

The hygiene hypothesis and asthma

Clare D. Ramsey^{a,b} and Juan C. Celedón^{a,b,c}

Purpose of review

Reduced exposure to childhood infections may explain the increased prevalence of allergic diseases in industrialized countries (the hygiene hypothesis). This review will examine recent epidemiologic studies of the hygiene hypothesis and asthma.

Recent findings

Recent studies have confirmed previous findings of an inverse association between increased exposure to other children during childhood and either allergen sensitization or hay fever. However, there is conflicting evidence regarding the relation between exposure to other children and asthma. Although it has been hypothesized that vaccinations may influence the development of asthma, recent findings do not support this association. Serologic evidence of exposure to certain gastrointestinal pathogens (eg, hepatitis A virus) has been inversely associated with either allergen sensitization or asthma in some, but not all, recent studies. Although heavy infestation with certain parasites (eg, helminths) is protective against allergen sensitization, there is conflicting evidence regarding the relation between parasitic infection and asthma. The results of recent studies suggest that the relation between endotoxin exposure and asthma is complex and likely influenced by factors related to the exposure itself, the host, and other covariates. Although it has been postulated that antibiotic use in early life is a risk factor for asthma, this hypothesis is not supported by recent findings.

Summary

For every exposure studied with regard to the hygiene hypothesis, there are inconsistent findings in relation to asthma. The hygiene hypothesis is not likely to be the sole explanation for the ongoing asthma epidemic in industrialized nations.

Keywords

asthma, hygiene hypothesis, allergen sensitization

Supported by the Department of Medicine of the University of Manitoba (Canada) and by Training Grant # 5 T32 HL07427 from the National Institutes of Health (Dr. Ramsey) and by Grant K01 HL04370 from the National Institutes of Health (Dr. Celedón).

Current Opinion in Pulmonary Medicine 2005, 11:14–20

Abbreviation

BCG bacille Calmette-Guérin

© 2004 Lippincott Williams & Wilkins
1070-5287

Introduction

Asthma is a major public health problem in industrialized countries [1,2]. Over the past several decades, the prevalence of asthma, hay fever, and eczema has increased substantially in countries with a “Western” lifestyle [1]. A potential explanation for the ongoing epidemic of allergic diseases is that declining family size and improved hygienic conditions have led to reduced exposure to infections in early childhood and more widespread expression of atopic diseases in industrialized nations (the hygiene hypothesis) [3].

A review of potential immunologic mechanisms underlying the hygiene hypothesis is beyond the scope of this review, and the reader is referred to recent reviews on this topic [4–6]. We examine epidemiologic studies of the hygiene hypothesis and asthma published in the past 2 years, focusing on the number of siblings; day care attendance in early life; crowding; general hygiene; mycobacterial exposure and vaccinations; gastrointestinal and parasitic infections; farming and endotoxin exposure; and antibiotics, probiotics, and the intestinal flora.

Household size, crowding, day care attendance, and general hygiene

There is consistent evidence of an inverse association between number of siblings and hay fever, but there are conflicting findings regarding the relation between number of siblings and asthma [7,8,9•]. Among 18,530 European adults, an increasing number of siblings was associated with decreased odds of hay fever but increased odds of asthma symptoms and reduced lung function; these findings were not appreciably changed after adjustment for potential confounders [9•]. Among British adults, there was an inverse association between number of siblings and allergen sensitization that was not changed after adjustment by physician-diagnosed infections in early childhood or previous infection with hepatitis A and *Helicobacter pylori* [8]. Although these findings

Curr Opin Pulm Med 11:14–20. © 2004 Lippincott Williams & Wilkins.

^aChanning Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, ^bDivision of Pulmonary and Critical Care Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, and ^cHarvard Medical School, Boston, Massachusetts, USA

Correspondence to Juan C. Celedón, 181 Longwood Ave, 4th floor, Boston, MA 02115, USA
Fax: 617 525 0958; e-mail: juan.celedon@channing.harvard.edu

could have been due to residual confounding by early infections, the authors hypothesized (as have others) that the protective effect of siblings against atopy may be due to *in utero* programming of the immune system [7,8].

