

RECENT ADVANCES

The development of childhood asthma: lessons from the German Multicentre Allergy Study (MAS)

Susanne Lau,^{1*} Renate Nickel,¹ Bodo Niggemann,¹ Christoph Grüber,¹ Christine Sommerfeld,¹ Sabina Illi,² Michael Kulig,³ Johannes Forster,⁴ Ulrich Wahn¹ and the MAS Group[†]

¹University Children's Hospital, Department of Pneumology and Immunology Berlin, Charité Campus Virchow, Augustenburger Platz 1, 13353 Berlin, Germany; ²University Children's Hospital Dr. von Hauner, Lindwurmstr. 4, 80337 München, Germany; ³Charité Institute of Social Medicine, Epidemiology and Health Economics, Humboldt University Berlin, Berlin, Germany; ⁴St. Josefskrankenhaus Department of Pediatrics, Hermann-Herder-Str. 1, 79104 Freiburg, Germany

KEYWORDS

childhood asthma, mite and cat exposure, sensitisation, ETS, early infections, prevention

Summary Epidemiological surveys have indicated that there has been a notable increase in the prevalence of both asthma and other allergic symptoms in children and young adults. Since it seems unlikely that genetic factors would contribute to the rising trend, environmental factors might play a major part in the development of childhood asthma.

In a prospective birth-cohort study, we assessed the relevance of different exposures such as mite and cat allergen exposure, environmental tobacco smoke (ETS) exposure, early infectious diseases and vaccinations for the development of childhood asthma up to the age of 10 years. Data up to 7 years of age have been evaluated. Of 1314 newborn infants enrolled in five German cities in 1990, follow-up data at age 7 years were available for 939 children (72%). Assessments included repeated measurements of specific IgE to food and inhalant allergens, measurement of indoor allergen exposure at 6 months, 18 months and 3 years of age and yearly interviews by a paediatrician. At age 7 years, pulmonary function was tested and bronchial responsiveness was determined in 645 children. At age 7, the prevalence of wheezing in the past 12 months was 10% (94 out of 938), and 6.1% (57 out of 939) parents reported a doctor's diagnosis of asthma in their children. Sensitisation to indoor allergens was associated with asthma, wheeze and increased bronchial responsiveness. However, no relationship between early indoor allergen exposure and the prevalence of asthma, wheeze and bronchial responsiveness was seen.

During the first 3 years of life, intra-uterine tobacco and consistent ETS exposure have an adjuvant effect on allergic sensitisation that is transient and restricted to children with a genetic predisposition for allergy.

Children sensitised to any allergen early in life and sensitised to inhalant allergens by the age of 7 years were at a significantly increased risk of being asthmatic at this age (odds ratio (OR) = 10.12; 95% confidence interval (CI) = 3.81–26.88). Children with repeated episodes (≥ 2) of runny nose before the age of 1 year were less likely to develop asthma by the age of 7 years (OR = 0.52; 95% CI = 0.29–0.92).

*Correspondence to: Susanne Lau. Tel.: +49 30 4505 66 182; Fax: +49 30 4505 66 931; E-mail: susanne.lau@charite.de

[†]MAS collaborators were as follows: Marketa Groeger MD, Düsseldorf; Fred Zepp MD, Wolfgang Kamin MD and Imke Bieber MD, Mainz; Uta Tacke MD, Freiburg; Volker Wahn MD, Schwedt; Carl-Peter Bauer MD, Gaissach; Renate Bergmann MD, Berlin; Erika von Mutius MD, München.

Our data do not support the hypothesis that exposure to environmental allergens directly causes asthma in childhood but that induction of specific IgE responses and the development of childhood asthma are determined by independent factors. Indoor allergen avoidance is recommended as first line treatment in secondary and tertiary prevention; however, conclusions should be drawn with caution about the possible effect of primary preventative measures. Since allergic asthma seems to be a Th2-disease, immunomodulating factors such as early childhood infections, LPS-exposure or other factors influencing gene–environment interaction and individual susceptibility seem to be relevant for the development of childhood asthma.

