

Age at Onset of Asthma and Allergen Sensitization Early in Life

Masahiko Kato¹, Yoshiyuki Yamada¹, Kenichi Maruyama² and Yasuhide Hayashi³

ABSTRACT

Background: Epidemiological evidence indicates that the age at onset of asthma and allergen sensitization in early life is decreasing in people from Western countries. To explore latent trends, we conducted a retrospective examination of the age at onset of asthma and specific IgE antibodies against inhalant allergens in Japanese asthmatic children.

Methods: We conducted a case series study of 103 consecutive children with atopic type of asthma (aged 2 years to 16 years, mean age 9.4 ± 3.4 years). Diagnoses of asthma and allergic rhinitis were defined according to Japanese guidelines. The onset of asthma and allergic rhinitis was also defined as any report of asthma and allergic rhinitis confirmed by a physician. Allergen sensitization was evaluated as specific serum IgE levels for 9 common inhalant allergens in peripheral blood. Atopic type of asthma was defined as a being positive for at least one aeroallergen.

Results: Mean age at asthma onset was 2.3 ± 1.9 years, which is slightly lower than that of previous reports, including those published in Japan. A high prevalence rate of up to 80% was found for perennial antigens including *Dermatophagoides* spp. and house dust, as reported previously. Notably, some of the children aged at 1 year tested positive for these allergens.

Conclusions: The age at onset of asthma seems to be decreasing in comparison with previous reports. Furthermore, the age at onset of allergen sensitization against inhalant allergens appears to follow this trend.

KEY WORDS

age at onset of asthma, allergen sensitization, allergen-specific IgE, allergic rhinitis, childhood asthma in Japan

INTRODUCTION

The prevalence of asthma increased during the second half of the 20th century in both children and adults in most countries, including Japan. In the past 10 years, the incidence of asthma seems to have reached a plateau or has even decreased slightly in some areas; however, it is still rising in many populations and remains high in developing countries. Despite the progress made in therapeutics, the morbidity and mortality rates of this chronic disease are substantial. Therefore, the prevention of asthma through the identification and management of risk factors and preclinical phases of the disease is a priority.¹

Childhood asthma has significant phenotypic heterogeneity. The age at onset of asthma has important

phenotypic and prognostic implications,² and an earlier age at onset is associated with increased asthma severity in children with symptoms that persist into school age and adolescence.³

The prevalence of allergic sensitization has also increased dramatically worldwide.^{4,5} Exposure to allergens in childhood is a risk factor for sensitization, and allergic sensitization is generally agreed to be an important risk factor for allergic diseases.^{6,7} On the other hand, it has been hypothesized that exposure to allergens in early childhood may induce tolerance and have a protective effect against sensitization.⁸ Early life events seem to have a major impact on the development of sensitization or tolerance.⁹

Against this background, in this study we investigated the latent age at onset of atopic types of asthma

¹Department of Allergy and Immunology, ²Department of Nephrology and ³Department of Hematology and Oncology, Gunma Children's Medical Center, Gunma, Japan.

Conflict of interest: No potential conflict of interest was disclosed.
Correspondence: Masahiko Kato, MD, Department of Allergy and Immunology, Gunma Children's Medical Center, 779 Shimohak-

oda, Hokkitsu-machi, Shibukawa, Gunma 377-8577, Japan.

Email: mkato@gcmc.pref.gunma.jp

Received 27 September 2013. Accepted for publication 12 February 2014.

©2014 Japanese Society of Allergology

by performing objective diagnosis of the disease based on the guidelines, and examined antigen sensitization to inhalant allergens in the Japanese pediatric population.

METHODS

PATIENTS

This study was a retrospective case series study of 103 patients with atopic types of asthma (65 boys, 38 girls; age range, 2-16 years) who attended Gunma Children's Medical Center from December 2010 to February 2011. This study was approved by the Ethics Committee of Gunma Children's Medical Center. Informed consent was obtained from parents, and assent was obtained from older children (usually over 9 years old). Diagnoses of asthma and allergic rhinitis were based on Japanese guidelines.^{10,11} Briefly, a diagnosis of asthma was confirmed on the basis of a history of recurrent wheezing and dyspnea on at least three independent occasions and reversible bronchoconstriction.¹⁰ Atopic type of asthma was defined as being positive for at least one aeroallergen. A diagnosis of allergic rhinitis was based on the presence of the three major symptoms of itching/sneezing of the nose, rhinorrhea, and nasal obstruction and on a positive test result from one of three examinations, namely, eosinophils in nasal smears, skin tests/specific anti-IgE antibodies, and a provocation test against allergens.¹¹ A questionnaire that included questions concerning asthma and nasal symptoms was completed by the parents. Parents were also interviewed by a physician who is a specialist in pediatric allergic diseases. Sensitization to an allergen was detected by serum-specific IgE antibody.

