

EDITORIAL

Will we be able to reverse the epidemiological trend?

Erika von Mutius

Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital, Ludwig Maximilian Universität, München, Germany

E-mail: erika.von.Mutius@med.lmu.de



To cite this article: von Mutius E. Will we be able to reverse the epidemiological trend?. *Pediatr Allergy Immunol* 2014; **25**: 9–11.

DOI:10.1111/pai.12193

Epidemiology and public health have first been implemented in the field of infectious diseases. The famous discoveries of John Snow in 1854 in London linking water supply sources to mortality from severe diarrhea even before the causing agent (*Vibrio cholerae*) was discovered (1) is a striking example. Ever since, epidemiology was an important discipline in the UK and the Commonwealth countries. The importance attributed to this discipline is reflected in the foundation of the London School of Hygiene and Tropical Medicine in 1899. The epidemiology of complex diseases such as asthma and allergies was built on this fertile ground, and the first studies reporting the prevalence of wheeze originated in English-speaking countries. In other areas, the epidemiology of complex diseases was not established. For example, the prevalence of asthma, COPD, atopic eczema, food and inhalant allergies had neither been assessed in the German Democratic Republic nor in West Germany until the 1980s.

The growing number of publications from English-speaking countries reporting an increase in the prevalence of wheeze and asthma (2) fueled interest and promoted this rather young discipline in many other countries. Eventually, the founding of the ISAAC (International Study of Asthma and Allergies in Childhood) Consortium in the 1990s created a worldwide network of epidemiologic research into the determinants of asthma and allergies [(3)].

Epidemiology first described pattern of disease occurrence over time and space. The alarming rapid increase in morbidity (prevalence, hospital admissions) and mortality of wheeze and asthma since the mid 1960s was confirmed in many studies and not fully attributable to increased awareness and changes in diagnostic labeling (2). Moreover, increasing rates of atopic sensitization added objective evidence. The ISAAC studies further demonstrated large geographic variability with exceedingly low prevalences in some areas as compared to rates affecting almost half the population in other regions (4). Studies showing strong differences in ethnically identical populations such as in East and West Germany (5); rural, mainland China and Hong Kong (6); Finnish and Russian Karelia (7); and children from farmers and non-farmers (8)

gave the strongest support to the importance of environmental factors as causing disease. However, clinical and epidemiological observations also showed that asthma and allergies run in families. This segregation was not fully attributable to shared environment suggesting important genetic components to disease causation.

These two streams of evidence – genetic and environmental influences – have been interrogated in further studies. The advent of new and increasingly affordable technologies has opened the field of genetics for the search of the asthma and allergy gene. These studies have been highly informative, though disappointing to some. Instead of identifying *the* asthma and *the* allergy gene, many genes and genetic loci have been identified, most of them with rather weak effects, only to a small extent explaining the heritability seen in family studies (9). Likewise, many environmental effects are weak. When considering one of the most consistent effects, that is, passive smoke exposure, odds ratios for its association with asthma and wheeze are in the order of magnitude of the strongest genetic signal from the chromosome 17 locus (10,11). These findings suggest that we are dealing with complex diseases to which many small influences rather than a few main factors contribute.

Many epidemiological studies in the 1970s to the turn of the millennium were based on assessing symptoms from parental reports and diagnoses made by physicians. Clinical experience and discrepant epidemiological findings suggested that these sources of information may not be completely reliable as diagnostic habits change and symptom awareness differs between individuals. Therefore, objective markers of disease such as detection of allergen-specific IgE antibodies, total IgE, measurements of lung function and airway responsiveness to various stimuli and markers of inflammation such as exhaled nitric oxide were included in population-based surveys. These findings have added to the heterogeneity as only partial overlap between disease manifestation and these markers has been demonstrated. For example, airway hyperresponsiveness and detectable IgE antibodies to common allergens are present in a significant proportion of asymptomatic subjects.

Epidemiology has furthermore shown that not all wheezing children will progress to a chronic course of asthma. Asthma may thus not be a single disease but rather a syndrome with more or less expression of associated features such as atopy, airway inflammation, eosinophilia, airway remodeling, Th2 immune responses, susceptibility to viral infections and may be also alterations in the airway microbiome. Clinical studies have corroborated this notion (12). Thus, asthma in itself may consist of many components that are assembled in varying configurations and are the result of a number of different pathogenetic processes. Likewise, atopic eczema may be composed of varying subtypes determined by genetic factors such as the filaggrin mutations, endotypes such as allergic sensitization to food and inhalant allergens, and environmental factors such as diet in varying combinations.

Epidemiology has added another important dimension to this puzzle: timing. All pediatric disciplines are confronted with maturing systems, in our context maturation of the lung, gut, immune system etc. These developmental pathways may open pre- and post-natal windows of opportunity for beneficial and adverse environmental impacting on the sources of the pathogenetic processes.

Where do we go from here? One path is certainly the further dissection of individual components on a population-based, patient-based and mechanistic level. This dissection is justified by the hope to find the decisive hubs or decision knots for preventive and therapeutic interventions, and to identify subpopulations of children and patients who will benefit most from such interventions. Does such an approach imply that we will have to abandon public health concepts targeting whole populations for asthma and allergy prevention like the ones we are putting into action when vaccinating young children?