© 2002 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Atopic diseases and asthma represent an increasing health problem in industrialised Western societies and are the most frequent chronic illnesses in childhood.^{1–3} The development of atopy is favoured by a shift towards Th2-like cytokines (interleukin-4 (IL-4), IL-5, IL-13) in humans promoting the production of IgE antibodies.^{4,5} Several potential determinants being responsible for the development of atopy and asthma have been proposed such as lack of severe and repeated infections,^{6,7} obesity and lack of physical exercise,⁸ decreased family size,^{9–11} changing dietary habits^{12,13} and increased indoor allergen exposure.^{14,15}

Children of farmers who have contact with livestock and therefore to Gram-negative bacteria and endotoxins from the lipopolysaccharides of the bacterial cell wall were found to have a lower risk for the development of hay fever and specific sensitisation than other children.^{16–18} Lifestyle seems to be an important influencing variable. Children with an anthroposophic lifestyle showed a lower prevalence of atopic diseases in a Swedish study.¹⁹

Exposure to house dust mite *Dermatophagoides* allergen has been considered to be one major risk factor for the development of asthma and specific sensitisation.^{20–24} Jennifer Peat and colleagues postulated that, in Australia, the risk of childhood asthma is increasing in parallel with increasing mite allergen exposure.^{14,21} The International Study of Asthma and Atopy in Childhood (ISAAC) showed that in areas with very high mite allergen exposure (Australia, Great Britain, New Zealand) the prevalence of asthma in childhood was higher than in other countries.^{25,26}

In cross-sectional studies a relationship between cat allergen exposure and specific sensitisation has been reported and cat sensitisation seems to be a major risk factor for asthma.^{27–29} However, there is some evidence that in certain circumstances high allergen exposure and contact with pets early in life may prevent asthma later on.^{30–32}

Several asthmatic phenotypes exist and many epidemiological studies have not used the same asthma definitions, making interpretation of the data even more complicated. However, asthma and atopy in childhood seem to run in parallel if certain perinatal or hereditary influences prevail,

rather than being subsequent stepping stones in a progressive atopic march. Some authors even doubt that atopy or allergen exposure are the most important risk factors for asthma.^{33,34}

Conflicting data have been published about the significance of tobacco smoke exposure in childhood and the development of atopic sensitisation and asthma.^{35–38}

Having older siblings has consistently been shown to reduce the risk of developing atopic diseases.^{9–11} This effect has been confirmed using markers of infectious burden such as number of older siblings,¹¹ attendance at day care facilities^{39,40} and positive serology to orofaecal infections^{41,42} but some authors failed to relate the protective effect of siblings to exposure to personal infections or infections in siblings.⁴³ However, whether such a protective effect operates for asthma remained unclear. Several authors have indeed reported that infections may enhance the development of asthma, particularly infections with respiratory syncytial virus.^{44,45} The longitudinal German Multicentre Allergy Study (MAS) is a birth-cohort study with regular assessment of asthma and asthmatic symptoms (Figs 1 & 2), measurements of specific IgE from age 1 year to 7 years and assessment of different exposure factors such as tobacco smoke, indoor allergens and infections and it therefore offers the ideal data for the analysis of the association of exposure factors, atopic sensitisation and the development of childhood asthma in an observational, prospective setting.⁴⁶ The aim of the study was to characterise the typical course of atopic sensitisation in the development of childhood asthma and to identify factors that influence and drive the atopic march from atopic sensitization to asthma.

THE SIGNIFICANCE OF INDOOR ALLERGENS FOR THE DEVELOPMENT OF SPECIFIC SENSITISATION AND ASTHMA IN CHILDHOOD^{47,48}

At the age of 7, the prevalence of “wheezing ever” was 17.4% (163/938), that of “ever asthma, diagnosed by a doctor” was 6.1% (57/939), while the period prevalence of

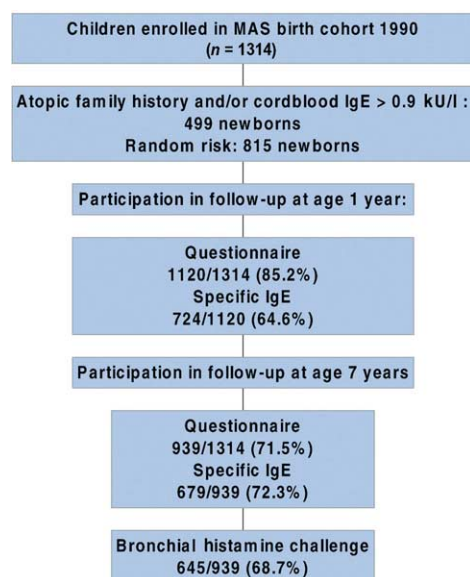


Figure 1 Study population at birth, at age 1 and at age 7 years.

"current wheeze", i.e. wheezing episodes during the last 12 months prior to the interview, was 10% (94/938). Fifty per cent of children with "current wheeze" reported wheezing episodes during the first 3 years of life and

70% showed specific sensitisation to inhalant and/or food allergens at age 7.

