

Importance of Allergy in Asthma: An Epidemiologic Perspective

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Abstract There has been a global epidemic of asthma during the past half-century. More recently, the prevalence has leveled off or declined in many Western countries, whereas the prevalence in less affluent nations is still increasing. The reasons for this and the different geographical patterns of asthma prevalence remain unclear. This paper provides an epidemiologic perspective on whether allergen exposure and allergies can explain these trends. In particular, the paper discusses 1) geographical and temporal trends in asthma and the role of allergens and allergy, 2) the importance of nonallergic mechanisms, 3) nonallergenic exposures that may modify the risk of allergies and asthma, and 4) new and emerging risk and protective factors. Although allergy and asthma are closely related, allergen exposure and allergy alone cannot explain current time trends and geographical patterns of asthma. Population-based studies focusing on recently identified risk and protective factors may provide further insight.

Keywords Asthma · Allergy · Atopy · Time trends · Global patterns · Nonallergic asthma · Epidemiology · Risk factors · Protective factors · Hygiene hypothesis

Introduction

The Western world has experienced an epidemic of respiratory allergy and asthma over the past half-century. Formal epidemiologic studies of respiratory allergies and

asthma commenced in parallel with this epidemic, and continue to the present day but thus far have largely failed to deliver the levels of etiologic understanding gained in epidemiologic studies of other common diseases. The roots of this failure lie in the problems of correctly identifying asthma and allergy. Although allergy is more easily identified today with the introduction of standardized allergen extracts and serum-specific IgE tests, this is not the case for asthma, which remains as difficult to identify now as it was in the 1950s [1]. However, the epidemiology of asthma is currently undergoing rapid development and has shifted attention from traditional risk factors that may exacerbate asthma to protective factors that may prevent respiratory allergies and asthma. This growth of interest is due to the realization that previous etiologic theories do not appear to explain the global increases in asthma prevalence.

Ten years ago, it was widely believed that asthma was almost exclusively an atopic disease in which allergen exposure led to atopic sensitization, and continued exposure resulted in the development of eosinophilic airway inflammation and symptoms. However, it has become evident that this picture is overly simplistic [2, 3], and epidemiologic studies have played a major role in the shift from the overemphasis on allergen exposure and respiratory allergies as the primary (or sole) cause of asthma to a more balanced view that appropriately acknowledges the importance of nonallergic mechanisms. In this review, we provide an epidemiologic perspective on the role of allergy in asthma. In particular, we focus on 1) geographical and temporal trends in asthma and whether allergen exposure and/or allergies can explain these trends, 2) the importance of nonallergic mechanisms underlying asthma, 3) nonallergenic exposures that may modify the risk of allergies and asthma, and 4) new and emerging risk and protective factors for allergies and asthma.

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Time Trends and Global Patterns of Asthma

Most studies that have used the same methodology in the same community at different times, including the International Study of Asthma and Allergies in Childhood (ISAAC) [4] and the European Community Respiratory Health Survey (ECRHS) [5], have reported that asthma prevalence has increased substantially in recent decades (Table 1 and Fig. 1) [6•, 7]. However, asthma prevalence now appears to have peaked or even begun to decline in many affluent countries [8], while it continues to rise in less affluent countries (Fig. 1) [9, 10]. However, this pattern has not always been consistent, particularly in less affluent countries; for example, a recent study in Turkish schoolchildren found that the prevalence of asthma, wheeze, hay fever, and eczema was lower in 2002 and 2007 than in 1992 [11]. Also, large gender differences in time trends have been observed in some studies [12, 13].

The ISAAC (Fig. 2) and ECRHS studies have shown large global differences in asthma prevalence. Both studies report a high prevalence of reported asthma symptoms in English-speaking and more developed countries; the ISAAC study intriguingly also shows a high prevalence in Latin America, which is in contrast to the general association with affluence [14, 15]. Across Europe, lower prevalence was observed in Eastern and Southern Europe, with some of the lowest rates reported in Albania and Greece [14]. Africa and Asia generally showed relatively low asthma prevalence and followed the trend of higher prevalence in more developed nations. Interestingly, even neighboring cities such as Hong Kong and Guangzhou showed a similar trend (i.e., Hong Kong [the more affluent city] had a prevalence of “current wheeze” [i.e., wheeze in the past 12 months] of 12.4%, compared with 3.4% in less affluent Guangzhou) [16].