In general, two public health approaches are conceivable: avoidance of risk factors or interventions with beneficial exposures. Air pollution, particularly exposure to heavy traffic and diesel exhausts, has been incriminated as risk factors for the development of pollen sensitization, hay fever and asthma (2). Reducing levels of ambient air pollution through legislation is an option. In fact, the ban of smoking in public spaces has resulted in significant decreases in hospitalization rates for asthma in a number of countries, (13) thereby significantly reducing the burden of disease.

The role of allergen exposure, in particular house dust mite exposure, for the new onset of asthma has been vividly discussed. A number of avoidance studies have supported the notion that on the general population level, reduction in house dust allergen levels by various means has failed as a primary prevention strategy (14). On the contrary, allergen exposure may be necessary to induce tolerance (15). These negative results do not preclude that secondary prevention and mite allergen avoidance in young wheezy children in whom atopy

has already become manifest may work. However, such a study has not been conducted. In turn, tertiary prevention of asthma exacerbations by reducing exposure to triggering allergens in the environment has become part of our routine recommendations in daily practice.

Increasing rates of obesity have been linked to the secular trends in asthma and allergy prevalences. Inflammatory processes induced by adipose tissues may contribute to chronic airway inflammation. While weight loss may improve asthma control, primary prevention of weight gain in children is very hard to achieve. Other dietary interventions have also failed (2).

Introduction of beneficial exposures may be more easily achievable than restrictions and ban of harmful influences. In this context, the hygiene hypothesis may come into play. The original observation underlying this hypothesis – increasing sibship size protects from hay fever and atopy (16) – may not be applicable in modern family and societal structures. Interestingly, the sharp fall in birth rates in East Germany after reunification may have contributed to the increasing rates of atopy in these regions (17). The more recent facet of this hypothesis implicating changes in the microbiome in the disease process may be worth further exploring. Although there is a wide heterogeneity of findings from intervention studies administering various pre- and probiotics for the primary prevention of atopic eczema, those including *Lactobacilli* may be worth pursuing (ref). Given the heterogeneity of study designs, type and timing of applications, study populations and number of enrolled subjects, rigorous intervention trials showing replication of results in well-designed studies conform to best clinical practice guidelines are mandatory before any recommendations can be given.

While in western affluent countries a plateau in the prevalence of asthma and allergic diseases may have been reached (2), other areas in transition from rural to urban lifestyles may experience similar secular trends. A very recent paper from Poland has shown striking increases in the prevalence of atopy among all age groups after joining the European Union. Loss of protective exposures associated with rural (farming) life styles in conjunction with acquisition of harmful influences conveyed by urban, westernized life styles may contribute to increasing asthma and allergy rates. Similar findings have also been reported from Mongolia (18).

Will we in the future be able to reverse or prevent the rise in asthma and allergies? It seems to me that we have not fully understood the relevant factors driving the onset of various components in the disease process. While epidemiologic studies of informative populations including biologic measures of potential underlying mechanisms are invaluable sources of inspiration, all generated hypotheses will eventually have to be rigorously tested in randomized clinical trials either for the primary, secondary or tertiary prevention of these diseases.

References

1. Hempel S ed. *The Medical Detective: John Snow and the Mystery of Cholera*. London: Granta Books, 2006.
2. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; **355**: 2226–35.
3. <http://isaac.auckland.ac.nz/>.
4. ISAAC Steering Committee (Writing Committee: Beasley R, K.U., von Mutius E,

- Pearce N). Worldwide variations in the prevalence of atopic diseases: the International Study of Asthma and Allergies in Childhood (ISAAC). *Lancet* 1998; **351**: 1225–32.
5. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994; **149**: 358–64.
6. Wong GW, Ko FW, Hui DS, et al. Factors associated with difference in prevalence of asthma in children from three cities in China: multicentre epidemiological survey. *BMJ* 2004; **329**: 486.
7. Vartiainen E, Petäys T, Haahtela T, Jousilahti P, Pekkanen J. Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia. *J Allergy Clin Immunol* 2002; **109**: 643–8.
8. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol* 2010; **10**: 861–8.
9. Moffatt MF, Gut IG, Demenais F, et al. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 2010; **363**: 1211–21.
10. Strachan DP, Cook DG. Health effects of passive smoking. 1. Parental smoking and lower respiratory illness in infancy and early childhood. *Thorax* 1997; **52**: 905–14.
11. Moffatt MF, Kabisch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007; **448**: 470–3.
12. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; **18**: 716–25.
13. Mackay D, Haw S, Ayres JG, Fischbacher C, Pell JP, et al. Smoke-free legislation and hospitalizations for childhood asthma. *N Engl J Med* 2010; **363**: 1139–45.
14. Custovic A, Simpson A. The role of inhalant allergens in allergic airways disease. *J Investig Allergol Clin Immunol* 2012; **22**: 393–401; quiz follow 401.
15. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol* 2012; **129**: 1187–97.
16. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; **299**: 1259–60.
17. Krämer U, Oppermann H, Ranft U, Schäfer T, Ring J, Behrendt H. Differences in allergy trends between East and West Germany and possible explanations. *Clin Exp Allergy* 2010; **40**: 289–98.
18. Viinainen A, Munhbayarlah S, Zevgee T, et al. The protective effect of rural living against atopy in Mongolia. *Allergy* 2007; **62**: 272–80.