Boys had a higher risk for atopy and asthma than girls at the age of 3 and 7 years. There was no difference in mite (Der p 1 + Der f 1) and cat (Fel d 1) allergen levels at 6 and 18 months between families with or without a family history for asthma or atopy. Families owning a cat showed a significantly higher exposure than families without a cat (20 µg/g Fel d 1 versus 0.046 µg/g, $P < 0.0001$, age 6 months). However, there was no difference in the prevalence of wheeze in the last 12 months and bronchial hyper-responsiveness (BHR) due to cat ownership.

There was a strong association between sensitisation to mite and/or cat allergens and wheezing (Fig. 3), which became significant around the 3rd year of life. Furthermore, children with sensitisation to indoor allergens showed higher bronchial responsiveness.

Indoor allergen exposure was strongly related to specific sensitisation at age 3 to 7 years (Fig. 4); however, at 7 years, this effect was more pronounced for mite than for cat. We were unable to detect a consistent dose-response relationship for early indoor allergen exposure and "doctor's diagnosed asthma", "wheezing within the last 12 months" or "wheezing ever" (Fig. 5). Similar results were seen for indoor allergen exposure on carpets at 4 and 5 years of age

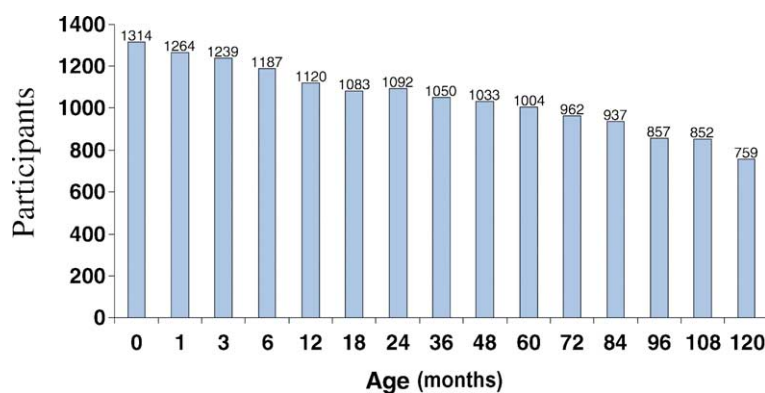


Figure 2 Participation rates for 1990–2000.

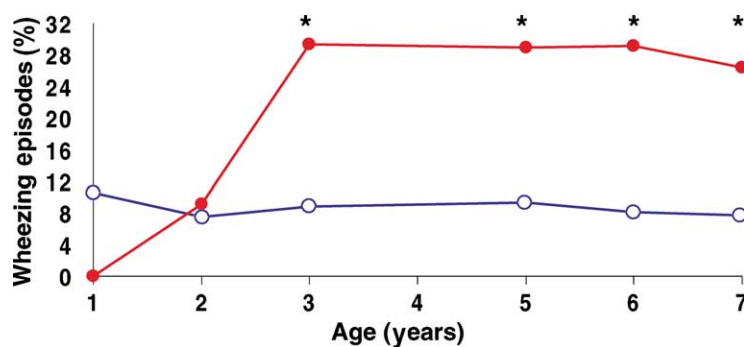


Figure 3 Sensitisation to house dust mite and wheezing up to 7 years of age. (●) sensitised; (○) not sensitised. * $P < 0.001$. Reproduced, with permission, from Lau et al.⁴⁸

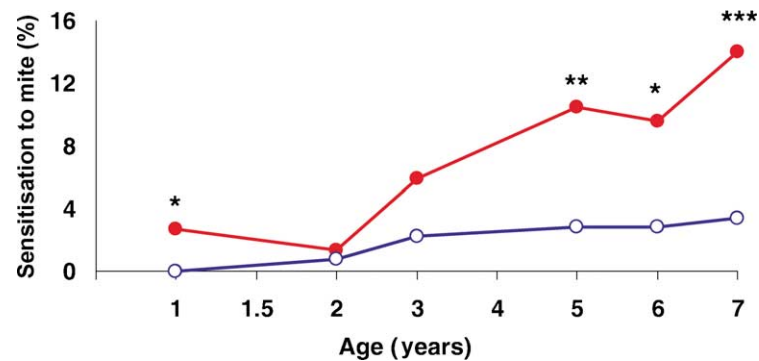


Figure 4 Exposure to house dust mite at 6 months of age and sensitisation to mite up to 7 years of age. (○) 1st quartile; (●) 4th quartile. * $P \leq 0.005$; ** $P \leq 0.01$; *** $P \leq 0.001$. Reproduced, with permission, from Lau et al.⁴⁸