Can Allergen Exposure and Atopy Explain the International Patterns and Time Trends?

Although there is substantial evidence to indicate that allergy is associated with asthma, and that allergen exposure may cause asthma in some instances (particularly in the case of occupational allergen exposure), there is little evidence to indicate that these factors can account for the time trends and international prevalence patterns. In particular, although it has been suggested that increases in dust mite allergen exposure due to lifestyle changes could account for the global increases in asthma prevalence, the only available study of English homes at two time points (1979 and 1989) did not find any change in house dust mite allergen levels [17], although

Table 1 Changes in asthma prevalence (defined as wheeze in the past 12 months, physician-diagnosed asthma, or other asthma symptoms) in children and young adults

Country	Time period	Asthma prevalence		Reference
		First study	Second study	
Australia	1964–1990	19.1%	46.0%	[82]
	1982–1992	10.4%	28.6%	[83]
	1992–2002	28.6%	23.7%	
	1987–1992	5.6%	9.3%	[84]
	1992–1995	9.3%	11.4%	[85]
	1993–2002	27.2%	20.2%	[83]
	1966–1975	6%	6%	[6•]
	1975–1981	6%	8%	
Canada	1981–2005	8%	19%	
	1980–1983	3.8%	6.5%	[86]
England	1980–1990 ^a	140/10,000 125/10,000	256/10,000 ^b 254/10,000 ^c	[87]
	1956–1975	1.8%	6.3%	[88]
	1966–1990	18.3%	21.8%	[89]
	1973–1986	2.4%	3.6%	[90]
England and Wales	1978–1991	11.1%	12.8%	[91]
	1970–1981	11.6% 8.8%	20.5% ^b 15.9% ^c	[92]
Finland	1961–1986	0.1%	1.8%	[93]
France	1968–1982	3.3%	5.4%	[94]
Germany	1991/2–1995/6	3.7%	4.1%	[95]
Israel	1986–1990	7.9%	9.6%	[96]
Italy	1974–1992	5.5%	12.2%	[97]
	1992–1998	12.2%	12.0%	
	1983–1993/5	2.9%	4.4%	[98]
Japan	1982–1992	3.3%	4.6%	[99]
	1992–2002	4.6%	6.5%	[100]
The Netherlands	1989–1993	13.4%	13.3%	[101]
	1993–1997	13.3%	11.9%	
	1997–2001	11.9%	9.1%	
New Zealand	1969–1982	7.1%	13.5%	[102]
	1975–1989	26.2%	34.0%	[103]
Norway	1985–1995	9.3%	13.2%	[13]
	1995–2000	13.2%	13.8%	
Papua New Guinea	1973–1984	0.0%	0.6%	[104]
Scotland	1964–1989	10.4%	19.8%	[105]
	1989–1994	19.8%	25.4%	[106]
	1994–2003	9.3%	9.3%	[107]
Spain	1971–1981	1.9%	2.8%	[108]
	1979–1999	2.5%	5.7%	[108]
	1985–1995	10%	14.5%	[109]
	1995–2005	14.5%	14.2%	
	1996–2006	11.7%	13.0%	[110]
	1990–2008	20%	16%	[111]
Switzerland	1992–1995	8.8%	7.8%	[112]
	1995–1998	7.8%	6.4%	
	1998–2001	6.4%	7.4%	
Tahiti	1979–1984	11.5%	14.3%	[113]
Taiwan	1974–1985	1.3%	5.1%	[114]
United Kingdom	1991–1998	33.9%	27.5%	[115]
	1991–1993	17.7%	22.0%	[116]
	1993–1998	22.0%	29.8%	

Table 1 (continued)

Country	Time period	Asthma prevalence		Reference
		First study	Second study	
United States	1964–1983 ^d	183/100,000	284/100,000	[117]
	1971–1976	4.8%	7.6%	[118]
	1981–1988	3.1%	4.3%	[119]
	1983–1992	9.2%	15.9%	[120]
Wales	1973–1988	9.8%	15.2%	[121]
	1988–2003	15.2%	19.7%	

^a Prevalence rates per 10,000 individuals^b Men^c Women^d Incidence rates per 100,000 individuals

marked increases have been observed in similar Australian studies [18].

