Section B

EPIDEMIOLOGY AND RISK FACTORS

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The growing worldwide burden of allergic rhinitis, asthma and atopic eczema has been properly defined as the “allergy epidemic”. During the last two centuries, this phenomenon has characterized countries undergoing their epidemiological transition phase. Respiratory allergies (allergic rhinitis and asthma) appeared first among the richest, then spread within the middle class and finally affected also the disadvantaged. Following a similar pattern, respiratory allergies and atopic eczema are nowadays on the rise in middle income countries, especially in the urban areas (Figure 1).

More recently, food allergies are clearly becoming more prevalent in westernized populations (Figure 2). This “second wave” of the allergy epidemic is already generating a heavy burden on health systems not well prepared to face this new challenge. The increasing prevalence of food allergies is associated with fatal anaphylaxis in children and adolescents.

A decline of microbial diversity was proposed since the late nineties as a major cause of the allergy epidemic. This area of the hygiene hypothesis, now defined “biodiversity hypothesis”, has found specific support in several epidemiological studies: 1) respiratory allergies are inversely related to the number of different foodborne infections; 2) a lower diversity of the gut microbial flora in the first week of life is associated with atopic eczema at 18 months (Figure 3); 3) the probability of developing asthma in farming children is inversely related to the range of exposure to environmental bacteria and fungi.

Two recent studies have coherently shown that reduced food diversity in infants’ diet is associated with atopic sensitization and allergic diseases later in childhood (Figure 4). A sufficiently high “antigenic burden” in early life, provided by infections and nutrition, can properly “educate” the immune system and prevent childhood allergic diseases. A reduced “antigenic burden” implies a reduced stimulation of the immune system and contributes, in genetically predisposed individuals, to dysregulated immune response leading to allergy.

The discovery of the lifestyle factors promoting allergy susceptibility will inspire primary prevention strategies to revert the allergy epidemic trend. Allergy prevention based on the administration of probiotics to pregnant mothers and to in-
**Figure 1** The spread of hay fever and allergic asthma according to socio-economic status and westernization level. (Reproduced with permission from Annals of Allergy, Asthma & Immunology, Vol. 89(S1). Matricardi PM, Bouygue GR, Tripodi S. Inner-city asthma and the hygiene hypothesis, 69–74. Copyright Elsevier 2002.)

**Figure 2** Observed and predicted values for the prevalence of food IgE sensitization in 20- to 54-year-olds in European cities. (reprinted from Allergy, Vol. 69. Burney PGJ et al. The prevalence of food sensitization among European adults. pp. 365–71. Copyright 2014 (Reproduced with permission from Burney PGJ, Potts J, Kummeling I, et al. The prevalence of food sensitization among European adults. Allergy, 2014 69: 365–71, with permission from Wiley Blackwell.)
KEY REFERENCES


Figure 3 Shannon-Wiener index after T-RFLP of 16S rDNA with AluI for cutting and TTGE, respectively, generated from the fecal microbiota of 1-week-old infants that at 18 months had atopic eczema or stayed healthy. For each group, median and 10th, 25th, 75th, and 90th percentiles are shown. *For T-RFLP, P<.01 and for TTGE, P<.05 (Reprinted from J Allergy Clin Immunol, 121/1, Wang M, Karlsson C, Olsson C, et al. Reduced diversity in the early fecal microbiota of infants with atopic eczema, 129-134, Copyright 2008, with permission from Elsevier.)

Figure 4 Association of increasing diversity of food introduced within the first year of life with (A) asthma and (B) food allergy among 856 children who participated in a birth cohort study, Protection Against Allergy Study in Rural Environments/EFRAIM. The figure shows the diversity score with all different food items for the entire study population. The solid lines represent the predicted value of (A) asthma or (B) food allergy, as a function of the score, and dashed lines represent the corresponding CI. The y-axis is the linear logit of (A) asthma or (B) food allergy, and the values are centered on 0 (50/50 odds) and extended to both positive and negative values. All models are adjusted for farmer, center, duration of breast-feeding, parents with allergy, maternal education, sex, and siblings. (Reprinted from J Allergy Clin Immunol, 133/4, Roduit C, Frei R, Depner M et al. Increased food diversity in the first year of life is inversely associated with allergic diseases, 1056-1064, Copyright 2014, with permission from Elsevier.)
Allergy is common in children, adolescents and adults. Epidemiological studies like the German MAS (Multicentre Allergy Study) showed age-related typical manifestations of atopic and allergic diseases. In the “Atopic March” infantile eczema and food allergy precede the onset of allergic airway disease (rhinitis and asthma).

However, there are individuals with isolated allergic airway disease (for example hay fever) starting later in life at school age without any signs of other atopic disease during infancy and preschool age. Equally, there are children with infantile eczema without any signs of food or inhalant allergy. Furthermore, remission and relapse of disease entities are possible at any time.

Studies on the molecular pattern of sensitisation to pollen allergens showed a preclinical phase, where sensitization (IgE antibodies in serum) to certain molecules of an allergen source (grass or birch) precedes symptoms. The likelihood of clinical allergy increases with the number of molecules recognized by IgE.

**ATOPIC ECZEMA**
The incidence of atopic eczema and food allergy to cow’s milk, hen’s egg, wheat and soy is highest during the first 2 years of life in childhood, however, there is a second peak of new onset of atopic eczema in puberty for females. Two thirds of young children with infantile eczema will lose their symptoms up to the age of three years. However, those children developing atopic eczema later in life (after the age of 5 years) are more likely to outgrow their eczema compared to those children, who had an earlier onset of disease (during the first year of life).

**ASTHMA**
In the German MAS cohort, the prevalence of asthma is 4% at 6 years of age and more prevalent in boys and 9% at age 20 years. The incidence of allergic asthma is highest during preschool and early school age (Figure 1). There is a second peak for new onset of asthma in females at puberty. Atopic family history is a major risk factor for the development of asthma (Figure 2). 29% of the German MAS cohort children with complete follow-up showed wheezing episodes during the
first three years of life (early wheezers). 9% started wheezing between the age of 3 to 6 years (late wheezers) and another 9% started wheezing after 6 years of age (very late wheezers). Early persistent wheezers (early start of wheezing before 3 years of age, wheezing also after 6 years of age) showed the highest rates of atopy. In this group, early atopic eczema, parental atopy and early sensitization (<3 years of age), especially to perennial allergens, turned out to be the major risk factors for persistence of asthma/wheeze at age 11-13 years.

