

BIOMARKERS

Associations of Age and Birth Cohort with Total and Specific IgE Antibody Levels

KAZUHARU TSUKIOKA, M.D.,^{1,*} SHIN-ICHI TOYABE, M.D.,² AND KOHEI AKAZAWA, M.D.³

¹*Niigata Allergic Disease Research Institute, Niigata, Japan.*

²*Department of Patient Safety, Niigata University Medical and Dental Hospital, Niigata, Japan.*

³*Department of Medical Informatics, Niigata University Medical and Dental Hospital, Niigata, Japan.*

Background. Total and antigen-specific IgE levels vary greatly with age; however, it is unclear whether they are more closely related to patient age or birth cohort. **Objective.** To determine whether birth cohort or age was more strongly correlated with total and specific IgE levels. **Methods.** We retrospectively examined the medical records of 5136 asthma patients who were treated at the Niigata Allergic Disease Research Institute Outpatient Clinic during the period from 1997 to 2005. The subjects were divided into four birth cohorts based on their year of birth: the first cohort was born in 1935 or earlier, the second in 1936–1955, the third in 1956–1975, and the fourth in 1976 or later. Their total IgE level and mite-, cedar-, and *Candida albicans* (Candida)-specific IgE levels were measured using the CAP RAST fluoroenzyme immunoassay test. **Results.** Univariate analysis revealed that total IgE level and mite-, cedar-, and Candida-specific IgE levels significantly decreased ($p < .001$) with advancing age. In addition, there were significantly higher IgE levels in later birth cohorts ($p < .01$). On multivariate analysis, there were associations of total IgE level and mite- and cedar-specific IgE levels with both age and birth cohort. However, there was no significant association between Candida-specific IgE antibody level and either age or birth cohort. **Conclusions.** The associations of total and specific IgE levels with age and birth cohort were different. Thus, in comparing the results of IgE antibody testing done in different years, even for patients of the same age, the possibility of a birth cohort effect on IgE levels should be considered.

Keywords age, asthma, birth cohort, IgE production, specific IgE, total IgE

INTRODUCTION

Changes in total and specific IgE levels due to environmental allergens vary greatly with age. During the period from infancy to puberty, these levels increase with advancing age (1–3), but, upon reaching adulthood, they begin to decrease steadily (4–6). Factors that are believed to contribute to this decrease have been reported and they include IgE class-specific regulatory T-cell dysfunction, T-cell alterations, changes in B-cell tolerance (7–9), and defects in age-dependent T-cell activation (10). However, it has also been suggested that large age-related differences in IgE values are the result of generational differences in the production of IgE antibodies (1–6). Reasons for the apparent differences seen between generations might include both environmental factors (more or less antigen exposure) and host factors (differences between generations with respect to their sensitivity to such antigens). Regarding environmental factors, cedar pollen-specific IgE levels are known to be strongly affected by the amount of airborne cedar pollen (11). Another example of a difference in environmental exposure was reported in a study (12) in which researchers found that total IgE and mite-specific IgE levels in children in New Zealand (where large numbers of indoor dust mites act as antigens) were much higher than those in children

from northern Sweden (where far fewer dust mites are present indoors). With respect to host factors, the number of children and young adults with atopic diseases has been increasing at an alarming rate (13–15). A possible explanation for this rise is the introduction of widespread antibiotic use in the 1970s. Although such antibiotic use has resulted in a drastic decrease in the number of infants with communicable diseases (15), it may have led to an increase in the prevalence of allergic airway diseases (16).

Although total and antigen-specific IgE levels vary with age and birth cohort, it is unclear whether they are more closely related to the former or the latter. Thus, we examined whether age or birth cohort was more strongly associated with total IgE and antigen-specific IgE levels.