Day care attendance in early life has been inversely associated with childhood asthma in some studies but not in others [10,11]. In a birth cohort study of children with a parental history of atopy, Celedón *et al.* [12••] found that day care attendance in early life was inversely associated with asthma at age 6 years among children without a maternal history of asthma (odds ratio [OR] = 0.3; 95% confidence interval [CI] = 0.1–0.7). Among children with a maternal history of asthma, there was no significant association between day care attendance in early life and asthma or recurrent wheezing. These findings suggest that a maternal history of asthma influences the relation between day care attendance in early life and asthma through yet-unidentified gene-by-environment interactions and/or shared exposures between mother and child in early life [12••]. Although early day care attendance has been inversely associated with allergen sensitization and/or eczema, little is known about the biologic mechanisms underlying this association [10,11,12••].

A recent matched case-control study from Sao Paulo, Brazil, showed that crowding (defined as four or more persons sharing the child's bedroom) was associated with a decreased incidence of asthma diagnoses (OR = 0.42; 95% CI = 0.21–0.87) but an increased incidence of lower respiratory tract infections in children aged 2 to 59 months [13]. Among 2250 adolescent boys in Pelotas, Brazil, crowding and living with other children in early childhood were inversely associated with asthma [14].

In the Avon Longitudinal Study of parents and children (ALSPAC), a high level of hygiene (as estimated by a hygiene score) was a risk factor for wheeze at 30 to 42 months of age. This association was essentially unchanged after adjustment for use of chemical cleaners and other potential confounders [15].

Mycobacterial infections and vaccinations

Although ecologic studies have found that active tuberculosis is inversely related to atopic diseases, there is little evidence to support the hypothesis that mycobacterial infections and/or immunization with bacille Calmette-Guérin (BCG) protect against atopy and asthma [16,17•,18,19]. Among Danish women who had been vaccinated, there was no association between age at BCG vaccination and either asthma or allergen sensitization [18]. In a large study of schoolchildren in Greenland, there was no association between either BCG vaccination or age at BCG vaccination and allergen sensitization [17•]. Among children in Gambia, there was no association between either a BCG scar or delayed-type hypersensitivity to tuberculin and allergen sensitization [19].

There has been conflicting evidence of an association between vaccination in infancy and asthma or atopy in childhood. Among 13,810 children in the ALSPAC study, pertussis vaccination was not associated with either childhood asthma or allergen sensitization [20••]. Among 29,238 children in the West Midlands General Practice Research Database, vaccination with either diphtheria, polio, pertussis, and tetanus or measles, mumps, and rubella was associated with asthma only among children with infrequent visits to a physician in the first 18 months of life. This finding was likely due to ascertainment bias (children with less access to medical care are less likely to be vaccinated and less likely to receive a diagnosis of asthma) [21].

Gastrointestinal and parasitic infections

Serologic evidence of previous infection with oral-fecal and food-borne microorganisms has been inversely associated with allergen sensitization in some cross-sectional studies but not in others [8,22,23••,24]. In a large study of subjects aged 6 to 59 years in the United States, hay fever (OR = 0.27; 95% CI = 0.18–0.41) and asthma (OR = 0.45; 95% CI = 0.31–0.66) were less common among individuals who had been previously infected with hepatitis A virus, *Toxoplasma gondii*, and herpes simplex virus 1 [23••]. By contrast, there was no association between previous infection with any of three organisms (hepatitis A, *H. pylori*, or herpes simplex virus) and either allergen sensitization or allergic diseases among Spanish and German university students [24]. Among Danish adults, allergen sensitization was inversely associated with having at least two markers of poor hygiene (previous infection with hepatitis A, *H. pylori*, or *T. gondii*) but positively associated with previous infection with at least two bacterial pathogens (*Clostridium difficile*, *Campylobacter jejuni*, or *Yersinia enterocolitica*) [25•]. These findings suggest that specific organisms may have different influences on allergen sensitization and/or serve as markers for other relevant infectious and noninfectious exposures.