**IGE SENSITISATION TO ALLERGENS**

The first allergens recognized by the immune system in terms of IgE production are food allergens. The most frequent food allergens inducing IgE-mediated sensitization are hen’s egg, cow’s milk and peanut. Although, sensitisation to inhalant allergens like cat, house dust mite and pollen allergens can be present already during the first 3 years of life, in most of the children the clinical relevance is observed later, at school age.

Atopy (sensitisation) in general is a risk factor for asthma at school age (Figure 3).
Sensitisation to indoor allergens (house dust mite and pets) is associated with allergic asthma. School children with sensitisation to perennial allergens (house dust mite, cat dander) being highly exposed to these allergens early in life are at risk to have impaired lung function at school age compared to children without sensitisation or with sensitisation and low exposure to indoor allergens during the first year of life.

Children with sensitisation to any allergen before the age of 3 years and sensitisation to inhalant allergens have an increased risk for asthma at school age (Figure 4).

ALLERGIC RHINITIS
There is a constant rise for the incidence and prevalence of allergic rhinitis (AR) from preschool and early school age until puberty.

Allergic rhinitis until the age of 5 years was found to be a risk factor for subsequent wheezing onset with an adjusted relative risk of 3.79 (p<0.001). This association was not attributable to the type of sensitization, the severity of sensitization or atopic dermatitis during the first 2 years of life. On a population level 41.5% (95% CI: 20.0-61.3) of all new cases of wheezing was attributable to preceding AR. Neither AR until the age of 2 years nor non-allergic rhinitis until the age of 5 years were significantly associated with wheezing onset in childhood.

The first manifestation of AR occurs in preschool children, where it is a risk factor for subsequent wheezing onset. Preschool children with rhinitis might thus benefit from early assessment of allergic sensitization to identify the children at high risk of developing wheezing.

ALLERGIC RHINITIS: SENSITISATION TO AEROALLERGENS
The 12-month prevalence of sensitization to indoor or outdoor allergens in the German MAS cohort rose with each time point of assessment, reaching almost 60% of all boys and a third of all girls at the age of 13 years (in children with one or two allergic parents). Children from non-allergic parents were less sensitized compared to...
those with allergic parents. Irrespective of parental allergy status the number of boys sensitized to aero-allergens was approximately twice the number of sensitized girls at age 13 years.

At the age of 13 years, 91% out of the 35 children with “severe persistent” AR (ARIA) were sensitized to at least one aero-allergen, whereas this proportion was only 70% among the 56 children with “mild persistent” AR (p=0.015). This difference was similar at the age of 10 years, although overall slightly less children with AR were sensitized (p=0.033). Among the asymptomatic children 18% (32/175) were sensitized to at least one common aero-allergen at the age of 13 years, compared to 24% (49/289) at the previous time point of assessment at the age of 10 years.

**KEY REFERENCES**


In contrast to most other complex diseases (for example diabetes or hypertension), allergic diseases generally start early in life. Therefore, the best way to study allergies is to recruit new born babies and follow them as they grow (so-called birth cohort). Birth cohorts overcome problems related to the lack of accuracy (or completeness) of the recollections when patients are asked about the events, which occurred many years ago. Such studies permit careful longitudinal assessment of symptoms, sensitization status, physician diagnoses and medication usage, and objective measures such as lung function.

Allergies are heritable, but despite lots of effort, we have had limited success identifying what genes are important, and this has yet to impact on patient care. Many factors in the environment contribute to the development of allergies (for example diet, immunizations, antibiotics, pets and tobacco smoke), but we don’t know how to modify the environment to reduce the risks. In birth cohorts, environmental exposures can be measured to allow the study of complex gene-environment interactions. Birth cohort studies have been instrumental in demonstrating the existence of a gene-environment interaction in the development of allergy, which helped to explain the disparities in genetic association studies in different settings around the world.

Several consortia bring together a number of ongoing birth cohort studies to facilitate data sharing. For example, the UK Study Team for Early Life Asthma Research (STELAR) brings together the network of all UK-based birth cohorts designed to study allergies with the experts in machine learning and epidemiologically-oriented health informatics. Similarly, EU-funded MeDALL (Mechanisms of the Development of Allergy)1 and EuroPreval/ifAM2 projects bring together thousands of children taking part in different birth cohorts across the continent, and will facilitate the generation of critically important knowledge on the mechanisms of initiation of allergy. Birth cohorts in The EARly Genetics and LifeCourse Epidemiology (EAGLE) Consortium are extensively collaborating to investigate the genetic basis of allergy and asthma-related phenotypes in childhood.

Numerous early breakthroughs have already been made. The ongoing birth cohort studies offer the best chance of identification of children at increased risk of allergy. This is the first and crucially important step towards the development of the evidence-based strategies for prevention of allergy development, and stratified

**KEY MESSAGES**

- Allergic diseases generally start early in life, thus birth cohorts are essential for elucidating disease mechanisms and natural course and evidence-based strategies for prevention and management.
- Birth cohort studies have been instrumental in demonstrating the existence of a gene-environment interaction in the development of allergy and in identifying children at risk for allergy.
- Several consortia (STELAR, MeDALL, EuroPreval/ifAM, EAGLE) bring together a number of ongoing birth cohort studies to facilitate data sharing.
**Figure 1** Longitudinal data collected over a number of years in birth cohort studies are a foundation for utilisation of the power of novel state-of-the-art data analysis techniques to build complex models to describe different types of allergic diseases. In doing so, we will understand the basic biological mechanisms that underlie the different allergies, and identify novel targets for future drug therapies.

(personalised) management of allergies (Figure 1). Existing birth cohorts of individuals now at various ages, from childhood to adulthood, should be considered a treasure, and every effort should be made to maintain long-term funding for such large efforts.

**KEY REFERENCES**

Allergic diseases are a heavy socio-economic burden worldwide. There is a deficit in public awareness, education and training and an urgent need for efficient prevention strategies. The rising trend in allergies has been associated with changes in life-style, such as improved hygiene measures, smaller family sizes and control of infections, which, taken together, result in an "under-challenged" immune system. On the other hand, lifestyle changes include the exposure to potentially harmful – indoor and outdoor – environmental pollutants suspected to keep our immune system in a constant state of alarm. How does this fit together?

