

News and commentaries

Is the increase in allergic asthma associated with an inborn Th1 maturation or with an environmental Th1 trigger defect?

The main reason for the asthma epidemic in industrialized countries is unknown. While childhood mortality from acute respiratory infection is still high in developing countries where asthma prevalence is low, there might be a suppressed natural selection in industrialized countries with a high asthma prevalence. Children with an inborn Th1 maturation defect might survive by better health care and antibiotic use at the cost of higher asthma and allergy rates. Another distinct group of children maybe represented by those having an environmental Th1 trigger deficit where the immune systems is not being sufficiently exposed in early life. Both, a Th1 maturation and a Th1 trigger defect may contribute to a dual Th1 allergy theory.

M. Wjst

Gruppe Molekulare Epidemiologie, Institut für Epidemiologie, GSF – Forschungszentrum für Umwelt und Gesundheit, Ingolstädter Landstrasse 1, Neuherberg/Munich, Germany

Key words: allergy; asthma; immunology; population genetics.

Matthias Wjst
Gruppe Molekulare Epidemiologie
Institut für Epidemiologie
GSF - Forschungszentrum für Umwelt und Gesundheit
Ingolstädter Landstrasse 1
D-85758 Neuherberg/Munich
Germany

Accepted for publication 15 July 2003

A study using the Mayo Clinic medical record system (1) reported a 55% increase in the age- and sex-adjusted annual incidence of definite and probable asthma between 1964 and 1983. This was due to an increased incidence among 1 to 14-year-olds. The reasons for this observations are largely unknown. They were discussed in the late 1980s as the negative side of industrial air pollution but following a seminal paper by David Strachan (2) – the discussion focuses now more on various aspects of early exposure to infections.

The hygiene hypothesis argues in a rather mechanistic way that early childhood infections are a Th1 stimulus of the otherwise Th2 skewed early immune response (3). Reduced infection rates in Western countries will maintain the initial Th2 bias, resulting in an increased risk of developing asthma and allergy. However, the hygiene hypothesis cannot account for the fact that there is very low incidence of allergy in developing countries where helminthic infection also favours Th2 biased immune response.

Infections seem to have an important role in a worldwide perspective. Acute respiratory infections (ARI) are still the main killer of under 5 (4). It is also well known that children with asthma are more likely to suffer from ARI than healthy children (5), most likely because of an already genetically biased immune system (6). Many children with potential asthma will therefore die before reaching reproductive age – still the current sad situation in many developing countries, where ARI is the

number one cause of death in children. Vaccination programmes, sufficient nutrition and antibiotic treatment, however, have reduced ARI mortality in Western countries during the last 50 years (4). On a population level the increased asthma incidence would therefore appear as the survival of the less or 'nonfittest'. Although contrary to Darwin's hypothesis (7) nonsurvival of the nonfittest seem to be much more a driving force on population genetics. The recently described association of early antibiotic use with asthma (8) could reflect this suppressed natural selection. Asthma prevalence rates combined with survival during the first 5 years of life illustrates this fact (Fig. 1). If we think of a selection process that may have already occurred several decades ago in the industrialized countries (9) the asthma prevalence should now be high. In countries where natural selection is still ongoing there should be a negative association of childhood mortality and asthma rates (7).

Is such a natural selection also possible from a longitudinal view of the 20th century? In Europe, mortality under the age of 5 has been about 250 of 1000 live born children in 1900. It dropped to 50 of 1000 around 1950 and is now about five of 1000 while the asthma epidemic started in the cohort born around 1950 (9). Only the recent decrease of mortality seems to be correlated with the introduction of antibiotics.

There might be many reasons for ecological fallacies as many environmental factors changed during this time

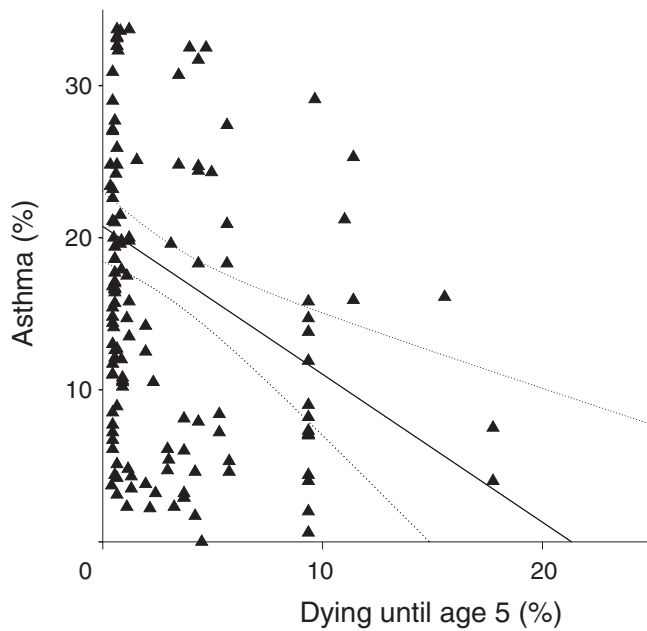


Figure 1. Association of asthma prevalence in 13–14-year-old children [taken from the International Study of Asthma and Allergies in Childhood (ISAAC) study (23)] and the sex-averaged probability to die before the age of 5 (<http://www.who.int/whr/2002/annex/en/#excel> by 20 November 2002). All 154 countries (except Hong Kong and Taiwan) could be matched with ISAAC data. First order regression and 95% confidence limit is given in the group of children with a sex-averaged probability to die before the age of 5.

period. There is, however, an interesting observation in immigrant studies (10). The prevalence of asthma in children who were born in India or Pakistan before coming to Britain was found to be much lower than in other Asian children who were born in Great Britain: the Indian born children have undergone a selection process ('survival of the fittest') while those born in Great Britain have not ('survival of nonfittest') indicated by the higher asthma prevalence.