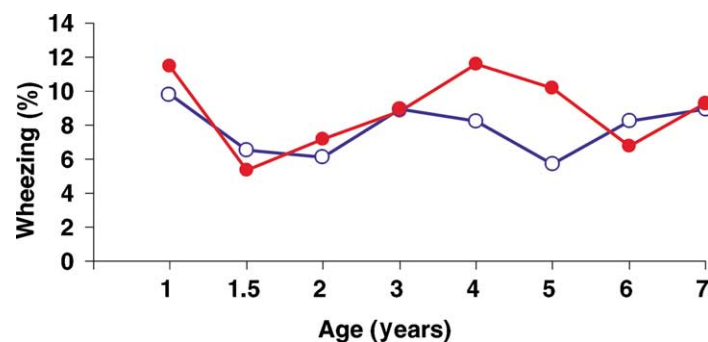


Figure 5 Exposure to house dust mite at 6 months of age and wheezing up to 7 years of age. (○) 1st quartile; (●) 4th quartile. Reproduced, with permission, from Lau et al.⁴⁸

and on mattresses at 5 years of age (data not shown). When stratifying the analysis for atopy (sensitisation to house dust mites and atopic dermatitis with sensitisation to food allergens, respectively), no association between indoor allergen exposure to house dust mites or cat dander and wheezing was seen (data not shown).

Furthermore, the level of exposure to indoor allergens was not related to the age of onset of wheezing, or to the severity of the disease defined as the frequency of wheezing episodes in the last 12 months at the age of 7 years (data not shown). Similar results were obtained when using histamine (PC_{20}) and forced expiratory volume in 1 second (FEV_1) as the definition of bronchial hyper-responsiveness. There was no relationship between baseline lung function (FEV_1 , forced vital capacity (FVC), FEV_1/FVC ratio, maximal expiratory flow at 75%, 50% and 25% of FVC ($MEF_{75,50,25}$), and indoor allergen exposure (data not shown).

BRONCHIAL HYPER-RESPONSIVENESS AND ASTHMA⁴⁹

Children in the MAS cohort showed a higher bronchial hyper-responsiveness after titrated histamine challenge at

age 7 years than other cohorts of slightly older age (age 9–13 years). However, a threshold concentration of 0.6 mg/ml histamine could discriminate between children with and without current wheeze (93% specificity and 45.9% sensitivity, PC_{20} FEV_1).

THE SIGNIFICANCE OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE FOR THE DEVELOPMENT OF SPECIFIC SENSITISATION AND ASTHMA⁵⁰

At the age of 3, children who were pre- and postnatally exposed to tobacco smoke had a significantly higher risk of sensitisation to food allergens (odds ratio (OR) = 2.3; 95% confidence interval (CI) = 1.1–4.6) than unexposed children (Fig. 6). Children who were only postnatally exposed by a smoking mother also had a 2.2 times higher risk (95% CI = 0.9–5.9) of sensitisation than did unexposed children. Smoking during pregnancy was a risk factor for wheezing during the first 3 years of life and for impaired lung function at age 7 in those children, who showed wheezing episodes only during the first years of life. It was also a significant risk

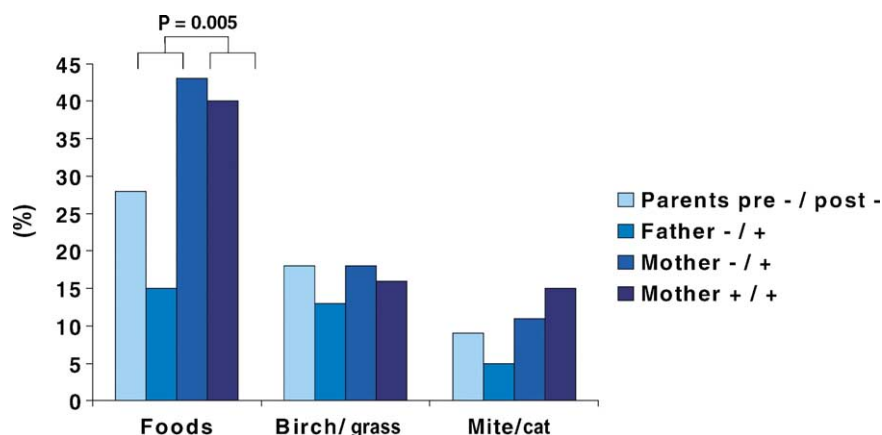


Figure 6 Tobacco smoke exposure pre- and postnatally and allergic sensitisation (≥ 0.35 kU/l) during the first 3 years of life. Reproduced, with permission, from Kulig *et al.*⁵⁰

factor for asthma at school age (OR = 2.46; 95% CI = 1.28–4.73).