INDOOR RISK FACTORS
In the western civilization, most individuals spend a considerable part of their lives indoors. Indoor exposure to mite, molds, chemicals and inhaled particles can elicit and/or exacerbate allergic diseases. The best assessed among the indoor pollutants are volatile organic compounds (VOCs) and environmental tobacco smoke (ETS), which is a mixture of VOCs, carbon monoxide and solid particles. In LINA (Lifestyle and environmental factors and their Influence on Newborns Allergy risk) birth cohort subgroup, prenatal and early life exposure to environmental tobacco smoke was positively correlated with circulating eosinophil and basophil precursors in cord blood, indicating allergy-promoting effects on susceptible children. In a murine allergic asthma model, long-term exposure to VOCs emitted from polyvinylchloride (PVC) flooring increased acute and chronic allergic lung inflammation.

OUTDOOR RISK FACTORS
A high degree of traffic and urbanization are hallmarks of Western civilization. A recent meta-analysis of prospective, multi-center trials did not find any clear association of modeled traffic-related air pollution and allergic sensitization in children (Figures 1 and 2). Other studies do show associations of exposure to diesel exhaust particles (DEP), NO2, ozone and particulate matter (PM), with asthma, allergic rhinitis or sensitization to aeroallergens. These conflicting results illustrate how exposure and confounding factors, e.g. genetic predisposition, lifestyle and nutrition interact closely in switching from health to disease (Figure 3). Apart from direct effects of outdoor pol-

**KEY MESSAGES**
- Allergy is an environmental disease as the most common and earliest onset chronic non-communicable disease
- Life-style and civilization related risk factors for allergy are encountered both indoors and outdoors
- Allergy-relevant indoor air pollutants include environmental tobacco smoke and volatile organic compounds
- Anthropogenic environmental factors influence pollen allergenicity indirectly via their effects on pollen-producing plants
- Climate change-related effects contribute to an increased allergen burden in outdoor air
- The growing evidence of man-made environmental risk factors for allergy highlights the importance of prevention strategies for improving public health
Environmental risk factors for allergy: outdoor/indoor pollution and climate change

Figure 1  Modification induced by anthropogenic pollutants to pollen allergens.

Figure 2 Climate change impact on the ecosystem of pollen-producing plants.
lutants on humans, pollen-producing plants are themselves subject to modification by anthropogenic pollutants (Figures 1 and 2). We recently identified ambient ozone as a major factor influencing allergen content and adjuvant lipid composition of birch pollen. This illustrates how anthropogenic environmental factors, via their effect on the allergen carrier, can indirectly influence the health of allergic patients.

CLIMATE CHANGE RELATED RISKS
Global warming is associated with elevated CO2 levels and prolonged vegetation periods. This, in turn, causes prolonged flowering seasons, which might increase the load of allergenic pollen. The aggressive spreading of allergenic neophytes, such as *Ambrosia artemisiifolia*, in southeastern and parts of middle Europe already led to de novo sensitizations in the exposed populations. Moreover, exposure to Ambrosia pollen might induce symptoms even in mugwort-sensitized patients due to the high degree in inter-species cross-reactivity.

KEY REFERENCES
MEASURING EXPOSURE TO ENVIRONMENTAL AIRBORNE ALLERGENS

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A key factor for the development of respiratory allergy is the contact between the respiratory organ and inhaled air containing the allergens. Airborne allergens can be found in a variety of sources (Table 1). The risks of respiratory allergy or elicitation of symptoms may be decreased by reducing exposure. Control measures should be based on allergen exposure monitoring performed according to well-defined and validated methods.

To measure exposure to airborne allergens, it is imperative to report the presence of the sources of allergens (mite counts, presence of pets), because allergen levels can stay high when there are no sources or their number is low.

The choice of optimal procedures depends on the setting and objectives of allergen monitoring (Figure 1): epidemiological (population) studies on exposure-response relation, intervention studies, diagnosis and follow-up of individual patients, hazard identification for disease clusters, identification of cases of “new allergy”, as part of routine monitoring or of a health surveillance program.

Indoor airborne allergen levels may be assessed in settled dust or in an air sample. A dust sample is collected from the bed, carpet or sofa by vacuuming a square yard area of the bed/carpet/sofa per 2 minutes with a vacuum cleaner with a collection device. The presence of allergens is quantified with an ELISA test. Recently, an alternative wipe sampling method has been implemented to collect allergens from floor dust, where allergens are measured by real-time quantitative PCR methodology. However, methods using settled dust might not provide accurate measurements of inhaled allergens. To measure airborne allergens in the air, a technique has been developed that involves collecting an integrated total suspended particulate sample through an impactor. Extracts of air samples are then analyzed by a modified ELISA using an amplification of the generated colorimetric signal.

The prevalent outdoor allergens are pollens and molds. Usually, pollen and mold counts are assessed, and not their derived allergens. A pollen count is nothing more than a measurement of how much pollen is in the air. It is expressed in terms of a concentration of pollen in the air in a specific area at a certain point in time. The exact measure is grains of pollen per cubic meter over a 24 hour period. Mold counts, like pollen counts, are a measurement of how many mold spores are in the air in a certain area at any given point in time. Monitoring pollen and mold counts on a daily basis during the...
# TABLE 1