METHODS

We retrospectively investigated the medical records of 5136 asthma patients (2080 males, 3054 females, 2 of unknown sex) who were treated at the Niigata Allergic Disease Research Institute Outpatient Clinic during the period from 1997 to 2005. The subjects comprised all patients treated for asthmatic conditions at the clinic during this period. The subjects were divided, based on their year of birth, into four birth cohorts: those born in 1935 or before (mean age $\pm$ standard deviation, 72.0 ± 5.1 years), those born in 1936–1955 (56.9 ± 7.3 years), those born in 1956–1975 (37.1 ± 8.4 years), and those born in 1976 or later (27.0 ± 10.3 years). These cohorts were defined based on recent historical events in Japan and

*Corresponding author: Kazuharu Tsukioka, M.D., Niigata Allergic Disease Research Institute, 4-4-1 Kobari, Nishi-ku, Niigata, Japan 950-2022; Tel: +81-(0)25-234-1666; Fax: +81-(0)25-234-1667; E-mail: sora.8.tsukioka@bj.wakwak.com

corresponded to (1) the period before World War II, (2) the period during and immediately after World War II (including the early period of post-war reconstruction), (3) the period of rapid economic growth, and (4) the period beginning at the end of rapid growth. Total and antigen-specific IgE levels were analyzed to determine if they were associated with birth cohort. A diagnosis of asthma was based on the Global Initiative for Asthma (GINA) 2006 criteria (17). We excluded asthma patients with co-existing chronic obstructive pulmonary disease from this analysis.

Subjects were classified as smokers if they reported any level of current smoking. Those who had quit smoking at least 1 year before assessment were classified as former smokers. Subjects with no history of a smoking habit were classified as never smokers.

Total serum IgE levels were determined with the CAP RAST fluoroenzyme immunoassay (FEIA; Fadia, Ltd., Uppsala, Sweden). The normal serum IgE level in subjects over 16 years of age is considered to be 100 to 140 IU/mL (5, 6, 18, 19), and levels over 140 IU/mL were classified as high in this study. The CAP RAST FEIA (Fadia, Ltd.) was used to determine antigen-specific IgE levels for dust mites (*Dermatophagoides pteronyssinus*), cedar pollen, and Candida. We selected these allergens for our analysis because dust mites are a primary cause of allergic diseases worldwide (20), Japanese cedar (*Cryptomeria japonica*) is found throughout Japan and is the most important source of pollinosis in Japan (21), and Candida is a recognized risk factor for severe asthma (22). Results for specific IgE levels were classified according to Phadebas test result (23), and prevalences in this study were estimated based on the proportion of patients with a Phadebas RAST score of 2 or higher (≥ 0.35 Phadebas RAST units/mL).

Some of the subjects in this study were also tested for other allergen-specific IgE antibodies, including dog ($n = 305$), cat ($n = 283$), pollen ($n = 1882$), and mold ($n = 1775$). Because fewer patients were tested for these allergens than for mite, cedar, and Candida, the results for these other allergens were not included in the analysis. Only those patients with cats or dogs at home were tested for those specific IgE antibodies. The test for pollen included the five common grass pollen allergens in the rice plant family (orchard, timothy, reed, *Torreyia nucifera*, and *Zoysia japonica*) and five weed pollen allergens in the chrysanthemum family (ragweed, mugwort, dandelion, goldenrod, and chrysanthemum). The tests for mold-specific IgE included six common mold allergens (*Penicillium*, *Cladosporium*, *Aspergillus*, *Candida*, *Alternaria*, and *Helminthosporium*). Due to the nature of these multiple pollen and mold tests, it was not possible to identify which of the allergens tested positive, so the results of those tests were not included in this study.

Trends were evaluated with the Cochran–Armitage test. Differences in categorical variables were analyzed using the chi-square test and Fisher’s exact test. Multivariate analysis was used to evaluate correlations between specific IgE antibodies and their antigens, with

forced inclusion of independent variables. Dummy variables were used to represent variables including birth cohort, gender, and smoking status. A value of $p < .05$ was considered statistically significant.

RESULTS

Tables 1 and 2 show the characteristics of the patients. The proportion of males was higher in the latest birth cohort as compared with the earliest birth cohort (Table 1). The proportion of former smokers is higher in the earlier cohorts, and the proportion of current smokers is reciprocally higher in the later cohorts (Table 2).