Several cross-sectional studies have examined the relation between parasitic infections and allergen sensitization and atopic diseases [5,26–28,29•,30–33]. These studies suggest that parasitic infections characterized by heavy infestation with geohelminths (*eg*, *Ascaris lumbricoides*) or *Schistosoma mansoni* are inversely associated with allergen sensitization and that parasitic infections characterized by light infestation with geohelminths may increase the risk of allergen sensitization. Of interest, a recent longitudinal study found that treatment of severe infestations with helminths leads to increased allergen sensitization [34•]. Although infection with hookworm was inversely associated with wheeze in Ethiopia, infection with *A. lumbricoides* or *Trichuris trichiura* was not associated with asthma symptoms other than exercise-induced wheeze in a recent study in Ecuador [27,29•].

Farming and endotoxin exposure

Exposure to farming in early life has been associated with a decreased risk of asthma and allergen sensitization among schoolchildren in Central Europe and Canada, and cross-sectional studies in children have shown that early exposure to microbial products such as endotoxin may be protective against atopic asthma and allergen sensitization through down-regulation of immune responses or stimulation of Th1 immunity [35–38]. Among schoolchildren in New Zealand, farm residence in early life was associated with an increased risk of hay fever but no increased risk of asthma [39]. In Norway, adult farmers who had two or more types of livestock had a higher risk of nonatopic asthma and a lower risk of atopic asthma than farmers without livestock [40•]. In that study, current exposure to endotoxin, fungal spores, and ammonia was positively associated with nonatopic asthma but negatively associated with atopic asthma [40•].

In a recent cross-sectional study in countries with high (Sweden) and low (Estonia) prevalence of atopic diseases, an inverse association between endotoxin exposure and atopic diseases was shown in Sweden but not in Estonia—a finding that may have been due to a low level of variation in endotoxin levels in Estonian homes and/or unmeasured factors associated with endotoxin exposure in both countries [41].

A cross-sectional study of German schoolchildren found that high levels of endotoxin in house dust were inversely associated with allergen sensitization [42]. In that study, there was no association between exposure to endotoxin in house dust and any of three allergic diseases (asthma, hay fever, and eczema). Among infants with a parental history of atopy, endotoxin exposure in early life has been associated with a reduced risk of atopic eczema but increased risks of wheezing in early childhood [43,44••,45]. Litonjua *et al.* [46••] studied 226 children who were younger than 5 years of age and who had a parental history of atopy over a 4-year period. In that study, exposure to high concentrations of endotoxin in house dust was associated with an increased risk of wheeze over a 4-year period of observation; however, that risk declined rapidly over time [46••]. Occupational studies have shown inhaled endotoxin to be a risk factor for occupational lung disease (including nonatopic asthma), and epidemiologic studies have demonstrated that the level of endotoxin in house dust is associated with exacerbations of preexisting asthma [47,48]. Thus, the relation between endotoxin exposure and asthma is complex and likely dependent on the exposure itself (timing, dose, and route), the host (genetic susceptibility), and other covariates. With regard to farming, endotoxin may be a marker of other relevant microbial and nonmicrobial exposures.

In a recent cross-sectional study of European schoolchildren from the Allergies and Endotoxin study, exposure to muramic acid (a constituent of peptidoglycan that is present in gram-negative and gram-positive bacteria) in mattress dust was inversely associated with current wheezing independently of endotoxin or farm exposure [49•]. However, there was no significant association between exposure to muramic acid in mattress dust and either allergen sensitization or asthma.

Antibiotics, probiotics, and the intestinal flora

The intestinal flora is, quantitatively, the most important postnatal source of microbial stimulation of the immune system [50]. Experiments in murine models suggest that bacterial colonization of the gut is essential for postnatal maturation of Th1 immune responses and induction of oral tolerance and that Toll-like receptor 4—dependent signals provided by the intestinal flora inhibit the development of allergy to food antigens [51,52]. Cross-sectional studies and small prospective studies have shown an association between the composition of the intestinal flora and atopy in children [53].