THE SIGNIFICANCE OF HEREDITY AND SOCIAL STATUS FOR THE DEVELOPMENT OF ASTHMA⁵¹

Maternal asthma was the strongest risk factor for the development of childhood asthma. The risk of aeroallergen sensitisation (OR = 1.76; 95% CI = 1.3–2.37) and the lifetime prevalence of hay fever (OR = 2.36; 95% CI = 1.76–3.17) and asthma (OR = 1.74; 95% CI = 1.08–2.8) was elevated in parents of high compared to low socio-economic status (SES). With high SES the risk of smoking in pregnancy (OR = 0.35; 95% CI = 0.23–0.51), in the home (OR = 0.31; 95% CI = 0.21–0.46), pet ownership (OR = 0.37; 95% CI = 0.26–0.55), high mite (OR = 0.42; 95% CI = 0.25–0.74) and high cat (OR = 0.38; 95% CI = 0.18–0.82) allergen concentration in house dust was reduced, but was elevated for breast feeding over more than 6 months (OR = 4.67; 95% CI = 2.9–7.48).

THE SIGNIFICANCE OF SENSITISATION PATTERNS FOR THE DEVELOPMENT OF CHILDHOOD ASTHMA⁵²

Sensitisation to hen's egg at the age of 12 months is predictive for allergic sensitisation to common indoor and outdoor allergens at 3 years.⁵³ Children with sensitisation to food and/or inhalant allergens during the first three years of life and inhalant sensitisation in the 7th year of life ("persistent sensitisation": Fig. 7) had a higher risk for asthma at age 7 than those children with early transient (only during the first 3 years of life) or no sensitisation (OR = 10.12; 95% CI = 3.81–26.88). Only those persistently sensitised children who had a positive parental history of asthma or atopy were at significantly increased risk of being asthmatic at age 7 years (OR = 15.56; 95% CI = 5.78–41.83). The onset of atopic sensitisation in atopic children with current asthma at the age of 7 years was significantly earlier than in atopic children without current asthma (39.4% before age 1 versus 21%, $P = 0.015$).

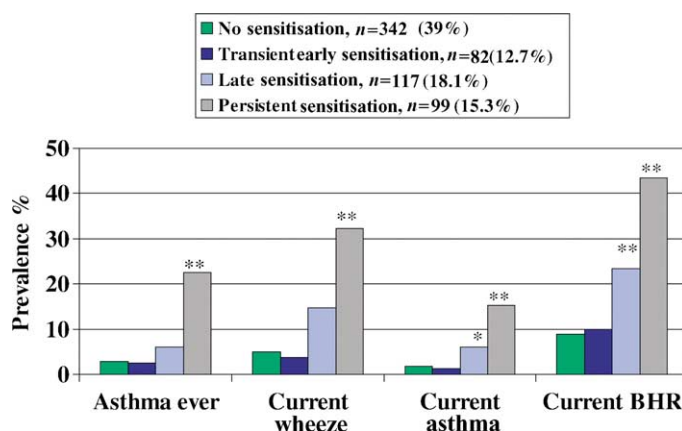


Figure 7 Prevalence of asthma and asthmatic symptoms at the age of 7 years, stratified for sensitisation pattern. BHR, bronchial hyper-responsiveness. * $P < 0.05$; ** $P < 0.001$. Reproduced, with permission, from Illi *et al.*⁵²

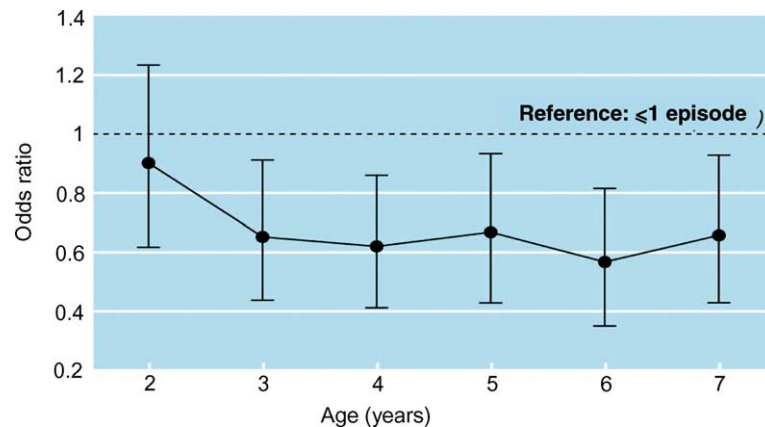


Figure 8 Repeated episodes of runny nose during the first year of life and wheezing (adjusted for parental education, smoking habits, history of atopy and age). Reproduced, with permission, from Illi et al.⁵⁴