Of the 5136 patients, 3832 were tested for total serum IgE, 3862 for mite-specific IgE, and 3726 for Candida-specific IgE. The proportion of subjects with a high total IgE level significantly increased at each step from the earliest to the latest birth cohort. The proportions of subjects with mite-, cedar-, and Candida-specific IgE antibodies also significantly increased from the earliest to the latest birth cohort (Table 3). However, the increase was modest for Candida-specific IgE (Figure 1).

Overall, significantly more men than women had high levels of total IgE and positive results for mite-, cedar-, and Candida-specific IgE (Supplementary Table 1 available online at [http://informahealthcare.com/doi/suppl/\[3109\]](http://informahealthcare.com/doi/suppl/[3109])). Even when the cohorts were analyzed individually, more men were positive for mite- and Candida-specific IgE. In analysis stratified by sex, the proportions of men and women with high total IgE and mite- and cedar-specific IgE increased from the earliest to the latest birth cohort. Candida-specific IgE also increased from the earliest to the latest birth cohort, but the trend was not observed in male patients. With regard to smoking status, as compared with never

TABLE 1.—Number of patients in each cohort, by gender.

Year of birth	Gender			Total
	Male	Female	Male:female	
≤1935	138	243	0.57	381
1936–1955	470	735	0.64	1205
1956–1975	726	1159	0.63	1885
≥1976	746	917	0.81	1663
	2080	3054	0.68	5134

TABLE 2.—Number of patients in each cohort, by smoking status.

Year of birth	Never smoker		Former smoker		Current smoker		Total
	Percentage		Percentage		Percentage		
≤1935	223	69.0	60	18.6	40	12.4	323
1936–1955	682	67.5	125	12.4	203	20.1	1010
1956–1975	861	57.2	112	7.4	532	35.3	1505
≥1976	922	64.9	58	4.1	440	31.0	1420
	2688	63.1	355	8.3	1215	28.5	4258

TABLE 3.—Proportion of patients with high total and antigen-specific IgE values in each birth cohort. Trends between cohorts were evaluated with the Cochran–Armitage test.

	Year of birth				Total	P-value
	≤1935	1936–1955	1956–1975	≥1976		
High total IgE levels	131/342	386/950	650/1367	825/1173	1992/3832	<.001
Percentage	38.3	40.6	47.5	70.3	52.0	
High specific IgE levels						
House dust mite	46/344	223/954	646/1384	933/1180	1848/3862	<.001
Percentage	13.4	23.4	46.7	79.1	47.9	
Cedar pollen	28/326	221/854	543/1274	481/1072	1273/3526	<.001
Percentage	8.6	25.9	42.6	44.9	36.1	
Candida	38/343	82/923	114/1330	169/1130	403/3726	.005
Percentage	11.1	8.9	8.6	15.0	10.8	

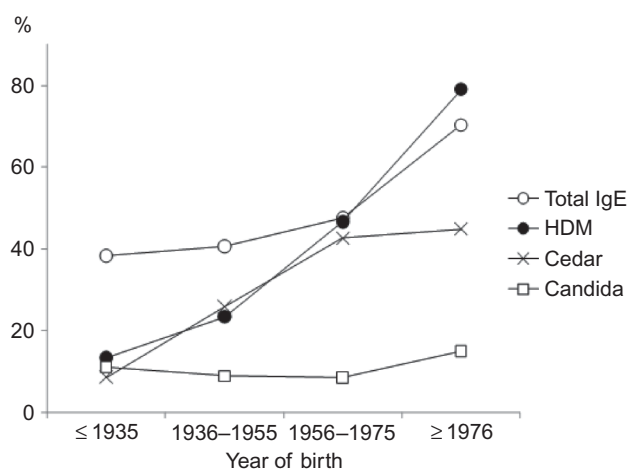


FIGURE 1.—The relationship between birth cohorts and proportion of patients with high IgE levels.

smokers, significantly higher proportions of former smokers and current smokers had high total IgE levels and positive results for mite-, cedar-, and Candida-specific IgE (Supplementary Table 2 available online at <http://informahealthcare.com/doi/suppl/10.3109/02770903.2011.558152>). In analysis stratified by smoking status, the proportions of patients with high IgE levels significantly increased from the earliest to the latest birth cohort in almost all strata. However, this trend was not observed for Candida-specific IgE levels in either former or current smokers. Figure 2 shows the relationship between patient age and the proportion of high IgE levels. The proportion of patients with high levels of total IgE and mite- and cedar-specific IgE decreased with increasing patient age. However, the proportion of Candida-specific IgE was almost constant between ages.