ASSAY

Serum levels of specific IgE against inhalant allergens were detected by immunofluorometric assay (ImmunoCAP; Phadia AB, Uppsala, Sweden) in peripheral blood samples from patients over 1 year old. Serum was separated from each blood sample within 1 h and stored at -20°C until used to evaluate allergen-specific IgE against the following allergens: *Dermatophagoides farinae*/*pteronyssinus*, house dust, Japanese cedar, orchard grass, ragweed, cat and dog dander, *Alternaria*, and *Cladosporium*. Specific IgE levels >0.35 kU/L were considered positive, as previously reported.¹²

STATISTICAL ANALYSIS

Patient characteristics were evaluated by Pearson's χ^2 test statistic and Fisher's exact test for categorical variables. Descriptive statistics are expressed as means and standard error of the mean. Unpaired data were analyzed using the Mann-Whitney U test. A statistically significant result was defined by a value of $P < 0.05$ (two-sided). All analyses were performed using the statistical software package SPSS for Windows,

Table 1 Patient characteristics

	Asthma
Number	103
Age, year, mean $\pm$ SD	9.4 $\pm$ 3.4
Male, %	63.1
Smokers at home, %	54.3
Pets at home, %	31.4
Cat, %	11.4
Dog, %	17.1
Allergic rhinitis, %	60.2
Eczema, %	40.0
Food allergy, %	51.4

version 19.0 (IBM SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient characteristics are shown in Table 1. The mean age of the 103 asthmatic patients was 9.4 ± 3.4 years old (boys 9.2 ± 3.3 and girls 9.3 ± 3.7 years). The percentage of smokers at home and pets at home was 54.3 and 31.4, respectively. Allergic rhinitis was diagnosed in 62 asthmatic patients (60.2%) whose mean age was 8.8 ± 3.5 years. Figure 1 shows the age at onset of asthma (Fig. 1A) and allergic rhinitis with asthma (Fig. 1B) and the mean age at onset were 2.3 ± 1.9 and 5.1 ± 2.1 years, respectively. The mean age at onset of allergic rhinitis was significantly higher than that of asthma alone ($p < 0.0001$). In addition, the mean age of subjects grouped by age at asthma onset was 8.7 ± 3.8 (under 1-year old at onset), 8.7 ± 3.6 (1 year old), 9.0 ± 3.1 (2 years old), 9.8 ± 3.7 (3 years old), 7.3 ± 1.7 (4 years old), 10.1 ± 2.2 (5 years old), 13.6 ± 2.2 (6 years old), 11.6 ± 4.1 (8 years old), and 10.8 ± 1.5 (9 years old), respectively.

We then examined the positive inhalant allergens in asthmatic patients (Fig. 2) and found that the number of patients with allergen-specific IgE against *Dermatophagoides* spp., house dust, and Japanese cedar was higher than for other aeroallergens. Next, we examined the prevalence of each inhalant allergen by age (Fig. 3). Notably, some of the children aged at 1 year tested positive for perennial antigens including *Dermatophagoides* spp. and house dust (Fig. 3A). Sensitization to allergens in cat and dog dander was also found in 1 year olds (Fig. 3C). Allergic sensitization to pollen, grass, and mold was slightly delayed compared with *Dermatophagoides* spp. and house dust (Fig. 3A-C).