THE SIGNIFICANCE OF EARLY CHILDHOOD INFECTIONS FOR THE DEVELOPMENT OF ASTHMA UP TO SCHOOL AGE⁵⁴

In addition to atopic disease and asthma we assessed other illnesses at follow up. The commonest type of infectious disease was viral infection with only 184 children (14%) not having had a viral infection in the first year of life. Longitudinal analysis showed a strong inverse association between repeated episodes of runny nose and asthma at age 7 (Fig. 8). Similarly, having one or more herpes virus infection in the first 3 years of life was inversely associated with asthma at age 7 (OR = 0.48; 95% CI = 0.26–0.89). We found no association between bacterial, fungal, gastrointestinal, or urinary tract infections in the first year of life with wheeze at the age of 4, 5, 6 or 7 years. However, the number of lower respiratory tract infections in the first 3 years of life showed a strong positive dose–response relationship with current wheeze and wheeze ever, the diagnosis of asthma and bronchial hyper-reactivity at age 7 (OR = 3.37; 95% CI = 1.92–5.92 for ≥ 4 lower respiratory tract infections).

Only recurrent runny nose showed an association with subsequent atopic sensitisation: children with two or more episodes of runny nose in the first year of life had half the risk of being sensitised to inhalant allergens at the age of 1 year (OR = 0.46; 95% CI = 0.28–0.76) or 3 years (OR = 0.53; 95% CI = 0.37–0.76). At the age of 5 years, however, this effect became non-significant.

BCG (bacille Calmette-Guérin) vaccination for the prevention of tuberculosis in early infancy was not associated with a decreased risk of atopic sensitisation.⁵⁵ An inverse relationship between cumulative received vaccine doses and atopy was observed. Measles/mumps, rubella, pertussis and diphtheria vaccination were particularly associated with a transient reduction of atopy, whereas vaccination against tetanus, polio and *Haemophilus influenzae* had no effect. Thus, regular childhood vaccination regimes may help to overcome a transient atopy-associated deficiency in Th1 function.

CONCLUSIONS

In the German MAS, the strongest risk factors for childhood asthma are maternal asthma, persistent sensitisation, maternal smoking during pregnancy and sensitisation to indoor allergens. While sensitisation to indoor allergen was clearly related to exposure, no direct association between indoor allergens in the home environment during early infancy and asthma could be shown. In turn, repeated infections during infancy seemed to be protective against atopy and asthma at school-age.

Imitation of the natural infectious burden could be a new therapeutic option in the prevention of asthma and atopic disease. A possible approach to Th1-stimulation may be a regular intake of lactobacilli in infancy.^{56,57} However, the Th1/Th2-dichotomy may only partly explain the increase in asthma and atopic disease as Th1 cytokines may also be involved in the chronic inflammatory process of asthma and atopic eczema. Recent data indicate that Th1 diseases are increasing,⁵⁸ therefore immunological dysregulation in Th1 and Th2 diseases may derive from other regulatory cells such as antigen presenting cells.

PRACTICE POINTS

- The increasing prevalence of asthma and atopic diseases in childhood seems to be influenced by various environmental factors.
- Factors determining the development of atopy are at least in part different from those inciting childhood asthma.
- Persistent sensitisation (early in infancy and at school age) and maternal asthma appear to be the major risk factors for asthma at school age.
- The role of indoor allergen avoidance seems to be clear for avoiding specific sensitisation,⁵⁹ but may not prevent asthma.

RESEARCH DIRECTIONS

- Intervention studies in infancy are needed to investigate the potential benefit of new therapies such as lactobacilli or lysate of Gram-negative bacteria containing lipopolysaccharide to stimulate Th1 immune responses.
- Regular childhood vaccination regimens may help to overcome a transient atopy-associated deficiency in Th1 function.

