these diseases, the first epidemiological step in exploring the etiology of these conditions involved descriptive epidemiology ("person, place, and time"), particularly international prevalence or incidence comparisons such as the MONICA project (Tuomilehto et al. 1987) and Cancer Incidence in Five Continents (Doll et al. 1966). These naturally led to the development of hypotheses as to the possible explanations for the observed global patterns, which were investigated in analytical studies (cohort and case-control studies), eventually evolving into more complex studies involving the use of biomarkers and genetic testing.

Because asthma epidemiology has arrived on the scene relatively late, there has been a natural tendency to jump straight into the use of relatively high-tech methods (e.g., BHR testing, atopy testing, IgE, airway eosinophil measurements, and more recently, genetic testing) focusing on very specific etiological mechanisms (e.g., TH_1/TH_2, eosinophilia), without the "reality check" which large-scale population comparisons provide. As a result, we have developed theories of asthma etiology (e.g., the TH_1/TH_2 theory, and the associated "hygiene hypothesis") which work well in mice, but do not seem to work so well in Latin America or inner city populations in the US (see Sect. 56.6.4) (Pearce and Douwes 2006). In the last couple of decades, epidemiology has played the major role in rectifying this situation, for example, by mounting standardized international prevalence surveys to provide global asthma maps, and other population comparisons (see Sect. 56.5), as a starting point for the more careful and appropriate development of theories of asthma etiology which not only work in the laboratory but which have the potential to explain what is happening in the population context. Of course, such population

comparisons are not the solution by themselves, but they are an essential first step in the process of identifying and understanding the causes and etiology of asthma.

Much of the confusion that has permeated asthma epidemiology has simply reflected confusion about what asthma is and how it should be defined. Ironically, most clinicians have little problem diagnosing and treating asthma, which is regarded simply as "variable airways obstruction" (e.g., "asthma is a disease characterized by wide variation over short periods of time in resistance to flow in the airways of the lung" (American Thoracic Society Committee on Diagnostic Standards 1962)) – a condition that is easily diagnosed on the basis of a clinical symptom history, perhaps supplemented by serial measurements of lung function (Pearce et al. 1998a). Despite some major therapeutic disasters (Pearce et al. 1998b), symptoms are relatively easy to control (at least for the eosinophilic phenotype; see Sect. 56.3.1). However, there has not been the same clarity in understanding the etiological mechanisms by which variable airways obstruction occurs, or in the methods used for measuring asthma in prevalence studies (Pekkanen and Pearce 1999). Epidemiology can make an important contribution in the development of a better understanding of the etiology of asthma and whether it constitutes several different conditions or a single condition. This in turn will help to redefine the best methods of defining asthma in clinical practice and in epidemiological surveys.

56.7.1 The Future of Allergy and Asthma Epidemiology

Although epidemiological research may not have yielded a target for asthma intervention (yet), it has made a major contribution in changing the focus from risk factors to protective factors and identifying populations with a "naturally" low prevalence of allergies and asthma. These observations provide interesting new avenues of research with a high likelihood of identifying novel targets for prevention and treatment.

So where could innovative new theories of the etiology of asthma come from? Global prevalence (and if possible, incidence) comparisons can play a major role in this process (Pearce 1999) as has been successfully demonstrated in asthma studies such as ISAAC (Asher et al. 1995) and ECRHS (Burney et al. 1994), but, clearly, they are just part of a larger scientific process, and these sorts of initiatives are now well established for many non-communicable diseases such as cancer (Doll et al. 1966) and coronary heart disease (WHO MONICA Project Principal Investigators 1988).

Perhaps the most promising new direction is the development of truly interdisciplinary research that integrates the usually separate worlds of epidemiology, social science and biomedical, and clinical research. Traditionally, these disciplines have been conducting research in relative isolation, a situation which has distinct disadvantages. In particular, (i) many animal models of disease are only partially applicable to human populations; (ii) clinical studies are generally not

well equipped to determine the causal exposures of primary causation; and (iii) epidemiological studies often do not fully acknowledge the complexity of the biological responses involved.