DISCUSSION

In this study, we found that the mean age at onset of asthma was 2.3 years, similar to that reported previously. There are a number of reports on the prevalence of asthma in different countries;¹³ however, few reports have examined the age at onset of asthma. A Japanese cohort study of asthmatic patients in an area

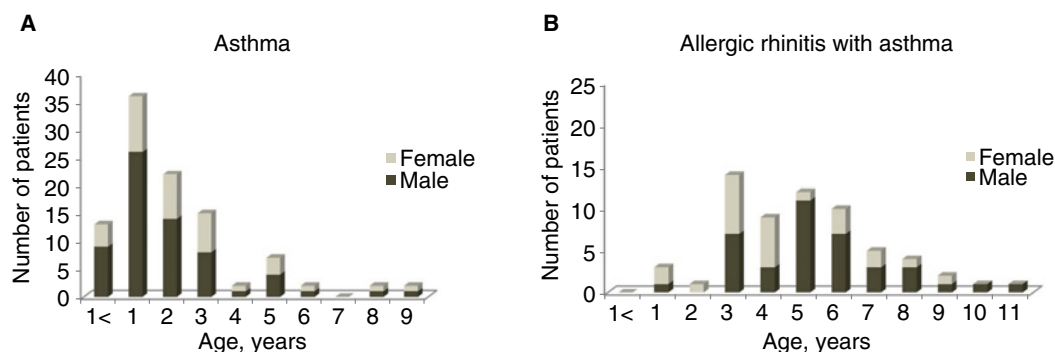


Fig. 1 Distribution of age at onset of asthma (A) and allergic rhinitis with asthma (B). Mean age at onset was 2.3 and 5.1 years, respectively.

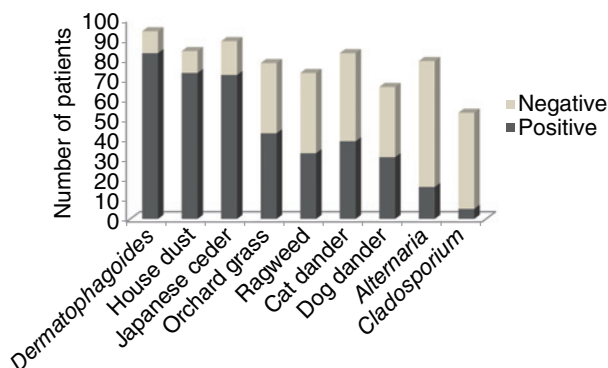


Fig. 2 Prevalence of inhalant allergens in asthmatic patients. Positive serum-specific IgE against inhalant allergens in asthmatic patients.

of western Japan in 2002 showed the age of onset as 2.5 years.¹⁰ A single center study in Japan in 2008 found it to be 2.8 years.¹⁴ Other cohort studies outside Japan also showed mean age at onset of asthma was 3.1 years in the CAMP study between 1993 and 1995 in the United States and Canada,^{15,16} 3.1 years in the BAMSE study between 1994 and 1996 in Sweden,^{17,18} 2.5 years in the GACRS study between 2001 and 2005 in Costa Rica,¹⁹⁻²¹ and 3.3 years in the PACT study between 2002 and 2004 in the United States.²² The present results suggest that the age at onset of asthma seems to be decreasing in comparison with these previous reports (Table 2).

We found that the age at onset of allergen sensitization to perennial inhalant allergens appears to be lowering and that some of the 1-year-old patients had specific IgE antibodies against such allergens. A recent multicenter cohort study in five European countries showed that serum-specific IgE antibodies against perennial allergens were detected in around 20% of healthy children at 12 months of age.¹² Another cohort study in allergic patients demonstrated that serum-specific IgE against *Dermatophagoides pteronyssinus* and dog and cat dander was present at 1

year of age and these allergens preceded the grasses, ragweed, and *Alternaria*.²³ These previous results are compatible with ours.

In this study we could not evaluate the relationship between the age at onset of asthma and allergen sensitization in individuals; however, the evidence suggests that sensitization and the symptoms of allergic diseases are strongly correlated. For example, the onset of atopic sensitization in children with current asthma at 7 years of age was significantly earlier than in atopic children without current asthma. Early atopic sensitization without sensitization to inhalant allergens at age 7 conferred no increased risk of asthma at this age. Only those children sensitized to an allergen early in life and sensitized to inhalant allergens by the age of 7 are at a significantly increased risk of being asthmatic at this age.²⁴ Another birth cohort study demonstrated that sensitization to perennial allergens, including house dust mites and cat and dog hair, developing in the first 3 years of life is associated with reduced lung function at school age; sensitization and exposure later in life produces much weaker effects, and sensitization to seasonal allergens does not play a part.²⁵ A recent cohort study also showed that sensitization to perennial rather than seasonal allergens has a greater association with asthma risk, while sensitization to seasonal allergens is more closely associated with rhinitis risk. Furthermore, increased levels of specific IgE against perennial allergens are associated with an increased asthma risk, while detectable levels of IgE against seasonal allergens are associated with an increased rhinitis risk.²⁶ These findings indicate that perennial allergen sensitization early in life is a risk factor for chronic asthma in children.