In infant mice, antibiotics lead to alterations of the intestinal flora and impaired Th1 immune responses that can be prevented by the subsequent administration of probiotics [54,55]. Although little is known about the long-term effects of antibiotic use on the intestinal flora of young children, it was postulated that antibiotic use in early life led to alterations in the intestinal flora and an increased risk of atopy and asthma in childhood. However, none of the epidemiologic studies published to date has found an association between early antibiotic use and allergen sensitization, and a recent large study showed no association between antibiotic use in early life and hay fever [56,57•]. Among 4408 children who were enrolled in a health maintenance organization from birth to the age of 5 years, Celedón *et al.* [58•] found no significant association between antibiotic use in the first year of life and asthma diagnosed in children between the ages of 2 and 5 years (OR for at least 5 courses *vs* no courses of antibiotics = 1.0; 95% CI = 0.7–1.4). Among 746 adults in the United Kingdom, Cullinan *et al.* [56] found no significant association between the use of antibiotics for reasons other than lower respiratory infections in the first 5 years of life and asthma (OR for antibiotic use in the first year of life = 0.95; 95% CI = 0.65–1.40). Thus, current evidence suggests that there is no causal association between antibiotic use in early life and asthma but rather that antibiotic use in early life is more common among children with asthma.

A potential protective effect of the use of probiotics in early life against atopic diseases was examined in a randomized, double-blind, placebo-controlled study of 107

Table 1. Studies from October 2002 to July 2004 on the relation between various exposures and atopic diseases

Study	Study population	Allergen sensitization	Asthma	Hay fever/allergic rhinitis
Number of siblings				
Svanes <i>et al.</i> [9•]	Adults (20–44 years)	N/A	R (wheeze)	P
Cullinan <i>et al.</i> [8]	Adults from the UK	P (number of brothers)	N/A	N/A
Day care attendance				
Celedón <i>et al.</i> [12••]	Children with a parental history of atopy	N/A	P (children without maternal history of asthma)	Null
Crowding				
Cardoso <i>et al.</i> [13]	Brazilian children aged 2–59 months	N/A	P	N/A
da Costa Lima <i>et al.</i> [14]	Brazilian male adolescents	N/A	P	N/A
Farm exposure				
Wickens <i>et al.</i> [39]	Children aged 7–10 years in New Zealand	Null	Null	R
Eduard <i>et al.</i> [40•]	Adult farmers from Norway	Null	R (non-atopic asthma) P (atopic asthma)	N/A
Microbial burden				
Endotoxin exposure				
Bottcher <i>et al.</i> [41]	Children from Estonia and Sweden	P (Sweden only)	N/A	N/A
Bolte <i>et al.</i> [44••]	Infants from a birth cohort in Germany	R (in those with parental history of atopy)	R (repeated wheeze in those with parental history of atopy)	N/A
Litonjua <i>et al.</i> [46••]	Infants with parental history of atopy	N/A	R (for wheeze, but declined over time)	N/A
Gehring <i>et al.</i> [42]	German children aged 5–10 years	P	Null	Null
Muramic acid				
van Strien <i>et al.</i> [49•]	European children from ALEX study	Null	P (current wheezing independent of endotoxin)	Null
Mycobacteria/BCG vaccination				
Krause <i>et al.</i> [17•]	Children aged 8–16 in Greenland (BCG vaccination)	Null	N/A	N/A
Bager <i>et al.</i> [18]	Danish women (BCG vaccination)	Null	Null	Null
Ota <i>et al.</i> [19]	Gambian schoolchildren (BCG and tuberculin response)	Null	N/A	N/A
Parasites				
Cooper <i>et al.</i> [29•]	Children aged 5–18 years in rural Ecuador	P	P (exercise-induced wheeze only)	Null
Cooper <i>et al.</i> [30]	Children aged 5–19 years in rural Ecuador	P (active and chronic infections)	N/A	N/A
Cooper <i>et al.</i> [31]	Children 7–17 years in Ecuador	P (any helminth)	N/A	N/A
Van den Biggelaar <i>et al.</i> [34•]	Children aged 5–14 years in Gabon	P (SPT to dust mite)	N/A	N/A
Gastrointestinal infections				
Matricardi <i>et al.</i> [23••]	Children and adults in the United States	P (aged < 40 years and HAV seropositive)	P (aged 6–59 years seropositive for HAV and HSV-1)	P (aged 6–59 years seropositive for HAV, <i>T. gondii</i> and HSV-1)
Uter <i>et al.</i> [24]	Spanish/Germans aged 18–20 years	Null ^a	Null ^a	Null ^a
Linneberg <i>et al.</i> [25•]	Danish subjects aged 15–69 years	P ^a R ^b	N/A	P ^a R ^b
Cullinan <i>et al.</i> [8]	British adults	Null (HAV, <i>H. pylori</i>) P (physician-diagnosed GI infections before age 5 years)	N/A	N/A
Vaccinations				
Maitra <i>et al.</i> [20••]	ALSPAC study (pertussis)	Null	Null	N/A
McKeever <i>et al.</i> [21]	Children aged 0–11 years (MMR and DPPT)	N/A	R (only in children with infrequent physician visits)	N/A
Antibiotics/probiotics				
Celedón <i>et al.</i> [58•]	Children in the U.S. (monitored up to age 5 years)	N/A	Null	N/A
Bremner <i>et al.</i> [57•]	British children (monitored up to age 5 years)	N/A	N/A	Null
Cullinan <i>et al.</i> [56]	UK adults	Null	Null	Null
Kalliomäki <i>et al.</i> [59•]	Children from a RCT of lactobacillus vs. placebo	Null	Null	Null