Because age, gender, and smoking status were associated with total and antigen-specific IgEs, multivariate regression analysis was performed to eliminate the possible confounding effects of these factors (Table 4). Total IgE and mite- and cedar-specific IgE levels were positively associated with later birth cohort and negatively associated with age (Table 4A, B, C). However, Candida-specific IgE levels were not significantly associated with birth cohort or patient age (Table 4D).

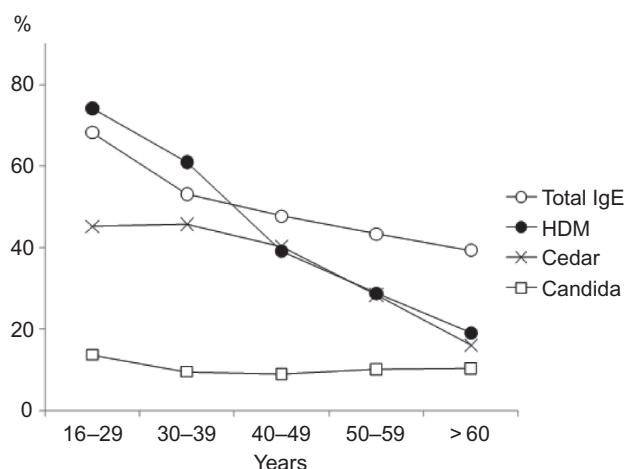


FIGURE 2.—The relationship between patient age and the proportion of patients with high IgE levels.

DISCUSSION

We investigated whether age or birth cohort was more strongly associated with total and antigen-specific IgE production in asthma patients. We observed that total IgE and mite- and cedar-specific IgE levels were associated with both age and birth cohort. Specifically, the values for these three variables gradually decreased with age and progressively increased in later birth cohorts. These findings indicate that when IgE data for different years are collected and compared—even when the actual ages of the patients are similar—it is necessary to consider birth cohort in addition to age. However, Candida-specific IgE was not associated with either age or birth cohort. Thus, it appears that the effects of age and birth cohort are antigen-specific.

We hypothesized that variations in environmental and individual factors explain the generational differences in total and allergen-specific IgEs. Therefore, to identify the differing environmental factors affecting each generation, we selected four generations that were representative of major periods in Japan's recent history.

It is known that air pollution in general and car exhaust in particular affect total IgE levels: diesel exhaust particulates (DEP) have been reported to increase production

TABLE 4.—Factors associated with total and antigen-specific IgE values. Multiple regression analysis was performed to determine factors that were associated with total IgE (A) and specific IgE against house dust mite (B), cedar pollen (C), and *Candida* (D). Independent variables were age, birth cohort, gender, and smoking status.