The association between house dust mite levels and asthma also appears tenuous, with the ISAAC [14] and ECRHS studies [15] consistently reporting uniformly high prevalence of asthma in English-speaking countries despite significant variation in house dust mite levels [19]. Similarly, Leung et al. [20] reported that asthma prevalence was high in Hong Kong (6.6% for asthma ever) and low in San Bu, China (1.6%), despite equivalent exposures to dust mite allergen. Similar patterns have been observed in Europe, with higher prevalences of asthma (5.9%) and dust mite sensitization (19.2%) in Munich in West Germany compared with Leipzig in East Germany (5.9% and 3.9%, respectively) [21] despite dust mite allergen levels being very similar

Fig. 1 International Study on Allergies and Asthma (ISAAC) phase 1 and 3: 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 1 and phase 3 (the plot also shows the confidence interval about zero change for a given level of prevalence [i.e., the average prevalence across phase 1 and phase 3] given a sample size of 3,000 and no cluster sampling effect). (*Reproduced from Thorax, Pearce N, Ait-Khaled N, Beasley R et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), volume 62:758–766, copyright 2007 with permission from BMJ Publishing Group Ltd*)

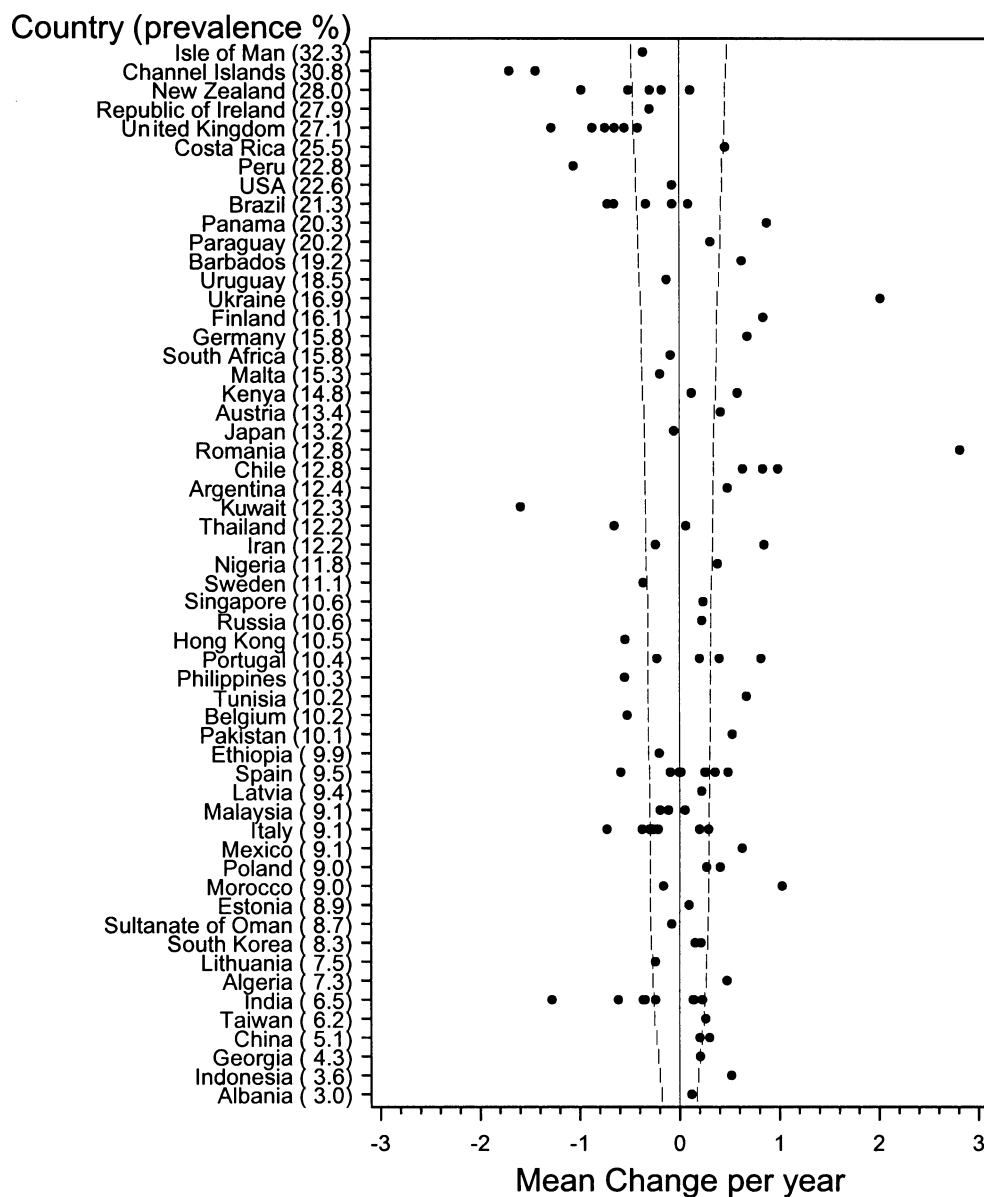
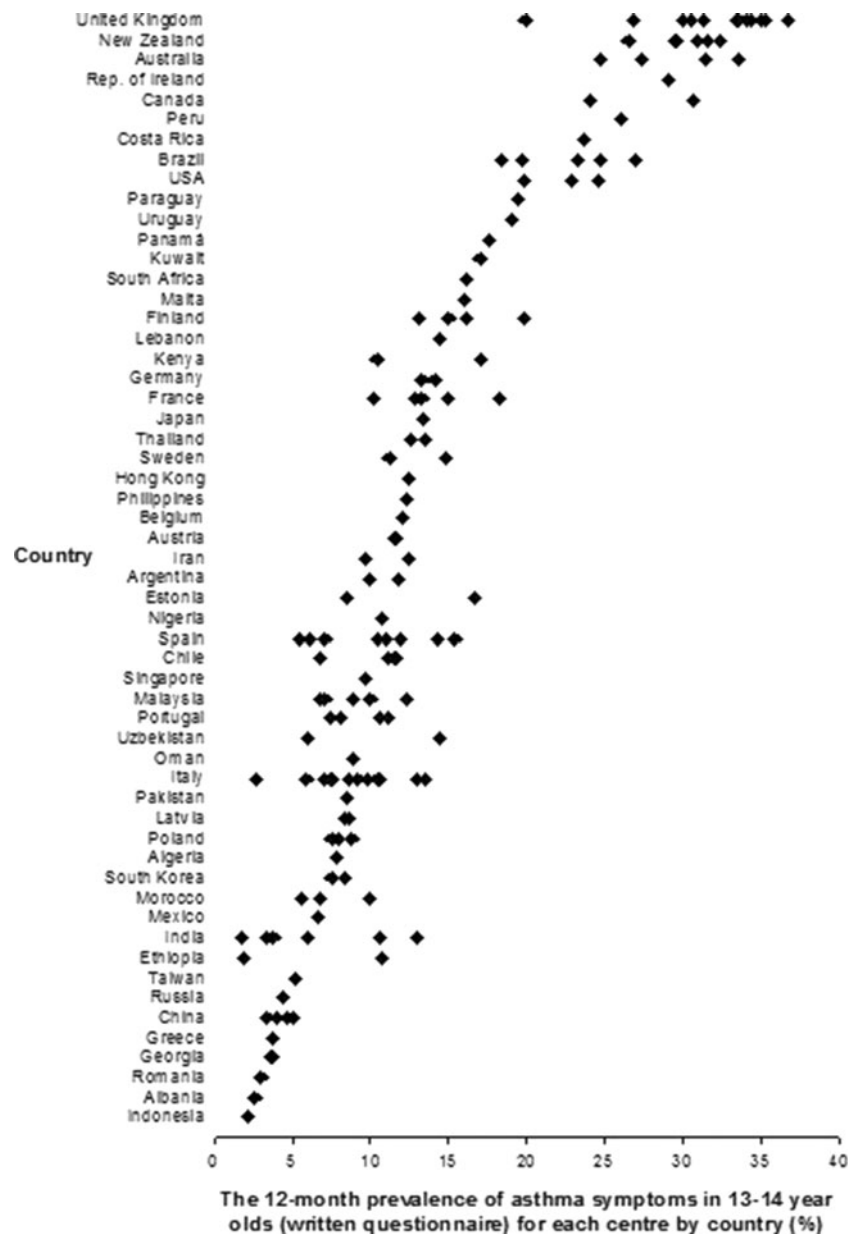