P, protective; R, risk factor; Null, no (null) association; N/A, not assessed; SPT, skin prick test; LRTI, lower respiratory tract illness; HAV, hepatitis A virus; HSV1, herpes simplex virus 1; MMR, measles, mumps, and rubella; DPPT, diphtheria, polio, pertussis, and tetanus.

^aHAV, *Helicobacter pylori*, and *Toxoplasma gondii*.

^b*Clostridium difficile*, *Campylobacter jejuni*, and *Yersinia enterocolitica*.

infants with a family history of atopy [59]. Treatment with lactobacilli or placebo was begun prenatally and then continued 6 months after birth. After 4 years of follow-up, there was a reduced risk of atopic eczema among children treated with probiotics (relative risk = 0.57; 95% CI = 0.33–0.97) [59•]. However, treatment with probiotics was not associated with reduced risks of allergen sensitization, asthma, or allergic rhinitis.

Conclusion

Recent findings support the hypothesis that reduced exposure to other children is associated with an increased risk of allergen sensitization (Table 1). However, no specific infectious agents or microbial components that may be transmitted through contact with other children and/or that protect against allergen sensitization and specific allergic diseases (*eg*, hay fever) have been confidently identified.

For every exposure studied with regard to the hygiene hypothesis, there are inconsistent findings in relation to asthma (Table 1). This is not surprising, because asthma comprises atopic and nonatopic phenotypes, and a significant proportion of cases of asthma are not diagnosed in childhood. Because most individuals with atopy do not have asthma and a significant proportion of individuals with asthma are not atopic, factors that may protect against the development of allergen sensitization may have no relation to asthma, and *vice versa*. In addition, exposures that may be protective against asthma in low-risk individuals (*eg*, those without a family history) may not be protective or may even be detrimental in individuals at high risk for asthma. Because of the complex pathogenesis of the asthma phenotype, reduced exposure to infectious agents or microbial components in early life is unlikely to be the sole explanation for the increased prevalence of asthma in industrialized nations. Longitudinal studies of the relation between accurately measured microbial exposures and carefully assessed asthma phenotypes in well-defined populations are needed to clarify whether and how microbial exposures in early life influence the development of atopic asthma in childhood.

Acknowledgments

The authors thank Dr. Scott T. Weiss for helpful comments on the manuscript.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
- Of outstanding interest