REFERENCES

- Burr ML, Butland BK, King S, Vaughan-Williams E. Changes in asthma prevalence: two surveys 15 years apart. *Arch Dis Child* 1989; **64**: 1452–1456.
- Von Mutius E, Martinez FD, Fritzsche C et al. Prevalence of asthma and atopy in two areas of West and East Germany. *Am J Respir Crit Care Med* 1994; **149**: 358–364.
- Yunginger J, Reed CE, O'Connell EJ, Melton LJ, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates 1964–1983. *Am Rev Respir Dis* 1992; **146**: 888–894.
- Matsui E, Kaneko H, Teramoto T et al. Reduced IFN γ production in response to IL-12 stimulation and/or reduced IL-12 production in atopic patients. *Clin Exp Allergy* 2000; **30**: 1250–1256.
- Tang ML, Coleman J, Kemp AS. Interleukin-4 and interferon- γ production in atopic and non-atopic children with asthma. *Clin Exp Allergy* 1995; **25**: 515–521.
- Shaheen SO, Aaby P, Hall AJ et al. Measles and atopy in Guinea-Bissau. *Lancet* 1996; **347**: 1792–1796.
- Shirakawa T, Enomoto T, Shimazu S, Hopkin JM. The inverse association between tuberculin responses and atopic disorders. *Science* 1997; **275**: 77–79.
- Shaheen SO. Obesity and asthma. *Clin Exp Allergy* 1999; **29**: 291–293.
- Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. *Clin Exp Allergy* 1997; **27**: 240–245.
- Strachan D. Hay fever, hygiene and household size. *BMJ* 1989; **299**: 1259–1260.
- Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic disease. *Thorax* 1998; **53**: 28–32.
- Hodge L, Salome CM, Hughes JM. Effect of dietary intake of omega-3 fatty acids and omega-6 fatty acids on severity of asthma in children. *Eur Respir J* 1997; **11**: 361–365.
- Weiland S, von Mutius E, Hüsing A, Asher MI. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe. *Lancet* 1999; **353**: 2040–2041.
- Peat JK, Li J. Reversing the trend: reducing the prevalence of asthma. *J Allergy Clin Immunol* 1999; **103**: 1–10.
- Sporik R, Holgate ST, Platts-Mills TAE, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. *N Engl J Med* 1990; **323**: 502–507.
- Braun-Fahrlander C, Gassner M, Grize L et al. Prevalence of hay fever and allergic sensitization in farmers' children and their peers living in the same rural community. *Clin Exp Allergy* 1999; **29**: 28–34.
- Von Ehrenstein OS, von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000; **30**: 187–193.
- Von Mutius E, Braun-Fahrlander C, Schierl R et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; **30**: 1230–1234.
- Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999; **353**: 1485–1488.
- Lau S, Falkenhofst G, Weber A et al. High mite allergen exposure increases the risk of sensitization in atopic children and young adults. *J Allergy Clin Immunol* 1989; **84**: 718–725.
- Peat JK, Tovey ER, Toelle BG et al. House-dust mite allergens: a major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; **153**: 141–146.
- Kühr J, Frischer T, Meinert R et al. Mite allergen exposure is a risk for the incidence of specific sensitization. *J Allergy Clin Immunol* 1994; **94**: 44–52.
- Kühr J, Frischer T, Meinert T, Barth R, Schraub S, Urbanek R. Sensitization to mite allergens is a risk factor for early and late onset of asthma and for persistence of asthma signs in children. *J Allergy Clin Immunol* 1995; **95**: 655–662.
- Custovic A, Smith A, Woolcock A. Indoor allergens are a primary cause of asthma. *Eur Respir Rev* 1998; **53**: 155–158.
- Asher MI, Keil U, Anderson HR et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**: 483–491.
- The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Lancet* 1998; **351**: 1225–1232.
- Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen N, van Vliet P. Early, current and past pet ownership: associations with sensitisation, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy* 2002; **32**: 361–366.
- Apelberg BJ, Aoki Y, Jaakkola JJK. Systemic review: exposure to pets and risk of asthma and asthma-like symptoms. *J Allergy Clin Immunol* 2001; **107**: 455–460.
- Plaschke P, Janson C, Norrman E, Björnsson E, Ellbjär, Järvholm B. Association between atopic sensitization and asthma and bronchial hyperresponsiveness in Swedish adults: pets and not mites are the most important allergens. *J Allergy Clin Immunol* 1999; **104**: 58–65.
- Roost HP, Künzli N, Schindler C et al. Role of current and childhood exposure to cat and atopic sensitization. *J Allergy Clin Immunol* 1999; **104**: 941–947.
- Hesselmar B, Aberg N, Aberg B, Eriksson B, Björkstén B. Does early exposure to cat or dog protect against later allergy development? *Clin Exp Allergy* 1999; **29**: 611–617.
- Platts-Mills TAE, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation asthma and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; **357**: 752–756.
- Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999; **54**: 268–272.
- Pearce N, Douwes J, Beasley R. Is allergen exposure the major primary cause of asthma? *Thorax* 2000; **55**: 424–431.
- Stick SM, Burton PR, Gurnin L, Sly PD, LeSouef PN. Respiratory function in newborn infants: effects of maternal smoking during pregnancy and a family history of asthma. *Lancet* 1996; **348**: 1060–1064.
- Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy: effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995; **152**: 977–983.
- Ronchetti R, Bonci E, Cutrera R et al. Enhanced allergic sensitisation related to parental smoking. *Arch Dis Child* 1992; **67**: 496–500.
- Young S, LeSouef PN, Geelhoed GC, Stick SM, Turner KJ, Landau LI. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991; **324**: 1168–1173.
- Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright L. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000; **343**: 538–543.
- Krämer U, Heinrich J, Wjst M, Wichmann HE. Age of entry to day nursery and allergy in later childhood. *Lancet* 1999; **353**: 450–454.