	Unstandardized coefficient			95% CI		
	β	SE	Standardized coefficient	Lower	Upper	P-value
(A)						
Female gender	−205.0	48.2	−0.080	−299.498	−110.546	<.001
Year of birth (1936–1955)	−167.3	92.3	−0.058	−348.193	13.662	.070
Year of birth (1956–1975)	−185.1	117.3	−0.070	−414.979	44.834	.115
Year of birth (≥1976)	125.2	137.5	0.046	−144.434	394.784	.363
Former smoker	−61.1	79.2	−0.015	−216.391	94.264	.441
Current smoker	143.3	52.7	0.052	39.963	246.603	.007
Age	−4.9	2.5	−0.067	−9.717	−0.099	.045
Constant	839.4	196.4		454.353	1224.397	<.001
(B)						
Female gender	−0.494	0.066	−0.118	−0.623	−0.365	<.001
Year of birth (1936–1955)	−0.141	0.126	−0.030	−0.388	0.106	.263
Year of birth (1956–1975)	0.167	0.160	0.039	−0.147	0.481	.298
Year of birth (≥1976)	1.722	0.188	0.387	1.353	2.091	<.001
Former smoker	−0.113	0.108	−0.016	−0.324	0.099	.298
Current smoker	0.000	0.072	0.000	−0.141	0.141	.998
Age	−0.026	0.003	−0.219	−0.033	−0.020	<.001
Constant	2.672	0.268		2.146	3.198	<.001
(C)						
Female gender	−0.061	0.057	−0.020	−0.173	0.051	.284
Year of birth (1936–1955)	0.316	0.109	0.093	0.104	0.529	.004
Year of birth (1956–1975)	0.613	0.139	0.198	0.341	0.885	<.001
Year of birth (≥1976)	0.505	0.163	0.158	0.186	0.825	.002
Former smoker	0.077	0.093	0.016	−0.105	0.258	.409
Current smoker	0.015	0.063	0.004	−0.108	0.138	.813
Age	−0.014	0.003	−0.168	−0.020	−0.009	<.001
Constant	1.303	0.234		0.844	1.761	<.001
(D)						
Female gender	−0.147	0.030	−0.093	−0.206	−0.087	<.001
Year of birth (1936–1955)	−0.108	0.057	−0.060	−0.220	0.005	.061
Year of birth (1956–1975)	−0.079	0.073	−0.049	−0.223	0.064	.279
Year of birth (≥1976)	0.116	0.086	0.069	−0.052	0.284	.174
Former smoker	0.031	0.049	0.012	−0.065	0.127	.528
Current smoker	0.103	0.033	0.060	0.038	0.168	.002
Age	0.002	0.002	0.039	−0.001	0.005	.250
Constant	0.297	0.123		0.055	0.539	.016

Note: CI, confidence interval of standardized correlation coefficient; SE, standard error of unstandardized correlation coefficient.

of IgE antibodies in humans (24, 25). Japan entered a period of sudden motorization after World War II; thus, different generations were likely exposed to varying levels of DEP. Furthermore, beginning in the 1960s, there was a sudden increase in mite-specific IgE due to better-insulated post-war housing and the increased popularity of carpets (26). In addition, after World War II, a large number of cedar forests were planted for the purpose of future harvesting and use in house building. However, because these forests have not been cut, the amount of cedar pollen released has increased each year. Levels of airborne pollen have increased dramatically since 1980, which has led to a 2.6-fold increase in the rate of cedar pollinosis in Japan between 1980 and 2000 (27). However, as this increase in airborne pollen occurred during an era of sudden motorization, DEP are a likely contributing factor. Indeed, it has been reported that the DEP have an adjuvant effect that encourages further production of cedar-specific IgE (28).

Candida is a fungus that is normally present in the human body and is a recognized risk factor for severe

asthma (22). Perhaps because *Candida* mainly acts indirectly as an allergen sensitizing the mucosa, its role in the pathogenesis of allergic conditions remains unclear (29). Studies indicate that *Candida* may result in the development or progression of allergic conditions, as an adverse effect of antibiotic therapy (16). It is thus important to consider the possibility that different birth cohorts received varying amounts of antibiotics during their lifetimes (15) and that this could result in variations in *Candida*-specific IgE levels.

Host factors vary by generation. This has become quite clear in recent years, in light of the sudden worldwide increase in the number of patients with atopic disorders and the corresponding increase in the number of asthma sufferers (13, 14, 30, 31). The hygiene hypothesis may account for some of this sudden increase (32, 33), but other explanations must be considered, including the possibility that overuse of antibiotics leads to changes in host factors related to the otherwise normal presence of *Candida* in the body (16).