- 1 Mannino DM, Homa DM, Akinbami LJ, et al.: Surveillance for asthma: United States, 1980–1999. *Morb Mortal Wkly Rep Surveill Summ* 2002, 51:1–13.
- 2 Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* 1998, 351:1225–1232.
- 3 Strachan DP: Hay fever, hygiene, and household size. *BMJ* 1989, 299:1259–1260.
- 4 Romagnani S: The increased prevalence of allergy and the hygiene hypothesis: missing immune deviation, reduced immune suppression, or both? *Immunology* 2004, 112:352–363.
- 5 Yazdanbakhsh M, Kreamsner PG, van Ree R: Allergy, parasites, and the hygiene hypothesis. *Science* 2002, 296:490–494.
- 6 Rautava S, Ruuskanen O, Ouweland A, et al.: The hygiene hypothesis of atopic disease: an extended version. *J Pediatr Gastroenterol Nutr* 2004, 38:378–388.
- 7 Karmaus W, Botezan C: Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health* 2002, 56:209–217.
- 8 Cullinan P, Harris JM, Newman Taylor AJ, et al.: Can early infection explain the sibling effect in adult atopy? *Eur Respir J* 2003, 22:956–961.
- 9 Svanes C, Jarvis D, Chinn S, et al.: Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax* 2002, 57:945–950.
- This large cross-sectional study of the relation between early exposure to children and allergic diseases confirmed a negative association between number of siblings and hay fever and found a positive association between number of siblings and asthma symptoms and lung function.
- 10 Ball TM, Castro-Rodriguez JA, Griffith KA, et al.: Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000, 343:538–543.
- 11 Kramer U, Heinrich J, Wjst M, et al.: Age of entry to day nursery and allergy in later childhood. *Lancet* 1999, 353:450–454.
- 12 Celedón JC, Wright RJ, Litonjua AA, et al.: Day care attendance in early life, maternal history of asthma, and asthma at age 6 years. *Am J Respir Crit Care Med* 2003, 167:1239–1243.
- The findings of this prospective birth cohort study of children with atopy suggest that a maternal history of asthma influences the relation between day care attendance in early life and childhood asthma.
- 13 Cardoso MR, Cousens SN, De Goes Siqueira LF, et al.: Crowding: risk factor or protective factor for lower respiratory disease in young children? *BMC Public Health* 2004, 4:19.
- 14 da Costa Lima R, Victora CG, Menezes AM, et al.: Do risk factors for childhood infections and malnutrition protect against asthma? A study of Brazilian male adolescents. *Am J Public Health* 2003, 93:1858–1864.
- 15 Sherriff A, Golding J: Hygiene levels in a contemporary population cohort are associated with wheezing and atopic eczema in preschool infants. *Arch Dis Child* 2002, 87:26–29.
- 16 Matricardi PM, Yazdanbakhsh M: Mycobacteria and atopy, 6 years later: a fascinating, still unfinished, business. *Clin Exp Allergy* 2003, 33:717–720.
- 17 Krause TG, Hviid A, Koch A, et al.: BCG vaccination and risk of atopy. *JAMA* 2003, 289:1012–1015.
- This cross-sectional study of 1575 schoolchildren in Greenland found no association between BCG vaccination and allergen sensitization. Among children who were vaccinated with BCG, there was no significant association between age at vaccination and allergen sensitization.
- 18 Bager P, Rostgaard K, Nielsen NM, et al.: Age at bacille Calmette-Guerin vaccination and risk of allergy and asthma. *Clin Exp Allergy* 2003, 33:1512–1517.
- 19 Ota MO, van der Sande MA, Walraven GE, et al.: Absence of association between delayed type hypersensitivity to tuberculin and atopy in children in The Gambia. *Clin Exp Allergy* 2003, 33:731–736.
- 20 Maitra A, Sherriff A, Griffiths M, et al.: Pertussis vaccination in infancy and asthma or allergy in later childhood: birth cohort study. *BMJ* 2004, 328:925–926.
- Among 13,810 children in the Avon longitudinal study of parents and children, there was no significant association between pertussis vaccination in infancy and either asthma or allergen sensitization.