<table>
<thead>
<tr>
<th>Allergens</th>
<th>Where, when</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pollen</strong></td>
<td>Pl p 1, Phl p5, Cyn d1, Amb a 1, Bet v ...</td>
</tr>
<tr>
<td></td>
<td>Outdoors</td>
</tr>
<tr>
<td></td>
<td>Spring/summer/autumn</td>
</tr>
<tr>
<td><strong>Mold</strong></td>
<td>Alt 1, Cla 1 ...</td>
</tr>
<tr>
<td></td>
<td>Both indoors (perennial) and outdoors (seasonal).</td>
</tr>
<tr>
<td></td>
<td>Indoors, molds can be found in any moist, dark place. Outdoors, mold results from vegetation degradation.</td>
</tr>
<tr>
<td></td>
<td>Mold floats easily in the air.</td>
</tr>
<tr>
<td><strong>House Dust mite (HDM)</strong></td>
<td>Dermatophagoidespteronyssinus (European HDM), Dermatophagoides farina (American HDM), Blomia tropicalis.</td>
</tr>
<tr>
<td></td>
<td>Indoor</td>
</tr>
<tr>
<td></td>
<td>Found in house dust, mattresses, bedding, upholstered furniture, carpets and curtains</td>
</tr>
<tr>
<td></td>
<td>HDM feed on shedded flakes of skin</td>
</tr>
<tr>
<td></td>
<td>HDM thrive in warm and humid environments.</td>
</tr>
<tr>
<td><strong>Pets</strong></td>
<td>Cat (Feld1), Dog (Can1)</td>
</tr>
<tr>
<td></td>
<td>Indoor</td>
</tr>
<tr>
<td></td>
<td>Major allergens are proteins secreted by oil glands in the animals’ skin and shedded in dander as well as saliva proteins, which sticks to the fur when the animal licks itself. Urine is also a source of allergens.</td>
</tr>
<tr>
<td></td>
<td>When the substance carrying the allergens dries they become airborne</td>
</tr>
<tr>
<td><strong>Hamster, squirrel, rabbit</strong></td>
<td>Indoor/occupational</td>
</tr>
<tr>
<td></td>
<td>Urine is the major source of allergens from these animals.</td>
</tr>
<tr>
<td><strong>Pests</strong></td>
<td>Mouse, rat, (Mus m1, Rat 1)</td>
</tr>
<tr>
<td></td>
<td>Indoor</td>
</tr>
<tr>
<td></td>
<td>Urine is the major source of allergens from these animals.</td>
</tr>
<tr>
<td><strong>Cockroach</strong></td>
<td>Blatella germanica (German cockroach) (Bla g 1)</td>
</tr>
<tr>
<td></td>
<td>Tiny protein particles shed or excreted by cockroaches</td>
</tr>
</tbody>
</table>
seasons when they are present is one of the most proactive steps to control asthma and allergies. Pollen and mold counts are collected using a special sampling trap that is typically placed on a rooftop several stories above the ground (Figure 2). The device has a sticky surface that collects grains of pollen and mold spore from the air. Specific pollen and mold are recognized using an electronic microscope.

Recent data have shown that pollen and mold counts do not represent allergen exposure. Air can be sampled for pollen and mold allergens with a high-volume cascade impactor equipped with stages for particulate matter (PM) >10 μm, 10 μm >PM >2.5 μm, and 2.5 μm >PM >0.12 μm. Allergens are determined with specific ELISA.

Precise assessment of allergen concentrations is needed to define the exposure thresholds inducing sensitization, symptoms and exacerbations of allergic diseases.

**KEY REFERENCES**


The prevalence of food allergy appears to have increased. Environmental factors must account for the apparent rise, not genetic predisposition. An over-arching effect may be the immune dysregulation attributable to the "hygiene hypothesis". Additional theories to explain increased atopy, include vitamin D insufficiency, reduced consumption of healthful dietary fats and antioxidants, and obesity. Theories suggesting early infant ingestion of food allergens as a risk for allergy have been substantially disproved. Early infant avoidance of food allergens could be a risk factor for allergy due to bypassing oral tolerance during a period of sensitizing cutaneous exposure. Food allergy is the result of a complex interaction of genetic, immunologic and environmental influences, indicating a challenge for identifying effective prevention strategies.

Probably as a response to early studies suggesting that infants exposed to whole cow milk proteins were at higher risk of milk allergy compared to those receiving breast milk or hypoallergenic formula, among other observations, various expert panels and professional organizations suggested avoidance of allergens for infants at risk. Some guidelines included allergen avoidance during pregnancy and lactation. The goal was to prevent exposure to food allergens for a presumed immature and allergy-prone immune system.

However, mounting studies suggest that extended avoidance of food allergens may be a risk factor for food allergies, rather than preventative. Why would this be? One possibility is that earlier exposure allows for oral tolerance. For example, in a study of the rate of peanut allergy among Jewish children in the United Kingdom compared to Israel, there was a ten-fold higher rate of allergy in the UK, where early peanut consumption was comparatively very low (Figure 1). Timing of ingestion may only be part of the story. Non-ingestion routes of exposure may be strongly sensitizing: for example, despite ingestion of raw fruits, many persons develop pollen-food related syndrome caused by inhalation of food-homologous proteins in pollens, bypassing oral tolerance. Similarly, it was suggested that topical exposure, especially via inflamed skin, i.e., atopic dermatitis, during abstinence from oral exposure could be a sensitizing route bypassing oral tolerance (Figure 2). Additional evidence is the observation that household consumption rates of peanut, particularly messy products that increase environmental exposure, are a risk factor for peanut allergy, especial-
ly if the infant has not ingested peanut early. Prior recommendations to avoid food allergens during pregnancy, breastfeeding and for children during weaning have been substantially rescinded, although counter-examples remain (Figure 3) and more studies are needed. Ultimately, the environmental and genetic determinants of food allergy are complex, presenting a challenge for identifying prevention strategies (Figure 4).

**KEY REFERENCES**


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**Figure 1** Early consumption of peanut was associated with a lower rate of peanut allergy. A - Prevalence of peanut allergy in children 4-18 years; B - Peanut protein consumption 8-14 month; United Kingdom n=5171; Israel n= 5615. (Data from Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008; 122(5):984-91. Reprinted from *J Allergy Clin Immunol*, 129/5, Lack G. Update on risk factors for food allergy, 1187-1197, Copyright 2012, with permission from Elsevier.)

**Figure 2** Cutaneous exposure to a food allergen, especially to inflamed skin, may be a sensitizing route. With a concomitant lack of oral exposure to induce tolerance, the effect could be promoting food allergy. (Reprinted from *J Allergy Clin Immunol*, 129/5, Lack G. Update on risk factors for food allergy, 1187-1197, Copyright 2012, with permission from Elsevier.)
Figure 3  Although some studies suggest maternal ingestion of allergens during pregnancy or lactation does not increase the risk of sensitization/food allergy, there remains some controversy and more studies are needed. Here, a study of high risk infants suggests higher maternal ingestion of peanut during pregnancy is related to higher peanut IgE antibody levels in early infancy (P trend < 0.001). (Reprinted from J Allergy Clin Immunol, 126/6, Sicherer SH, Wood RA, Stablein D, et al. Maternal consumption of peanut during pregnancy is associated with peanut sensitization in atopic infants, 1191-1197, Copyright 2010, with permission from Elsevier.)