It is still unclear how other pieces fit into this puzzle. A family history turned out to be the strongest risk factor for asthma but it is hard to understand how a genome that does not undergo any change within a generation can impose such a strong disease risk. I will address this question in two ways, on a functional and a genetic level.

On a functional level, the intrauterine and foetal compartment is Th2 skewed by a multilayered control within the innate immune system (11–13). If we assume that there exists an additional syndrome of a Th1 Maturation Defect with high IgE levels (TH1MD), this TH1MD syndrome may have an evolutionary benefit of effective helminthic elimination but the disadvantage of too many individuals not surviving infections. Vaccination programmes and antibiotic use will allow primarily

children with TH1MD to survive; they will suffer from more frequent respiratory syncytial virus (RSV) infections and asthma (11).

The paradox on the genetic level, an evolutionary benefit but lethal outcome, could be explained by heterozygote advantage known for several genetic diseases. Let us consider a locus with two alleles that have different fitness, where the heterozygote may have an intermediate between the two forms of homozygotes. The mode of selection in this case would be dominant resulting in an increase of the advantageous allele. Until recently, virtually no patient with cystic fibrosis lived long enough to reproduce. It has therefore been speculated as the 'cystic fibrosis transmembrane conductance regulator' (CFTR) gene encodes a membrane chloride channel which is required by *Salmonella typhi* that heterozygotes are relatively resistant to typhoid fever. There are many other examples (with β 2-thalassaemia being the most prominent example) where heterozygote advantage have been suggested.

A distinct group may be represented by those children who have a Th1 Trigger Deficit (TH1TD) being not sufficiently exposed in early life to endotoxins, as observed in recent epidemiological studies (14). Endotoxin exposure seemed to be ubiquitous in our previous environment. They are known to induce interleukin (IL)-12 in antigen presenting cells which itself inhibits the atopic response. Endotoxin also induces interferon (IFN)- γ , which down-regulates the maturation of Th2 cells (15).

The hypothesis of dual Th1 processes could help to resolve the paradox that endotoxin prevents the primary induction of allergic asthma (14) but at a later time turns out to be a risk for the same disease (16) – the first phase is a TH1TD and the second a TH1MD effect. It may also resolve the old conundrum if infection protects against allergy (2) or allergy protects from infection (7) – both could be viewed as janus faces of the same syndrome (17).

Additional support for a dual Th1 defect comes from about 250 cases of Job-Buckley syndrome (or hyper-IgE syndrome, HIES) (18), where patients are suffering from hyperimmunoglobulin E and recurrent staphylococcal infections maintaining the early Th2 bias and being at the same time incapable of Th1 switch to mount a sufficient infection response. A chemotactic defect in neutrophils has been attributed to a defective Th1 production of IFN- γ , a major activator of neutrophils when stimulated by IL-12.

It is difficult to argue also with population-based studies here. The main problem of observational epidemiological studies relate to the different time windows examined (which is additionally complicated by recurrent exposures boosting Th2 memory). Different outcomes like upper and lower respiratory infection are also difficult to compare as well as various severity grades. Infections may even occur in the absence of any overt clinical sign. Furthermore, the co-occurrence of even

antagonistic effects of viral, bacterial and helminthic infection would have to be considered.

Ignoring this for a moment, we can look on a recent cohort study of children in the Boston area. Daycare in the first year of life – a proxy for early exposure to respiratory pathogens, showed an increased risk for asthma in children with a maternal history of asthma (probably TH1MD), which completely reverted being protective in children without a maternal history of asthma (probably non-TH1TD) (19). Another example comes from the Tucson cohort (6), where children with elevated cord serum IgE levels had fewer respiratory tract illnesses in the first 6 months of life. A third example comes from the Munich cohort (20), where an inverse relationship was found between total serum IgE and the number of fever episodes during the first years of life, pointing also towards a TH1MD effect.

The development of long-term T cell memory seems to be specific for certain allergens raising the possibility of bystander stimulation of ongoing T cell response by intermittent RSV infections (11). Genomic variants in the lipopolysaccharide (LPS) receptors CD14 or TLR4 as well as in the IL-1 pathway (unpublished own work) may play an important role for stimulating the innate immune system (21). Perpetuation of the inflammatory response or counter regulation by IL-10 or TGF- β might be important (3).

If there is a really suppressed natural selection can still be answered in sub-Saharan rural Africa, which is supposed to be the ancestral homeland of modern humans (22). Genomic variants in the innate immune system are expected to have a high prevalence at birth but will vanish from the population pool 5 years later. In Western countries we will probably not see this effect having already a high asthma prevalence.

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