- 21 McKeever TM, Lewis SA, Smith C, et al.: Vaccination and allergic disease: a birth cohort study. *Am J Public Health* 2004, 94:985–989.
- 22 Matricardi PM, Rosmini F, Riondino S, et al.: Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ* 2000, 320:412–417.
- 23 Matricardi PM, Rosmini F, Panetta V, et al.: Hay fever and asthma in relation to markers of infection in the United States. *J Allergy Clin Immunol* 2002, 110:381–387.
- This cross-sectional study of 21,260 children and adults in the United States found an inverse association between serologic evidence of previous infection with foodborne and orofecal organisms and hay fever and asthma.
- 24 Uter W, Stock C, Pfahlerberg A, et al.: Association between infections and signs and symptoms of "atopic" hypersensitivity: results of a cross-sectional survey among first-year university students in Germany and Spain. *Allergy* 2003, 58:580–584.
- 25 Linneberg A, Ostergaard C, Tvede M, et al.: IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2003, 111:847–853.
- The findings of this cross-sectional study in Danish adults suggest that previous exposure to certain gastrointestinal pathogens (eg, *C. difficile*) may be a marker of an increased risk of allergen sensitization.
- 26 van den Biggelaar AH, van Ree R, Rodrigues LC, et al.: Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* 2000, 356:1723–1727.
- 27 Scrivener S, Yemaneberhan H, Zebeignus M, et al.: Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet* 2001, 358:1493–1499.
- 28 Dold S, Heinrich J, Wichmann HE, et al.: Ascaris-specific IgE and allergic sensitization in a cohort of school children in the former East Germany. *J Allergy Clin Immunol* 1998, 102:414–420.
- 29 Cooper PJ, Chico ME, Bland M, et al.: Allergic symptoms, atopy, and geohelminth infections in a rural area of Ecuador. *Am J Respir Crit Care Med* 2003, 168:313–317.
- Among 4433 schoolchildren in a rural area of Ecuador, infection with geohelminths was inversely associated with allergen sensitization. However, there was no association between helminthiasis and asthma symptoms other than exercise-induced wheeze.
- 30 Cooper PJ, Chico ME, Rodrigues LC, et al.: Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. *J Allergy Clin Immunol* 2003, 111:995–1000.
- 31 Cooper PJ, Chico ME, Rodrigues LC, et al.: Risk factors for atopy among school children in a rural area of Latin America. *Clin Exp Allergy* 2004, 34:845–852.
- 32 Palmer LJ, Celedón JC, Weiss ST, et al.: *Ascaris lumbricoides* infection increases risk of asthma and atopy in children from rural China. *Am J Respir Crit Care Med* 2002, 165:1489–1493.
- 33 Medeiros M Jr, Almeida MC, Figueiredo JP, et al.: Low frequency of positive skin tests in asthmatic patients infected with *Schistosoma mansoni* exposed to high levels of mite allergens. *Pediatr Allergy Immunol* 2004, 15:142–147.
- 34 van den Biggelaar AH, Rodrigues LC, van Ree R, et al.: Long-term treatment of intestinal helminths increases mite skin-test reactivity in Gabonese schoolchildren. *J Infect Dis* 2004, 189:892–900.
- Although a large proportion of children participating in this randomized controlled trial of antihelminthic therapy were lost to follow-up, this study found that long-term treatment of helminthiasis was associated with an increased risk of skin test reactivity to house dust mite among Gabonese schoolchildren.
- 35 Riedler J, Braun-Fahrlander C, Eder W, et al.: Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 2001, 358:1129–1133.
- 36 Ernst P, Cormier Y: Relative scarcity of asthma and atopy among rural adolescents raised on a farm. *Am J Respir Crit Care Med* 2000, 161:1563–1566.
- 37 Braun-Fahrlander C, Riedler J, Herz U, et al.: Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002, 347:869–877.
- 38 Gereda JE, Leung DY, Thatayatikom A, et al.: Relation between house-dust endotoxin exposure, type 1 T-cell development, and allergen sensitisation in infants at high risk of asthma. *Lancet* 2000, 355:1680–1683.
- 39 Wickens K, Lane JM, Fitzharris P, et al.: Farm residence and exposures and the risk of allergic diseases in New Zealand children. *Allergy* 2002, 57:1171–1179.
- 40 Eduard W, Douwes J, Omenaas E, et al.: Do farming exposures cause or prevent asthma? Results from a study of adult Norwegian farmers. *Thorax* 2004, 59:381–386.
- This cross-sectional study of 1614 farmers in Norway found that exposure to at least two types of livestock was negatively associated with atopic asthma but positively associated with nonatopic asthma.
- 41 Bottcher MF, Bjorksten B, Gustafson S, et al.: Endotoxin levels in Estonian and Swedish house dust and atopy in infancy. *Clin Exp Allergy* 2003, 33:295–300.