Fig. 2 International Study on Allergies and Asthma (ISAAC) phase 1: wheeze in the previous 12 months for each center by country ordered according to the mean prevalence for all centers in the country. (Reprinted from The Lancet, volume 351, issue 9111, Beasley et al. [122])



between the two cities [22]. Also, regions with low dust mite exposure (e.g., arid or mountainous areas) appear to have a prevalence of asthma comparable to or even higher than that of areas in which house dust mite exposure is high [19]. Results of recent birth cohort studies also do not support a major role for mite allergen exposure in the development of asthma [23•]. Of course, house dust mite allergens are not the only allergens, but they are the predominant allergens in many parts of the world; thus, most studies on allergies and asthma have focused on mite allergens. However, studies including measurements of other common allergens, including cat, dog, and cockroach allergens, also show little or no evidence that allergen exposure is associated with the prevalence of asthma at the population level [24].

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 example, a comparison of asthma and atopy in 9- to 11-year-olds in Albania and the United Kingdom showed large differences in the prevalence of current wheeze (4.4% and 9.7% respectively) and 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 [25]. Similarly, large differences in atopy have been observed in children from two Spanish cities (Madrid and Cartagena) with completely different sensitization patterns (predominantly perennial vs seasonal, respectively) despite similar asthma symptom

prevalence [26]. The ISAAC and ECRHS studies further confirm that atopy and asthma are only poorly correlated at a global level (see below). Also, time trends for atopy and asthma can differ substantially in the same geographic areas. For example, a recent study of 7- to 8-year-olds in Sweden showed a significant increase in allergic sensitization over a 10-year period (1996–2006) despite asthma symptoms remaining stable over the same period [12].

How Much Asthma is Attributable to Allergy/Atopy?

If allergen exposure and atopy cannot explain the observed geographic patterns and time trends, then how important is allergy in asthma? A systematic review of population-based studies found that the proportion of asthma cases that are attributable to atopy is usually less than one half [27], and this has since been confirmed in other studies [2]. The ECRHS study found that the proportion of asthma cases attributable to atopy in adults ranged widely from 4% to 61% among study centers, with an overall estimate of only 30% for all centers combined [28]. This was confirmed in the ISAAC study, which also showed that the association between atopy and asthma decreased with level of economic development. This is consistent with a recent study among 3,960 children in Ecuador that found a population-attributable fraction of only 2.4% for recent wheeze and atopy [29]. A similar study in Salvador, Brazil, suggested the proportion of asthma attributable to atopy to be 24.5% [30], which, although higher than in Ecuador, is substantially lower than the 50% in most Western countries.

We acknowledge that in some (but not all) clinical studies, a higher proportion of asthmatic children react to skin prick tests compared with epidemiologic studies involving random population surveys. There are two possible explanations for this. First, it is possible that clinical populations do not represent a true random sample of asthmatics because of the extensive “filtering” process involved in seeking health care for asthma symptoms and subsequently being diagnosed with the condition; this process of identifying and diagnosing asthmatic patients may be affected by several factors, including socioeconomic status, the presence of other symptoms, and the severity and/or recognition of the asthma symptoms themselves. Alternatively, population-based epidemiologic studies do not identify asthmatics with sufficient validity because these are primarily based on questionnaires rather than full clinical examinations. However, the available evidence indicates that this is unlikely to be a serious problem in population-based studies because the standard asthma symptom questionnaires validate well against physician-diagnosed asthma [31].