In our study, of the subjects with asthma, 54.3% had smokers at home and 31.4% had pets at home, which were slightly higher rate than those in previous reports.²⁷⁻³⁰ Epidemiology studies suggest that passive smoking is significantly associated with the development of asthma in atopic children.³¹ However, other studies found that no association between pas-

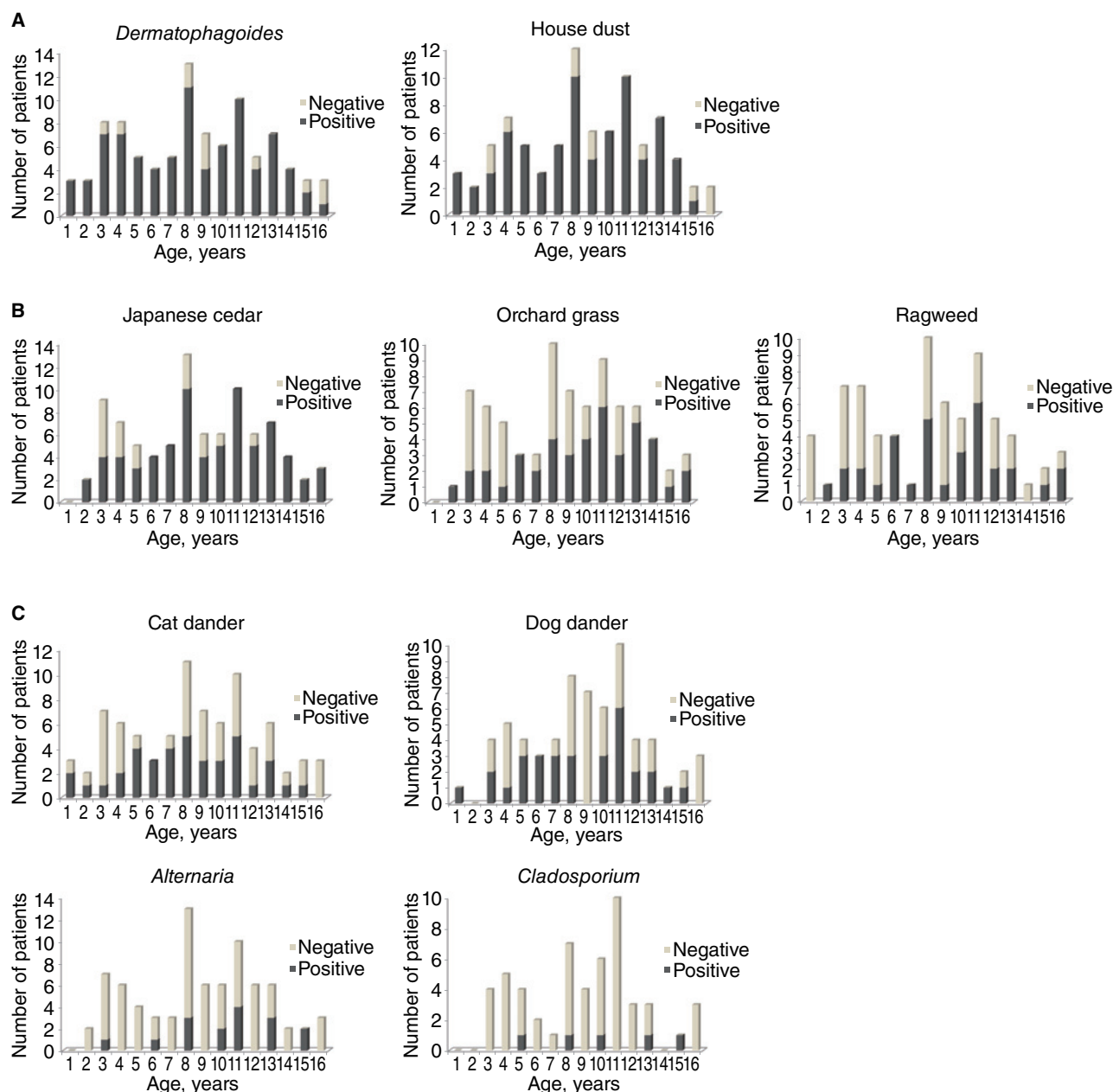


Fig. 3 Age distribution of inhalant allergens in asthmatic patients. Positive serum-specific IgE levels against *Dermatophagoides farinae/pteronysinus* (A: left), house dust (A: right), Japanese cedar (B: left), orchard grass (B: center), ragweed (B: right), cat (C: upper left) and dog (C: upper right) dander, *Alternaria* (C: lower left), and *Cladosporium* (C: lower right) in asthmatic children by age.