It has been reported that the effect of age on IgE production is allergen-specific. Mite-specific IgE production is known to decline after age 40 years and to decrease sharply after age 70 (34). In contrast, until approximately age 50 years, cedar pollen-specific IgE markedly increases in the presence of a high level of airborne pollen (11). However, after age 60 years, no corresponding increase was seen in pollen-specific IgE, even when the amount of airborne pollen increased. As expected, the immune response of adults in their fifties was between those noted in the older and younger groups (11). In a longitudinal study of subjects over a period of 13 years, the investigators observed a rapid increase in the number of subjects testing negative for cedar-specific IgE after reaching age 60 (35). This finding is consistent with the observation that adults with seasonal pollinosis experience gradual, natural remission after age 60 (11). In this respect, cedar pollen-specific IgE production seems to differ from that of mite-specific IgE, possibly because of differences in their allergenic properties or in the manner in which cedar pollen and mite antigens stimulate IgE antibody production.

Finally, previous studies have reported that total and specific IgE production is associated with gender and smoking status. Those findings were confirmed in this study.

A limitation of this study was that there were fewer patients in the oldest birth cohort. Thus, the possibility of survivor bias cannot be excluded.

In conclusion, these results suggest that a patient's birth cohort may be important in any analysis of factors influencing total or antigen-specific IgE production.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

REFERENCES

- Matricardi PM, Bockelbrink A, Keil T, Gruber C, Niggemann B, Hamelmann E, Wahn U, Lau S. Dynamic evolution of serum immunoglobulin E to airborne allergens throughout childhood: results from the Multi-Centre Allergy Study birth cohort. *Clin Exp Allergy* 2009; 39:1551–1557.
- Matricardi PM, Bockelbrink A, Gruber C, Keil T, Hamelmann E, Wahn U, Lau S. Longitudinal trends of total and allergen-specific IgE throughout childhood. *Allergy* 2009; 64:1093–1098.
- Lévesque B, Duchesne JF, Cingras S, Allard P, Delvin E, Aubin J, Rhaind M, Lajoie P, Ernst P. Total and specific immunoglobulin E and their relationship to respiratory symptoms in Québec children and adolescents. *Can Respir J* 2005; 12:426–432.
- Court CS, Cook DG, Strachan DP. The descriptive epidemiology of house dust mite-specific and total immunoglobulin E in England using a nationally representative sample. *Clin Exp Allergy* 2002; 32:1033–1041.
- Kerhof M, Droste JHJ, de Monchy JGR, Schouten JP, Rijcken B, Dutch ECRHS Group. Distribution of total serum IgE and specific IgE to common aeroallergens by sex and age, and their relationship to each other in a random sample of the Dutch general population aged 20–70 years. *Allergy* 1996; 51:770–776.
- Omenaas E, Bakke P, Elsayed S, Hanoa R, Gulsvik A. Total and specific serum IgE levels in adults: relationship to sex, age and environmental factors. *Clin Exp Allergy* 1994; 24:530–539.
- Fujiwara M, Kishimoto S. IgE antibody formation and aging. 1. Age-related changes in IgE antibody formation and avidity for the DNP-determinants in mice. *J Immunol* 1979; 123:263–268.
- Pauwels R, Bazin H, Platteau B, Van Der Straeten M. The effect of age on IgE production. *J Immunol* 1979; 36:145–149.
- Gerber V, Ponnappan U, Heusser CH, Blaser K, Cinader B. Age- and strain-dependent polymorphism in IgE antibody against the phosphorylcholine hapten. *Eur J Immunol* 1986; 16:713–716.
- al-Rayes H, Pachas W, Mirza N, Ahern DJ, Geha RS, Vercelli D. IgE regulation and lymphokine patterns in aging humans. *J Allergy Clin Immunol* 1992; 90:630–636.
- Okawa T, Konno A, Yamakoshi T, Numata T, Terada N, Shima M. Analysis of natural history of Japanese cedar pollinosis. *Int Arch Allergy Immunol* 2003; 131:39–45.