Figure 4  A complex interplay of genetic, immunologic and environmental influences likely conspires to result in food allergy, here with peanut as an example. (Reprinted from J Allergy Clin Immunol, 120/3, Sicherer SH, Sampson HA. Peanut allergy: emerging concepts and approaches for an apparent epidemic, 491-503, Copyright 2007, with permission from Elsevier.)
Global Atlas of Allergy
Section B - Epidemiology and risk factors

During the last half of the 20th century, the perennial indoor allergens progressively increased in importance and became the primary allergens related to asthma worldwide. While the individual’s home is an important site of exposure, it is now clear that exposure to indoor allergens in other homes or schools can play an important role in sensitization and symptoms. Comparing sensitization of children with asthma in different communities makes it clear that the community prevalence of a particular allergen may be as important as the specific levels in the child’s home. Although dust mites are ubiquitous in damp climates, they may be completely absent in ultra-dry environments such as Norbotten in Sweden and apartments in Chicago.

Exposure in the Home and in the Community as a Cause of Sensitization
Children spend up to 95% of their time at home, at school, or in other enclosed spaces. Initially it was assumed that the home had to be the primary site of sensitization; however, two findings have confused the simple message:

1. Studies designed to avoid exposure to dust mite carried out in Manchester and Sydney have not succeeded in preventing sensitization to this allergen.

2. Many but not all studies on cat exposure have found less sensitization to cats among children with higher exposure (Figure 1). For cat allergens, it is now clear that Fel d 1 on dander particles is present in schools and homes without a cat. Thus, exposure of children without a cat is sufficient to cause sensitization.

The Rise in Indoor Living and the Rise in Asthma
The dramatic rise in electronic indoor entertainment from 1950 to 2000 paralleled the rise in asthma among children. The resulting changes in lifestyle led to both a major increase in time spent indoors and progressive “improvements” in homes. These changes not only allowed accumulation of allergens in fitted carpets, sofas, bedding, etc. but in humid climates allowed abundant growth of dust mites. Over this same period, almost all studies have shown strong associations between sensitization to indoor allergens and asthma in children over 5 years old and young adults (Table 1).

Exposure to Indoor Allergens

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Key Messages
- During the last half of the 20th century, the perennial indoor allergens progressively increased in importance and became the primary allergens related to asthma worldwide.
- While the individual’s home is an important site of exposure, it is now clear that exposure to indoor allergens in other homes or schools can play an important role in sensitization and symptoms.
- Comparing sensitization of children with asthma in different communities makes it clear that the community prevalence of a particular allergen may be as important as the specific levels in the child’s home.
- Although dust mites are ubiquitous in damp climates, they may be completely absent in ultra-dry environments such as Norbotten in Sweden and apartments in Chicago.
Environmental risk factors for asthma: home environment

The increase in asthma has been documented as “wheezing” in ISAAC, as use of inhalers, or as presentation with acute asthma either to ED or hospital. In each of these settings, evaluation of sensitization has shown a strong correlation between asthma and the perennial and predominantly indoor allergens. In rural settings in Africa, Ecuador, Nepal, etc., sensitization as judged by skin prick tests may be present, but wheezing is more likely to correlate with evidence of Ascaris or other parasitic infections. In recent studies, in Costa Rica, New Zealand, Ghana, Ecuador and Norbotten,
there is consistent evidence that the western model of asthma relates to higher titers of IgE antibodies to one or more of the perennial allergens. Thus, overall we have a model where, increased time spent indoors in overheated and under ventilated buildings leads to sensitization to the predominant allergen in the community, which may be derived from mites, cockroaches, or animal dander. The major rise in prevalence of asthma in children is most likely to be due to the combination of increased exposure to indoor allergen and the associated sedentary lifestyle.

KEY REFERENCES
Environmental risk factors for allergy: working environment

Environmental agents at the workplace may lead to several allergic and non-allergic conditions. Occupational rhinitis or asthma, but also occupational chronic cough may develop upon exposure to agents at work. Sensitizing agents - in most cases high molecular weight (HMW) allergens, and sometimes low molecular weight (LMW) allergens - may induce an IgE mediated allergic reaction, responsible for allergic occupational rhinitis and asthma. Less frequently, single or multiple exposures to irritants will lead to non-allergic irritant-induced occupational rhinitis or asthma. Apart from these occupational diseases caused by work, environmental stimuli at work may also lead to worsening of pre-existing rhinitis, asthma or cough (work exacerbated rhinitis, asthma or cough). Figure 1 shows examples of allergens and stimuli responsible for the different work-related disorders. Chronic cough at work can be considered as a separate work-related disorder. Table 1 shows the occupations and causes of work-related chronic cough. There is some overlap between the different categories of eliciting agents. Sensitizers may also have irritating properties. Irritants may lead to occupational disease, but also to worsening of pre-existing disease.

The level of exposure is considered as the key factor for the development of occupational disorders. The risk increases with high exposure. Less is known of the impact of exposure pattern (duration, continuous or intermittent, peak exposures).

Apart from exposure, host factors may determine the risk of occupational rhinitis and asthma. Atopy is a risk factor for the development of IgE-mediated sensitization to HMW allergens in the working environment, and to a lesser extent for development of occupational rhinitis or asthma. The presence of atopy, however cannot be used to identify and exclude susceptible workers. Smoking has been associated with some work-related allergies such as allergies to bell peppers and platinum salts, but not in others. Possibly, the influence of smoking on development of occupational allergy dependents on the specific allergens involved. Finally, genetic factors may be associated with increased susceptibility to occupational asthma.
**Figure 1** Causes of work-related rhinitis or asthma.