- 42 Gehring U, Bischof W, Fahlbusch B, et al.: House dust endotoxin and allergic sensitization in children. *Am J Respir Crit Care Med* 2002, 166:939–944.
- 43 Phipatanakul W, Celedón JC, Raby BA, et al.: Endotoxin exposure and eczema in the first year of life. *Pediatrics* 2004, 114:13–18.
- 44 Bolte G, Bischof W, Borte M, et al.: Early endotoxin exposure and atopy development in infants: results of a birth cohort study. *Clin Exp Allergy* 2003, 33:770–776.
- Among 1942 German infants monitored from birth to the age of 2 years, these authors showed that exposure to high levels of endotoxin in house dust was associated with an increased risk of repeated wheeze in children with a parental history of atopy.
- 45 Park JH, Gold DR, Spiegelman DL, et al.: House dust endotoxin and wheeze in the first year of life. *Am J Respir Crit Care Med* 2001, 163:322–328.
- 46 Litonjua AA, Milton DK, Celedón JC, et al.: A longitudinal analysis of wheezing in young children: the independent effects of early life exposure to house dust endotoxin, allergens, and pets. *J Allergy Clin Immunol* 2002, 110:736–742.
- This longitudinal study of children younger than 5 years found that exposure to increased concentrations of endotoxin in house dust was associated with an increased risk of wheeze over a 46-month period of observation. However, the risk of wheeze associated with endotoxin exposure declined over time.
- 47 Michel O, Kips J, Duchateau J, et al.: Severity of asthma is related to endotoxin in house dust. *Am J Respir Crit Care Med* 1996, 154:1641–1646.
- 48 Rizzo MC, Naspitz CK, Fernandez-Caldas E, et al.: Endotoxin exposure and symptoms in asthmatic children. *Pediatr Allergy Immunol* 1997, 8:121–126.
- 49 van Strien RT, Engel R, Holst O, et al.: Microbial exposure of rural school children, as assessed by levels of N-acetyl-muramic acid in mattress dust, and its association with respiratory health. *J Allergy Clin Immunol* 2004, 113:860–867.
- The findings of this cross-sectional study suggest that microbial exposures other than endotoxin influence the development of asthma in children living in rural communities.
- 50 Salminen S, Bouley C, Boutron-Ruault MC, et al.: Functional food science and gastrointestinal physiology and function. *Br J Nutr* 1998, 80(Suppl 1): S147–S171.
- 51 Sudo N, Sawamura S, Tanaka K, et al.: The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997, 159:1739–1745.
- 52 Bashir ME, Louie S, Shi HN, et al.: Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *J Immunol* 2004, 172:6978–6987.
- 53 Bjorksten B: Effects of intestinal microflora and the environment on the development of asthma and allergy. *Springer Semin Immunopathol* 2004, 25:257–270.
- 54 Oyama N, Sudo N, Sogawa H, et al.: Antibiotic use during infancy promotes a shift in the T(H)1/T(H)2 balance toward T(H)2-dominant immunity in mice. *J Allergy Clin Immunol* 2001, 107:153–159.
- 55 Sudo N, Yu XN, Aiba Y, et al.: An oral introduction of intestinal bacteria prevents the development of a long-term Th2-skewed immunological memory induced by neonatal antibiotic treatment in mice. *Clin Exp Allergy* 2002, 32:1112–1116.
- 56 Cullinan P, Harris J, Mills P, et al.: Early prescriptions of antibiotics and the risk of allergic disease in adults: a cohort study. *Thorax* 2004, 59:11–15.
- 57 Bremner SA, Carey IM, DeWilde S, et al.: Early-life exposure to antibacterials and the subsequent development of hayfever in childhood in the UK: case-

control studies using the General Practice Research Database and the Doctors' Independent Network. *Clin Exp Allergy* 2003, 33:1518–1525.

This case-control study nested within a large cohort (N = 116,493) of children who were registered in 605 general practices from birth to the age of 5 years found no significant association between antibiotic use in early childhood and hay fever.

- 58** Celedón JC, Fuhlbrigge A, Rifas-Shiman S, et al.: Antibiotic use in the first year of life and asthma at age 5 years. *Clin Exp Allergy* 2004, 34:1011–1016.
- This study of 4408 children who were enrolled in a health maintenance organization from birth to the age of 5 years found that antibiotic use was associated with

asthma diagnosed in children before the age of 2 years but not with asthma diagnosed in children between the ages of 2 and 5 years.

- 59** Kalliomaki M, Salminen S, Poussa T, et al.: Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003, 361:1869–1871.

This small randomized controlled trial of probiotics as preventive therapy for allergic diseases lost approximately a third of the participating subjects to follow-up. Although there was an inverse association between the use of probiotics and atopic dermatitis, the use of probiotics was not significantly associated with allergen sensitization or asthma.