41. Matricardi P, Rosmini F, Ferrigno L *et al.* Cross-sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997; **314**: 999–1003.
42. Matricardi PM, Rosmini F, Riondino S *et al.* Exposure to foodborne microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiologic study. *BMJ* 2000; **320**: 412–417.
43. McKeever TM, Lewis SA, Smith C *et al.* Early exposure to infections and antibiotics and the incidence of allergic disease: a birth cohort study using the West Midlands General Practice research database. *J Allergy Clin Immunol* 2002; **109**: 43–50.
44. Forster J, Tacke U, Krebs H *et al.* Respiratory syncytial virus infection: its role in aeroallergen sensitization during the first two years of life. *Pediatr Allergy Immunol* 1996; **7**: 55–60.
45. Stein RT, Sherrill D, Morgan WJ *et al.* Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 1999; **354**: 541–545.
46. Bergmann RL, Bergmann KE, Lau-Schadendorf S *et al.* Atopic diseases in infancy. The German Multicenter Atopy Study (MAS-90). *Pediatr Allergy Immunol* 1994; **5(supplement 1)**: 19–25.
47. Wahn U, Lau S, Bergmann R *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; **99**: 763–769.
48. Lau S, Illi S, Sommerfeld C *et al.* Early exposure to house-dust mite and cat allergens and the development of childhood asthma: a cohort study. *Lancet* 2000; **356**: 1392–1397.
49. Niggemann B, Illi S, Madloch C *et al.* Histamine challenges discriminate between symptomatic and asymptomatic children. *Eur Respir J* 2001; **17**: 246–253.
50. Kulig M, Luck W, Lau S *et al.* Effect of pre- and postnatal tobacco smoke exposure on specific sensitization to food and inhalant allergens during the first 3 years of life. *Allergy* 1999; **54**: 220–228.
51. Bergmann R, Edenharter G, Bergmann KE, Lau S, Wahn U. Socioeconomic status is a risk factor for allergy in parents but not in their children. *Clin Exp Allergy* 2000; **30**: 1740–1745.
52. Illi S, von Mutius E, Lau S *et al.* The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001; **108**: 709–714.
53. Nickel R, Kulig M, Forster J *et al.* Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997; **99**: 613–617.
54. Illi S, von Mutius E, Lau S *et al.* Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. *BMJ* 2001; **322**: 390–395.
55. Grüber C, Kulig M, Bergmann R, Guggemoos-Holzmann I, Wahn U. Delayed hypersensitivity total, immunoglobulin E, specific sensitization and atopic manifestation in longitudinally followed early bacille Calmette-Guérin-vaccinated and nonvaccinated children. *Pediatrics* 2001; **107**: 1–7.
56. Kalliomäki M, Salminen S, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; **357**: 1076–1079.
57. Murosaki S, Yamamoto Y, Ito K *et al.* Heat-killed *Lactobacillus plantarum* L-137 suppresses naturally fed antigen-specific IgE production by stimulation of IL-12 production. *J Allergy Clin Immunol* 1998; **102**: 57–64.
58. Kero J, Gissler M, Hemminki E, Isolauri E. Could TH1 and TH2 diseases coexist? Evaluation of asthma incidence in children with coeliac disease, type 1 diabetes, or rheumatoid arthritis: a register study. *J Allergy Clin Immunol* 2002; **108**: 781–783.
59. Schwieger A, Kuehr J, Arshad H *et al.* Mite allergen avoidance measures lead to a reduction of respiratory symptoms in toddlers – the SPACE study. *Allergy* 2001; **56(supplement 86)**: 187.