**TABLE 1**

Causal agents of work related chronic cough

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miners</td>
<td>Methylmethacrylate</td>
</tr>
<tr>
<td>Cement and glass bottle production</td>
<td>Aliphatic polyamines</td>
</tr>
<tr>
<td>Construction workers</td>
<td>Grain and flour mills</td>
</tr>
<tr>
<td>Farming workers</td>
<td>Spices</td>
</tr>
<tr>
<td>Food industry</td>
<td>Dust due to World Trade Center collapse</td>
</tr>
<tr>
<td>Mushroom factory</td>
<td>Vapor Gases Dusts Fumes</td>
</tr>
<tr>
<td>Wood industry</td>
<td>Cattle and swine confinement farms</td>
</tr>
<tr>
<td>Dental technicians</td>
<td>Cleaning products</td>
</tr>
<tr>
<td>Fire-fighters</td>
<td>Second-hand smoking</td>
</tr>
<tr>
<td>Bakery</td>
<td></td>
</tr>
<tr>
<td>Mechanic and repair jobs</td>
<td></td>
</tr>
<tr>
<td>Spice factory</td>
<td></td>
</tr>
<tr>
<td>Greenhouse</td>
<td></td>
</tr>
<tr>
<td>Cleaners</td>
<td></td>
</tr>
</tbody>
</table>

**KEY REFERENCES**


Asthma is the most prevalent chronic disease of childhood. Given its significant health as well as socioeconomic burden, investigators around the world have sought to define environmental and genetic factors that contribute to asthma inception in early life. One important environmental factor demonstrable in multiple studies has been respiratory tract infections. From a genetics perspective, atopy and genetic variation at the 17q21 locus (that appears to be independent of atopy), are risk factors for asthma development. Interestingly, both appear to be dependent, at least in part, on antecedent preschool human rhinovirus (HRV) wheezing illnesses.

EARLY CHILDHOOD RESPIRATORY VIRAL INFECTION AND ASTHMA IN CHILDHOOD

Although early childhood respiratory syncytial viral (RSV) infections have been documented to contribute to future asthma risk, recent advances in molecular diagnostic testing have enabled investigators to establish a relationship between HRV wheezing illnesses and asthma. In an evaluation of a high risk birth cohort, Jackson et al. found that infection with HRV in the first three years of life was the virus most significantly associated with the development of asthma at age 6 years (Figure 1).

Mechanisms responsible for these developments are currently being intensely evaluated. Wark et al. found that cells from asthmatic patients had decreased production of both type I and III interferons, two important cytokines in the host’s innate immune response to viral infections. Recently, Caliskan and colleagues demonstrated that allelic variation at a highly replicable genetic locus for asthma was associated with significant asthma risk only in children who wheezed with HRV (not RSV) infections in early life. Since genes contained within this locus have functions that involve calcium membrane flux and the unfolded protein response, it is possible that alterations in these pathways may further influence host immune response to viral infections at critical times in the lung development. Recently, infections with HRV-C have been noted to be associated with more significant clinical illnesses that may be of even greater severity in atopic children.

COMBINED VIRAL INFECTION AND AEROALLERGEN SENSITIZATION

The relationship of atopy with the subsequent development of asthma is widely recognized. Aeroallergen sensitization in the first 2 to 3 years of life has been reported to be a risk factor for the subsequent development of asthma.
The development of multiple early sensitizations increases not only the risk of developing childhood asthma, but its clinical severity in terms of hospital admission rates as well.

Preschool viral wheezing illnesses and the development of allergic sensitization can both independently increase asthma risk. The presence of both can further influence the development of asthma, as demonstrated by data generated independently in two high-risk birth cohorts. In one of the high-risk birth cohort, Aeroallergen sensitization without documented preschool RV wheezing increased asthma risk by age six years (OR = 3.4) (Figure 2). If both RV wheezing and Aeroallergen sensitization were present at age three, the risk of developing asthma by age 6 years was substantially increased (OR = 80).

Jackson et al. longitudinally evaluated which development occurs first: allergic sensitization predisposing to viral-induced wheezing, or the reverse. Using a four stage statistical model, the study found that allergic sensitization is more likely to precede viral-induced wheezing. Moreover, HRV wheezing illnesses were the most likely infections accounting for this temporal developmental sequence. Allergic sensitization may increase lower airways inflammation and symptoms based on the ability of IgE receptor numbers and bridging to be associated with reduced dendritic cell production of type I and type III interferons with decreased viral host defense (Figure 3).

**INFLUENCE OF HRV WHEEZING ILLNESSES INDEPENDENT OF ATOPY**

Genome-wide association studies of childhood asthma risk have revealed a high susceptibility locus on chromosome 17q21. Genetic variation in this 17q21 region has been associated with increased childhood asthma risk but not with atopy. Caliskan and colleagues demonstrated that this association is in fact limited only to children who had HRV wheezing illnesses in the first three years of life. Importantly, this genotype-attributable increased risk is totally independent of allergic sensitization (atopy).

**CONCLUSION**

At least two distinct mechanistic pathways may predispose children to asthma (Figure 4), both dependent on antecedent HRV wheezing illnesses. The first pathway, termed 17q21, appears to be dependent on an asthma susceptibility locus and totally independent of the presence of allergic sensitization. The second pathway, termed FcεRI, is dependent on the development of allergic sensitization. Continued evaluation of mechanisms responsible for these pathways hopefully will provide insight into disease treatment and prevention strategies.

**KEY REFERENCES**

Figure 3 The process of allergic sensitization may influence innate immune responses to human rhinovirus (HRV) infection. Incubation of peripheral blood mononuclear cells (PBMCs) with HRV without cross linking of the high affinity receptor for IgE antibody (FcεRI) (left panel) results in decreased production of type I and type III interferons (IFN). Following cross-linking of this receptor (right panel) this decrease is further reduced.

Figure 4 Two distinct mechanistic pathways dependent on antecedent HRV wheezing illnesses predispose children to asthma. The first pathway, termed 17q21, appears to be dependent on an asthma susceptibility locus and totally independent of the presence of allergic sensitization. The second pathway, termed FcεRI, is dependent on the development of allergic sensitization.
**ENVIRONMENTAL RISK FACTORS FOR ALLERGY: HELMINTH INFECTIONS**

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Over 1 billion people worldwide are infected with parasitic worms. Most of these individuals are found in tropical regions of the world, where such infections are linked to poverty and rural living. Both helminths and allergens are potent inducers of T helper 2 (Th2) responses that lead to high levels of immunoglobulin (Ig) E, tissue eosinophilia, mast cells as well as the secretion of Th2 cytokines such as interleukin (IL)-4, IL-5, IL-9 and IL-13.