- Erwin EA, Rönmark E, Wickens K, Perzanowski MS, Barry D, Lundbäck B, Crane J, Platts-Mills TAE. Contribution of dust mite and cat specific IgE to total IgE: relevance to asthma prevalence. *J Allergy Clin Immunol* 2007; 119:359–365.
- Kusunoki T, Hosoi S, Asai K, Harazaki M, Furusho K. Relationships between atopy and lung function: results from a sample of one hundred medical students in Japan. *Ann Allergy Asthma Immunol* 1999; 83:343–347.
- Nakagomi T, Itaya H, Tominaga T, Yamaki M, Hisamatsu S, Nakagomi O. Is atopy increasing? *Lancet* 1994; 343:121–122.
- Akasawa A, Matsumoto K, Tomikawa M, Tsujimoto G, Eto Y, Saito H. Prevalence and gene expression screening of atopic subjects among medical students in Japan. *J Allergy Clin Immunol* 2001; 107: S278 (Abstract).
- Noverr MC, Noggle RM, Toews GB, Huffnagle GB. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. *Infect Immun* 2004; 72:4996–5003.
- Global Initiative for Asthma Management and Prevention. NHLBI/WHO Workshop Report. National Institute heart, Lung, and Blood Institute, 2006:57–63.
- Al-Obaidi AHA, Al Samarai AGM, Al Samarai AKY, Al Janabi JM. The predictive value of IgE as biomarker in asthma. *J Asthma* 2008; 45:654–663.
- Kawakatsu S, Kishimoto H, Imai H, Sato A. Reference values for the total serum IgE levels by RIST, RIA-PRIST, and EIA-PRIST. *Arerugii* 1986; 35:238–244 (in Japanese).
- Platts-Mills TA, Thomas WR, Aalberse RC, Vervloet D, Chapman MD. Dust mite allergens and asthma: report of a second international workshop. *J Allergy Clin Immunol* 1992; 89:1046–1060.
- Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol* 2003; 91:288–296.
- Madani Y, Barlow A, Taher F. Severe asthma with fungal sensitization: a case report and review of literature. *J Asthma* 2010; 47:2–6.
- De Filippi I, Yman L, Schröder H. Clinical accuracy of updated version of the PHADEBAS RAST test. *Ann allergy* 1981; 46:249–255.
- Takenaka H, Diaz-Sanchez D, Saxon A. Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effect on B-cell IgE production. *J Allergy Clin Immunol* 1995; 105:103–115.
- Diaz-Sanchez D, Saxon A, Takenaka H. Diesel exhaust particles induce local IgE production in vivo and alter the pattern of IgE messenger RNA isoforms. *J Clin Invest* 1994; 94:1417–1425.
- Takaoaka M. Changes in living environments and their relationship to dust mite numbers: is the number of allergic diseases increasing? In: Do allergic diseases increase? T. Miyamoto, ed. Tokyo: Kokusai Igaku Shuppan, 1987:54–57 (in Japanese).
- Kaneko Y, Motohashi Y, Nakamura H, Endo T, Eboshida A. Increasing prevalence of Japanese cedar pollinosis: a meta-regression analysis. *Int Arch Allergy Immunol* 2005; 136:365–371.
- Takahuji S, Suzuki S, Koizumi K, Tadokoro K, Miyamoto T, Ikemori R, Muranaka M. Diesel-exhaust particulates inoculated by the

- intranasal route have adjuvant activity for IgE production in mice. *J Allergy Clin Immunol* 1987; 79:639–645.
29. Asero R, Bottazzi G. Clinical features of patients showing *Candida* hypersensitivity: an observation study. *J Invest Allergol Clin Immunol* 2004; 14:309–311.
30. Kay AB. Allergy and allergic diseases. First of two parts. *N Engl J Med* 2001; 344:30–37.
31. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; 355:2226–2235.
32. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299(6710):1259–1260.
33. Liu AH, Murphy JR. Hygiene hypothesis: fact or fiction? *J Allergy Clin Immunol* 2003; 111:471–478.
34. Nakazawa T, Houjyo S, Dobashi K, Sato K. Influence of aging and sex on specific IgE antibody production. *Intern Med* 1994; 33:396–401.
35. Okamoto Y, Horiguchi S, Yamamoto H, Yonekura S, Hanazawa T. Present situation of cedar pollinosis in Japan and its immune responses. *Allergol Int* 2009; 58:155–162.

Copyright of Journal of Asthma is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.