Clinical studies using sputum induction and/or bronchoalveolar lavage to measure airway inflammation in asthmatics have also indicated that less than 50% of asthma cases are attributable to eosinophilic airway inflammation, generally considered a hallmark of allergic asthma [32, 33]. Repeated assessments of airway inflammation over time have shown that the noneosinophilic asthma phenotype is reproducible in the short term (4 weeks) and long term (1–5 years) [33]. However, in a recent study of 94 patients, inhaled corticosteroid withdrawal led to an increase in prevalence of the eosinophilic phenotype, from 39% to 67% [34]. Thus, corticosteroids may mask the eosinophilic phenotype, and therefore, the prevalence of noneosinophilic asthma may be less than previously thought.

There is also evidence from large-scale, genome-wide studies supporting the hypothesis that the link between atopy and asthma may not be as strong as previously suggested. In particular, while some loci (e.g., ORMDL3/GSDMB) are reasonably strongly associated with early-onset disease, very few were associated with both IgE levels and asthma/wheeze [35•].

Thus, evidence from studies of eosinophilia and asthma is consistent with that from studies of atopy and asthma: in both instances, a substantial proportion of asthma cases appears to be due to nonallergic mechanisms. However, this assumes that atopy and eosinophilia are valid markers of allergy and that the methods used to measure atopy provide comparable results. It also assumes that atopy is a single entity. Recent studies have questioned these assumptions. In particular, the ISAAC phase 2 study suggests that in nonaffluent countries, a higher proportion of children have positive skin prick tests with no detectable specific IgE compared with those in affluent countries [36]. Genetic studies also show inconsistent associations with atopy as defined by increased IgE levels, positive skin prick tests, or both [37]. Moreover, in a birth cohort study [38], dynamic variation in IgE levels was observed, with multiple sensitizations and remissions, and persistent sensitization resulting in high levels of IgE and early onset of asthma. Similarly, it has been shown that the timing and type of sensitization affect the strength of the association with asthma [39]. Thus, a positive IgE response may not represent a single phenotype; instead, it may represent different vulnerabilities relating to risk of asthma and severity [40].

We do not consider that these new findings invalidate the earlier observations that a large proportion of asthma is due to nonallergic mechanisms (particularly because similar results are obtained using airway eosinophilia), but clearly, more studies are required to refine these estimates using improved measures of atopy (or atopic phenotypes) and airway eosinophilia.

Nonallergenic Exposures that May Modify the Risk of Allergy and Asthma

As allergen exposure does not appear to be the primary driver of recent time trends and global patterns, the research focus has shifted from allergens that may cause sensitization and/or provoke asthma attacks to factors that may “program” the initial susceptibility to asthma. This also in part has involved 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.

The Hygiene Hypothesis

The hygiene hypothesis postulates that growing up in a more “hygienic” environment may increase the risk of developing respiratory allergies and asthma. This was prompted by evidence that overcrowding and unhygienic conditions were associated with a lower prevalence of atopy, eczema, hay fever, and asthma [41]. Having a large number of (older) siblings and attendance at day care centers were determined to be particularly protective [42]. An increase in infections has been proposed as an explanation for these findings, and several studies have shown a direct association between infections (e.g., hepatitis A, measles) or immunization with bacillus-Calmette-Guérin (BCG) and a lower prevalence of atopy and allergies [43]. However, the results for airborne viruses (measles, mumps, rubella, and chickenpox) and BCG vaccination were inconsistent [44, 45]. Also, it may be that this protective effect is only specific for certain infections and at particular times of life. For example, a recent study found that croup (OR, 0.3; 95% CI, -0.12–0.72) and repeated ear infections (OR, 0.58; 95% CI, 0.35–0.98) in the first 12 months of life were inversely associated with atopy, while bronchiolitis was positively associated with subsequent asthma (OR, 2.77; 95% CI, 1.23–6.22), and nasal catarrh was associated with subsequent allergic rhinitis (OR, 2.99; 95% CI, 1.03–8.67) [46]. Furthermore, interplay between some early-life respiratory infections and allergic sensitisation may increase the risk of asthma development [47].