sive smoking and the development asthma was observed.^{32,33} Although pets are known to aggravate asthma in sensitized individuals, controversy remains about whether early life pet exposure is a risk factor or a protective factor in their development.³⁴ Current guidelines issued in Australia,³⁵ the United States,³⁶ and the United Kingdom,³⁷ and by the Global Initiative for Asthma³⁸ all agree there is currently insufficient evidence to provide any recommendations in relation to pet-keeping in early life and the development

of asthma and allergic disease because systematic reviews,^{34,39} and a meta-analysis⁴⁰ have reached different conclusions. For examples, early reviews found pet-keeping increased the risk of sensitization and allergic disease with later reviews finding no effect. A meta-analysis reported less risk of childhood asthma associated with cats, but increased risk with dogs.⁴⁰ These observations collectively indicate that further cohort studies are required for exploring the exact role of passive smoking and exposure to pets on the

Table 2 Reports of age at onset of asthma

Study	Area	Study year	Number	Male, %	Age at enrollment, year	Age at onset of asthma, year
CAMP study ^{15, 16}	United States/Canada	1993-1995	573	59.5	8.9	3.1
BAMSE study ^{17, 18}	Sweden	1994-1996	107	64.5	Birth	3.1
GACRS study ¹⁹⁻²¹	Costa Rica	2001-2005	591	59.3	9.0	2.5
Nishima <i>et al.</i> ¹⁰	Japan	2002	2780	62.5	6-12	2.5
PACT study ²²	United States	2002-2004	233	63.1	9.9	3.1
Masuda <i>et al.</i> ¹⁴	Japan	2008	130	66.2	5.3	2.8
Our study	Japan	2010-2011	103	63.1	9.4	2.3

development of asthma.

In conclusion, the present study and previous reports suggest that the age at onset of asthma seems to be decreasing and the age at onset of allergen sensitization against inhalant allergens appears to follow this trend. Further prospective studies are needed to investigate both perennial and seasonal antigen sensitization, and the age of asthma onset to clarify the relationships between allergen sensitization, the development of disease, and the risk factors for the onset of allergic diseases.

REFERENCES

- Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006;**355**:2226-35.
- Nartinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**:133-8.
- Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 2003;**111**:661-75.
- 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**:1225-32.
- Nowak D, Suppli Ulrik C, Von Mutius E. Asthma and atopy: has peak prevalence been reached? *Eur Respir J* 2004;**23**:359-60.
- Wahn U, Bergmann R, Kulig M, Forster J, Bauer CP. The natural course of sensitisation and atopic disease in infancy and childhood. *Pediatr Allergy Immunol* 1997;**8**:16-20.
- Nickel R, Lau S, Niggemann B *et al.* Messages from the German Multicentre Allergy Study. *Pediatr Allergy Immunol* 2002;**13** (Suppl 15):7-10.
- 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**:1129-33.
- Upham JW, Holt PG. Environment and development of atopy. *Curr Opin Allergy Clin Immunol* 2005;**5**:167-72.
- Japanese Society of Pediatric Allergy and Clinical Immunology. [*Japanese Pediatric Guideline for the Treatment and Management of Asthma 2012*]. Tokyo: Kyowa Kikaku, 2012 (in Japanese).
- The Committee of Guidelines for Management of Allergic Rhinitis. [*Practical Guideline for the Management of Allergic Rhinitis in Japan*]. Tokyo: Life Science, 2013 (in Japanese).
- Depner M, Ege MJ, Genuneit J *et al.*, and PASTURE Study Group. Atopic sensitization in the first year of life. *J Allergy Clin Immunol* 2013;**131**:781-8.
- Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. Institute of Health, National Heart, Lung, and Blood Institute, Updated 2006.
- Masuda S, Fujisawa T, Katsumata H, Atsuta J, Iguchi K. High prevalence and young onset of allergic rhinitis in children with bronchial asthma. *Pediatr Allergy Immunol* 2008;**19**:517-22.
- The Childhood Asthma Management Program (CAMP): design, rationale, and methods. Childhood Asthma Management Program Research Group. *Control Clin Trials* 1999;**20**:91-120.
- Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;**343**:1054-63.
- Kull I, Melen E, Alm J *et al.* Breast-feeding in relation to asthma, lung function, and sensitization in young school-children. *J Allergy Clin Immunol* 2010;**125**:1013-9.
- Melen E, Nyberg F, Lindgren CM *et al.* Interactions between glutathione S-transferase P1, tumor necrosis factor, and traffic-related air pollution for development of childhood allergic disease. *Environ Health Perspect* 2008;**116**:1077-84.
- Hunninghake GM, Soto-Quiros ME, Avila L *et al.* Sensitization to *Ascaris lumbricoides* and severity of childhood asthma in Costa Rica. *J Allergy Clin Immunol* 2007;**119**:654-61.
- Ly NP, Soto-Quiros ME, Avila L *et al.* Paternal asthma, mold exposure, and increased airway responsiveness among children with asthma in Costa Rica. *Chest* 2008;**133**:107-14.
- Brehm JM, Celedon JC, Soto-Quiros ME *et al.* Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009;**179**:765-71.
- Sorkness CA, Lemanske RF, Mauger DT *et al.* Long-term comparison of 3 controller regimens for mild-moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007;**119**:64-72.
- De Amici M, Ciprandi G. The age impact on serum total and allergen-specific IgE. *Allergy Asthma Immunol Res* 2013;**5**:170-4.
- Illi S, von Mutius E, Lau S *et al.*, and Multicenter Allergy Study Group. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol* 2001;**108**:709-14.
- Illi S, von Mutius E, Lau S *et al.*, and Multicenter Allergy