Despite the similar immunological profiles associated with both helminths and allergies, there is little overlap in the geographical distribution of these two health problems. Moreover, in developing countries, among urban populations of high socioeconomic status (SES), improved hygiene and fewer infections have been linked to an increase in allergic disorders. Indeed, a number of studies have found a negative association between helminth infections and allergic disorders among rural and low SES urban populations within these countries (Figure 1).

Mechanistically, chronic helminth infections have been shown to induce an immune regulatory network in the host characterized by regulatory T and B cells, alternatively activated macrophages and modified dendritic cells (Figure 2). This leads to an anti-inflammatory environment that prevents the down-stream effector phase of Th2 responses associated with allergic disorders. However, the timing and duration of helminth infection are key, since infections early in life and/or chronic infections are more effective in down-modulating allergic disease. In addition, the species of helminth is also an important determinant in the modulation of allergic disorders.

Another mechanism that might explain the inverse association between helminth infection and allergy may involve helminth-induced IgE cross-reactivity. Current helminth infections are associated with increased levels of allergen-specific IgE that do not translate into skin reactivity or clinical symptoms (Figure 3). Moreover, this helminth-induced IgE appears to be of low affinity and does not lead to mast cell degranulation.

In fact, in developing countries, strong correlations are observed between allergen-specific IgE and symptoms of allergy among urban
populations of high SES. However, in rural populations as well as urban low SES groups, helminth-induced IgE cross-reactivity and regulatory networks may prevent the translation of allergen-specific IgE into skin reactivity or allergic symptoms (Figure 4). Therefore, allergen-specific IgE has limited diagnostic value for allergic disease in helminth-endemic areas.

Future studies taking an international perspective will be essential for our understanding of environmental risk factors and underlying mechanisms to develop new treatments that can halt the allergy epidemic worldwide.

**KEY REFERENCES**


Figure 3 Differences in the prevalence of mite sensitization when measured as IgE or as SPT among 5-16 year olds from three populations living in Ghana (urban and more rural areas of the Greater Accra region which is undergoing rapid urbanization) and on two Islands in Indonesia (semi-urban and rural parts of Flores Island as well as among high SES and low SES subjects living in an urban centre of Sulawesi Island). The data presented are from Hamid F, Wiria AE, Wammes LJ, Kaisar MM, Djuardi Y, Versteeg SA, Wahyuni S, van Ree R, Sartono E, Supali T, Yazdanbakhsh M. Risk Factors Associated with the Development of Atopic Sensitization in Indonesia. PLoS One. 2013 19;8(6) :e67064 as well as unpublished data from field studies in Ghana and Sulawesi, Indonesia.

Figure 4 (i) In developing countries, the regulatory network induced by helminths and helminth-induced IgE cross-reactivity prevent the translation of Th2 responses into allergic disorders among groups with chronic helminth infections. (ii) In the same countries, among groups with no helminth infections, specific IgE translates into skin prick test positivity and allergy symptoms from field studies in Ghana and Sulawesi, Indonesia.
Interest in the role of immune development as a risk factor for atopy was first stimulated by experimental studies on the sequelae of \textit{de novo} exposure of immunologically naïve animals to aeroallergens. Such exposure triggered an initial "default" response comprising low-level Th2-immunity, including specific IgE production, which was eventually terminated by emergence of specific T-regulatory cells (Tregs) that induced a state of long-lived immunological tolerance, protecting the animals against sensitization at subsequent re-exposures. These findings served to focus human studies on the etiology of atopy on the life period (infancy), during which the naïve immune system first encounters allergens. A number of resultant observations attest to the validity of this approach:

(i) data from birth cohorts (Fig 1) demonstrate an initial induction of aeroallergen-specific IgE in both atopic and non atopic children during infancy, preceding subsequent stabilization of "tolerized" versus "sensitized" immunophenotypes, as the immune system progressively programs alternate forms of T-cell memory;

(ii) the rate of postnatal maturation of Th-cell functional competence (as measured by capacity to generate "balanced" Th1/Th2 cytokine responses) is slower in children at high risk for allergy development;

(iii) subsequent studies have extended the range of cell types manifesting atopic risk-associated developmental deficiencies to additional populations within the innate and adaptive immune system including monocytes, dendritic cells and Tregs.

Following the advent of the Hygiene Hypothesis in the late 1980s, interest has progressively increased in the role of the gut microbiome as the "driver" of postnatal development of immunocompetence. Recent findings suggest a link between postnatal development of immunity to organisms within the respiratory microbiome and risk for atopic asthma.

Since many of these functional deficiencies are already evident in cord blood the trajectory for postnatal immune maturation seems at least partially preset before birth. Observations stemming from the "farm barn" studies in Europe...
have identified TLR-dependent microbial signaling to innate immune cells in the maternal decidua as the potential mechanism: this may result in stabilization of the immunological milieu in the placenta, contributing to protection of the integrity of the local vasculature responsible for delivering nutrients to the fetus, thus optimizing in utero growth and development (Figure 2).

KEY REFERENCES


The development and phenotypic expression of allergic disease depends on the interaction between genetic and environmental factors such as exposure to allergens together with risk and/or protective factors (Table 1). Over the last decades an increase in the prevalence of allergic diseases has been reported worldwide. From prospective birth cohort studies, possible protective and risk factors have been identified (Table 2, 3). A family history of allergic disease (asthma, allergic rhinoconjunctivitis, atopic eczema or food allergy) in first degree relatives, is strongly associated with an increased risk for allergic disease.

Considering that the increase in the prevalence of allergic diseases cannot be ascribed solely to genetic factors, most studies on development of allergic diseases have focused on the influence of in environmental factors, e.g. early feeding (breastfeeding vs. cow’s milk formula), diets/nutrients, exposure to allergens, tobacco smoking, pollution, farm vs. urban environment, and infectious load. Many hypotheses have been proposed based on observed associations between environmental factors and development of allergic diseases. Such associations can only be used for generation of hypotheses.

Many hypotheses on causes of the increase in allergic diseases have been suggested, most often without convincing and consistent results (Table 4). The concept of the hygiene hypothesis has been extensively investigated and has influenced our understanding of early-life events. According to this hypothesis, early exposure to common bacterial triggers such as endotoxins, LPS or helminths might have an allergy preventive effect. The hygiene hypothesis may in part explain the increase in the incidence of allergic diseases. However, multifactorial environmental factors may play a role and interact (Table 3).