Exposure to specific microbial agents, such as bacterial endotoxin, also has been suggested to be protective. Studies in rural and nonrural environments have reported a significant inverse association between indoor endotoxin levels and atopic sensitization, hay fever, and atopic asthma [48]. Recent work from ISAAC phase 2 supports these previous data; combined across countries, household endotoxin levels were inversely related to asthma ever (OR, 0.53; 95% CI, 0.29–0.96) and current wheeze (OR,

0.77; 95% CI, 0.64–0.93). However, the relationship with atopy was much weaker after adjustment for gender, parental allergies, and exposure to cat and house dust mite allergens [49]. Overall, the available data are inconsistent, with some studies showing positive associations. For example, one birth cohort found that early endotoxin exposure was associated with an increased risk of atopy at age 2 years [50], whereas two similar birth cohort studies found a protective effect on atopy in 2-year-olds [51] and asthma symptoms in 4-year-olds [52].

Interestingly, different microbial exposures may also show differential effects on atopy and asthma, as suggested by a recent birth cohort study that showed both gram-positive and gram-negative bacteria to be inversely associated with asthma, whereas only gram-negative bacteria were associated with allergic sensitization [53].

Animal Contact

Several studies have shown that the presence of pets in the home early in life is inversely associated with atopy and asthma in children and adults [54]. This effect may be particularly strong with multiple exposures; in a study of 1,035 members of the Dunedin birth cohort, children of parents with an atopic history who owned both a dog and a cat were less likely to be atopic at 13 years, whereas owning only one of these pets showed no protective effect [55]. These results should, however, be interpreted with caution, as avoidance behavior (removal of pets in families with asthmatic children) may have contributed to this inverse association, although the evidence for this is weak [54]. Other studies found no association or a positive association between pet exposure and asthma despite showing an inverse association with atopy [56]. Increased microbial exposure associated with animal contact may underlie the observed protective effects.

Farming

Several studies have found consistently low prevalences of allergies and asthma in farmers’ children, both in high-income countries (including the United States and countries in Europe) and in low-income countries [57]. These protective effects also have been observed in adult farmers [57] despite the increased risks of other respiratory conditions (e.g., chronic obstructive pulmonary disease and farmer’s lung).

The observed protective effects of farming on allergies and asthma have been particularly strong for animal contact, which may be due to the associated exposures to microorganisms [58] or their components. 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 [58]. Exposures early in life, including the prenatal period, appear particularly protective, although continued exposure may be required to maintain optimal protection [59]. Consumption of unpasteurized farm milk also has been suggested to play a role [57] and may in exposures to probiotic bacteria or other currently unidentified nonmicrobial components in farm milk.

Helminth Infection

Helminth infection is thought to explain the low prevalence of allergic disease in countries in which these infections are endemic [60]. In a cross-sectional study of children in Ecuador, *Trichuris trichiura* infection was inversely associated with atopic wheeze [29]. The evidence of the protective effects of helminth infections is further strengthened by a large study examining the effect of long-term helminth infection on allergen skin test reactivity and allergic symptoms in school-aged children. In comparison with untreated children, the prevalence of allergen skin test reactivity was double in the treated group, and there was also an increased prevalence of recent eczema symptoms. However, these findings were not seen with asthma or rhinoconjunctivitis [61].

Can Protective Factors Explain the International Patterns and Time Trends?

The hygiene hypothesis suggests that growing up in a more sanitary environment with less microbial exposure may enhance the atopic (T-helper type 2) immune response. If correct, this would explain an increase in atopic/allergic asthma. However, because about one half of asthma cases involve nonatopic mechanisms [27], and the proportion is considerably higher in low-income countries, it is questionable whether the protective factors described above on their own can explain the large increases or the global patterns observed, particularly because some evidence suggests that nonatopic asthma may have increased more than atopic asthma [62]. Also, although housing conditions are unlikely to have become more hygienic in inner-city US populations, asthma prevalence has increased significantly in those populations, particularly among African Americans living in poverty [63]. A similar anomaly is the high asthma prevalence in countries in Latin America [14], which appear unlikely to have lower exposures to infectious or noninfectious microbial agents than European countries

such as Spain and Portugal, which have the same dominant languages (and to a large extent, culture) and lower asthma prevalence. Finally, the hygiene hypothesis is unlikely to explain why asthma prevalence is now apparently decreasing in affluent countries, as exposures to “protective” factors are likely to have decreased rather than increased in recent times. Also, there is no indication that exposures to suspected risk factors such as environmental tobacco smoke, house dust mites, and air pollution have decreased significantly.