- Study (MAS) group. Perennial allergen sensitisation early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006;**368**:763-70.
26. Stoltz DJ, Jackson DJ, Evans MD *et al*. Specific patterns of allergic sensitization in early childhood and asthma & rhinitis risk. *Clin Exp Allergy* 2013;**43**:233-41.
 27. Plaschke PP, Janson C, Norrman E, Björnsson E, Ellbjär S, Järholm B. Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. *Am J Respir Crit Care Med* 2000;**162** (Pt 1): 920-94.
 28. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest* 2006;**129**: 309-16.
 29. Forno E, Lasky-Su J, Himes B *et al*. Genome-wide association study of the age of onset of childhood asthma. *J Allergy Clin Immunol* 2012;**130**:83-90.
 30. Uddenfeldt M, Janson C, Lampa E, Rask-Andersen A. Sensitization to pets is a major determinant of persistent asthma and new asthma onset in Sweden. *Ups J Med Sci* 2013;**118**:111-21.
 31. Cantani A, Micera M. Epidemiology of passive smoke: a prospective study in 589 children. *Eur Rev Med Pharmacol Sci* 2005;**9**:23-30.
 32. Martín-Pujol A, Fernández E, Schiaffino A *et al*, and RESPIR · NET research group. Tobacco smoking, exposure to second-hand smoke, and asthma and wheezing in schoolchildren: a cross-sectional study. *Acta Paediatr* 2013;**102**:e305-9.
 33. Tanaka K, Miyake Y, Sasaki S, Ohya Y, Hirota Y; Osaka Maternal and Child Health Study Group. Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. *J Asthma* 2008;**45**:833-8.
 34. Fretzayas A, Kotzia D, Moustaki M. Controversial role of pets in the development of atopy in children. *World J Pediatr* 2013;**9**:112-9.
 35. Prescott SL, Tang MLK. The Australasian Society of Clinical Immunology and Allergy position statement: summary of allergy prevention in children. *Med J Australia* 2005; **182**:464-7.
 36. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol* 2007;**120**:S94-138.
 37. Douglas G, Higgins B, Barnes N *et al*. British guideline on the management of asthma: a national clinical guideline. *Thorax* 2008;**63**:iv1-iv121.
 38. Bateman ED, Hurd SS, Barnes PJ *et al*. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;**31**:143-78.
 39. Lodge CJ, Allen KJ, Lowe AJ *et al*. Perinatal cat and dog exposure and the risk of asthma and allergy in the urban environment: a systematic review of longitudinal studies. *Clin Dev Immunol* 2012;**2012**:176484.
 40. Takkouche B, González-Barcala FJ, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. *Allergy* 2008;**63**:857-64.