A strong association between exposure to allergens and IgE sensitization has been documented and also a strong association between sensitization and development of allergic disease, such as allergic asthma and rhinoconjunctivitis. Sensitization to foods appears first, followed by sensitisation to indoor allergens (e.g. house dust...
mites, pets) and later by sensitization to outdoor allergens (e.g. pollen, mould). However, sensitization may be a transient normal phenomena followed by development of tolerance.

THE CONCEPT OF AVOIDANCE
For decades, primary prevention addressing prevention of sensitization and development of clinical allergic disease has mostly focused on avoidance of exposure to allergens (e.g. foods, indoor allergens). Over the last decade, a new concept of primary prevention has emerged. Earlier it was believed that breastfeeding and avoidance of cow’s milk proteins could prevent development of cow’s milk protein allergy. However, human milk contains cow’s milk proteins, if the mother has an intake of cow’s milk. Other food proteins are also present in human milk. Thus, foreign proteins cannot be avoided by exclusive breastfeeding. The concept of avoidance of foods during breastfeeding is wrong. Infants are exposed to small amounts of foreign proteins (reduced exposure), which may rather lead to tolerance than to clinical allergic disease. Furthermore, breast milk contains many immune-modulating factors that may influence the development of allergy (Table 5).
Other routes of exposure occur via inhalation (proteins in house dust), or via the skin. Likewise, exposure to inhalant allergens cannot be totally avoided, and observational and interventional studies on avoidance/reduction of indoor allergen exposure (house dust mite, cat) have not shown convincing results. However, multifaceted allergy avoidance during infancy with avoidance of both foods and airborne indoor allergens have shown a persisting reduction of asthma. Importantly, the development of allergy to environmental allergens is a complex gene-environment interaction and some susceptible/predisposed individuals may benefit from reduction of allergen exposure. Further studies on the influence of both genetic and environmental factors are warranted. The present recommendations for primary prevention of allergic diseases are shown in Table 6 and 7.

**KEY REFERENCES**


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**TABLE 5**  
Factors in human milk influencing development of allergy

<table>
<thead>
<tr>
<th>Factors</th>
<th>Inducing</th>
<th>Protective</th>
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<tbody>
<tr>
<td>Antigens (e.g. food proteins)</td>
<td>Sensitising allergens</td>
<td>Tolerising allergens</td>
</tr>
<tr>
<td>Cytokines</td>
<td>IL-4</td>
<td>TGF-beta</td>
</tr>
<tr>
<td></td>
<td>IL-5</td>
<td>sCD 14</td>
</tr>
<tr>
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<td>IL-13</td>
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<td>Immunoglobulins</td>
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<td>PUFA</td>
<td>Arachidonic acid</td>
<td>N3-PUFA</td>
</tr>
<tr>
<td></td>
<td>N-6 PUFA</td>
<td>Other</td>
</tr>
</tbody>
</table>

**TABLE 6**  
Evidence-based recommendations for primary prevention of food allergy

- For all infants:
  - No special diet during pregnancy or for the lactating mother
  - Exclusively breastfeeding for 4-6 months

- Further recommendations for infants with atopic predisposition:
  - If supplement is needed during the first 4 months a documented hypoallergenic formula is recommended

**TABLE 7**  
Evidence-based recommendations for prevention of allergy to inhalant allergens

- Avoid exposure to tobacco smoke
- Avoid pets at home if parents or siblings are allergic to pets

**Common sense:**
- Restrict exposure to house dust mites and pets for children with atopic disposition
The number of microorganisms living in and on our body surfaces outnumber human cells by a factor of 10.

The microbiome is essential for a healthy immune response.

The gut microbiome plays an important role in protecting from the development of allergic airway disease in mice.

Exposure to a rich and diverse microbial environment such as seen on traditional farms protects from allergic diseases.

The role of microbiome

All plants, animals and humans live in close association with microbial organisms. Historically, microbiologists have isolated and grown microorganisms to identify pathogens causing disease. The advent of DNA-based sequencing methods has allowed amplification of DNA from microorganisms and thereby identification of a large variety of microorganisms that have never been cultured before. The Human Microbiome Project has shown that the human body contains trillions of microorganisms, which outnumber human cells by 10 to 1 (Figure 1). Their genes encode products essential for human survival. In the gastro-intestinal tract microbes break down many of the proteins, lipids and carbohydrates from our diet into nutrients so that we can absorb them. Moreover, microbes produce beneficial compounds such as vitamins. The microbiome also profoundly affects the host's immune response. Mice raised under germ-free conditions have profound deficits in innate and adaptive immunity suggesting that the microbiome educates a child's immune system.

Experimental studies in mice, furthermore suggest that the microbiome has a role for the development of allergic diseases. Germ-free mice develop more easily allergic asthma than conventionally raised mice. Reconstitution of neonates—but not adult—germ free mice with a conventional microbiota protected the animals from allergic disease. This protective effect may be mediated by activation of immune responses by microbial compounds. Alternatively or additionally metabolites secreted by microbes such as short-chain fatty acids may mediate these beneficial effects. Changes in the microbiome will occur with diet and antibiotics as long as they are ingested. But also microbial exposures in the environment will affect the microbiome and thereby the risk of allergic diseases.

Children being raised in environments rich in microbial exposures such as on traditional farms (Figure 2) have a much lower prevalence of asthma, hay fever and allergic sensitization as children grown up in urban settings. The diversity of the microbial exposure has been shown to account for the asthma-protective farm effect (Figure 3). In urban areas high exposure to environmental microbes (e.g. by keeping dogs indoors) also relates to a lower prevalence of allergic disease. A recent mouse study has demonstrated the pivotal role of the gut microbiome in mediating this protective environmental exposure. Some birth cohort studies also suggest that the composition of the gut microbiota may be a predictor for the onset of atopic eczema in young children, but these observations are not consistent and need further confirmation.
KEY REFERENCES
1. http://genome.cshlp.org/content/19/12/2317.full.html
Figure 2 Protection from childhood asthma and allergies has been shown for young children growing up on traditional farms rich in microbial exposures in the environment.

Figure 3 The diversity of bacterial and fungal exposure in the environment protects from childhood asthma. (From New Engl J Med, Ege MJ, Mayer M, Normand AC, et al. Exposure to environmental microorganisms and childhood asthma, 364, 701-9, Copyright © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)