Mice do not get asthma, and even after manipulation to produce an "asthma model," they do not exhibit the pathophysiology that is consistent with asthma in humans (Wenzel and Holgate 2006). Thus, although we have learnt a great deal about immunology in mice in the past few decades, these mouse models have provided only limited understanding of the underlying immunological mechanisms of human asthma. Nonetheless, most biomedical research on asthma continues to be conducted in mice. Similarly, the overemphasis of allergen exposure as the "causal" factor of asthma, as well as the lack of appreciation of the heterogeneity of asthma in many epidemiological studies, has guided biomedical and clinical research into studying (almost exclusively) allergic mechanisms and allergy-specific treatment options, with very little consideration of other potentially relevant mechanisms. In particular, there are now several studies suggesting that corticosteroid treatment is less or non-effective in asthma phenotypes that do not involve allergic mechanisms and subsequent non-eosinophilic airway inflammation (Berry et al. 2007), despite these phenotypes being very common (Douwes et al. 2002a; Simpson et al. 2007). Also, studies of asthma genetics continue to be based on populations of mixed phenotypes limiting the potential to find meaningful results. This "tunnel vision" has led to assumptions that findings in Western countries can be extrapolated to the rest of the world, and it has taken international collaborations such as the ISAAC study, to show that, for example, the strong associations between atopy and asthma symptoms that have been repeatedly observed in Western countries are not so evident in low- and middle-income countries (Weinmayr et al. 2007). Thus, considering the complex interplay between environmental exposures, genetic susceptibility, immunological mechanisms, as well as social and cultural factors involved in asthma development – and indeed most non-communicable diseases – an interdisciplinary approach bringing together expertise from each of these disciplines is most desirable, as it is likely to open up new avenues of cutting edge research, yielding greater explanatory power, more efficient use of research funding, and more efficient translation into disease prevention. Also, a closer link with biomedical research will ensure the development of more sensitive and valid methods that can be widely applied in population studies to improve both disease definition (including the assessment and recognition of disease phenotypes) and relevant exposures.

Epidemiologists have a major role to play in coordinating, integrating, and expanding these efforts, and that the "population perspective" (Pearce 1996, 1999) provides a valid reference point and "reality check" for such interdisciplinary work. However, although epidemiology is well placed to take the lead in developing interdisciplinary research, we also see a role for more "traditional" epidemiology. In particular, epidemiology has a strong tradition of generating new hypotheses or refuting old dogmas. Studies such as ISAAC (see Sect. 56.5.3) are an excellent example where the use of a one-page questionnaire conducted in more than one million children worldwide has made a major impact on how we think about asthma etiology (Enarson 2005).

56.8 Conclusions

Despite decades of intensive biomedical and epidemiological research, the etiology and pathogenesis of asthma is still poorly understood. In particular, a large number of potential risk factors for asthma have been identified including genetic factors, allergen exposure, demographic parameters, diet, obesity, indoor and outdoor pollution, passive and active tobacco smoking, occupational exposures, viral infections, stress/anxiety, and the use of paracetamol (acetaminophen). However, none of these risk factors on their own appears to explain the substantial global increases in asthma prevalence observed in the last few decades. They also cannot explain the significant differences in asthma prevalence between countries. Recent studies have shown that the increase in asthma prevalence appears to have leveled off in many high-income countries, with some even showing a decrease. The reasons for this are also unclear. As a consequence, a single target for intervention has not (yet) been identified.

Understanding why these changes in prevalence are occurring, and ascertaining which elements of the "package" of twentieth century economic development and lifestyle changes are responsible, is essential in order to develop effective intervention programs to halt the current global asthma epidemic. Recent epidemiological studies have provided innovative theories of the etiology of asthma, such as the hygiene hypothesis, which have considerable potential to guide the development of feasible primary (and secondary) prevention options. However, given the complex gene-environment interactions (Vercelli 2009) and diverse asthma phenotypes (Douwes et al. 2002a), any single type of intervention is unlikely to prevent all or even a substantial proportion of asthma cases – a "one size fits all" approach is unlikely to work. Epidemiology (alongside other disciplines) has a major role to play in developing new theories regarding asthma causation and the subsequent development and evaluation of effective prevention strategies. However, for these efforts to be maximally effective, they would need to be part of a multidisciplinary program that includes expertise (in addition to epidemiology) in biomedical, clinical, genetic, psychological, and other disciplines.

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