New and Emerging Risk and Protective Factors for Asthma

Several new and emerging risk and protective factors may have followed a similar time trend as asthma prevalence and/or paralleled the international pattern of asthma prevalence. These include changes in diet and paracetamol use, vitamin D levels, and obesity (described below). However, the evidence that these risk/protective factors play a major role in asthma causation is still weak, and a direct link with atopy/allergies has not been well-established. Therefore, further studies are needed to test the robustness of these observations.

Diet

It has been hypothesized that increases in asthma prevalence are the result of reductions in dietary antioxidant intake. This is supported by results from the ISAAC phase 2 and other studies [64, 65], which found that fruit, vegetable, and fish consumption were associated with a lower prevalence of current wheeze and asthma. Trans-fatty acids and hamburger consumption, on the other hand, may be associated with an increased risk [66•]. The KOALA birth cohort found that development of some atopic disorders was associated with prenatal exposures to n-6 versus n-3 fatty acids, but this finding was not consistent for all atopy/allergies [67]. Maternal folate supplementation during pregnancy also has been purported as a risk factor for asthma in childhood [68].

Paracetamol

It also has been speculated that changes in paracetamol use may be a contributing factor, with the ISAAC phase 3 study showing an association between paracetamol use in the first year of life and current asthma symptoms [69]. Other studies, including an Ethiopian birth cohort study, have confirmed these findings [70]. However, the evidence is inconsistent, with some studies showing no association

after adjustment for confounding factors [71]. Thus, results to date are largely inconclusive [72].

Vitamin D

Several studies have shown protective effects of higher levels of maternal vitamin D intake on the development of asthma in children [73]. However, vitamin D levels in these studies were based on dietary questionnaire findings. In a recent study in which vitamin D levels were measured in cord blood, a similar protective effect of vitamin D was found, with an inverse association with wheezing at age 15 months, 3 years, and 5 years, but not with incident asthma by age 5 years [74]. Also, infant vitamin D supplementation has been reported to be associated with an increased risk of atopy and allergic rhinitis in adulthood [75], whereas a more recent study showed that vitamin D supplementation may prevent asthma exacerbation caused by respiratory infection [76].

Obesity

Studies have shown an association between body weight and asthma in adults and children, and prospective studies suggest that obesity precedes asthma [77, 78]. However, findings supporting this have not been entirely consistent [77]. The evidence linking obesity and atopy is also conflicting, with some studies suggesting that obesity is associated with asthma independent of atopy [79]. For example, a recent study showed that the association between obesity and asthma was largely confined to children with nonallergic asthma [80]. Similarly, in a study of adults in Sweden, wheezing in nonobese individuals was associated with elevated exhaled nitric oxide levels (typically a marker of atopy), whereas obese individuals with wheezing had lower exhaled nitric oxide levels than obese individuals without wheezing [12]. Therefore, obesity has been suggested to be associated with a unique asthma phenotype characterized by differences in both mechanical factors (decreased lung volumes) and underlying inflammation [81].

Conclusions

In conclusion, although it is clear that allergens can cause asthma (asthma due to occupational allergens is a clear example), and atopy is associated with asthma, it is increasingly accepted that they cannot explain recent time trends and global differences in asthma prevalence. As a result, the research focus has changed from the traditional risk factors (i.e., allergens and atopy) to factors that “program” the initial susceptibility to (allergies and)

asthma. Although the initial results are promising and appear to be more consistent with time trends and global patterns, these protective factors cannot explain the more recent reduction in asthma prevalence in some affluent countries. Also, they may not apply to nonatopic asthma, which makes up a large proportion of asthma cases. Therefore, we need to continue our search for alternative risk/protective factors (e.g., vitamin D, obesity) and etiologic hypotheses/mechanisms that may have greater explanatory powers.

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- Of importance
- Of major importance

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