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Japanese cedar pollinosis in Tokyo residents born after massive national afforestation policy

To the Editor,

Seasonal allergic rhinitis caused by pollen from Japanese cedar (JC pollen), sugi (*Cryptomeria japonica*), is called Japanese cedar pollinosis (JC pollinosis) and considered a national affliction in Japan. A national policy resulted in the planting of Japanese cedar trees between the early 1950s and early 1970s that covered almost 18% of the total land area of Japan to provide wood for home construction. However, wood tariffs were reduced in 1964 and then imported wood replaced Japanese cedar trees for this purpose.¹ However, the planted cedars continued to thrive, which caused increasing amounts of airborne JC pollen, especially after the 1970s, and levels still continue to increase.²

Tokyo prefecture has conducted four decennial surveys since 1987 to monitor the prevalence of JC pollinosis among Tokyo citizens. The authors contributed to the fourth iteration of the survey, which included planning in 2016, and medical examination and data analysis in 2017. The results of these surveys showed an exponentially increasing prevalence of 10.0% in 1987, 19.4% in 1997, 28.2% in 2007, and 45.6% in 2017,³ representing a 4.6-fold increase over the past 30 years. The present analysis is a cross-sectional, as opposed to a longitudinal cohort study. However, the prevalence of JC pollinosis among those aged between 0 and 14 years in 1987 (=born in or after 1973) and who reached ages between 30 and 44 years by 2017 increased 23.0-fold from 2.4% to 55.2%. On the one hand, the age-group born in or after 1973 (A1973) is considered as the generation of the postmassive afforestation period, and on the other hand, the age-group born in or before 1972 (B1972) is the generation born before or during the afforestation. We therefore hypothesized that exposure to large amounts of JC pollen during the neonatal period or early infancy, as with those in A1973, increases risk and enhances the severity of JC pollinosis among individuals born in and around March, which is the peak season for JC pollen. Thus, the present post hoc analysis of data derived from the fourth Tokyo survey (2017) aimed to determine differences in risk by birth month, risk of sensitization, and severity of JC pollinosis between A1973 and B1972.

Detailed methods are written in the Data S1. Briefly, the fourth decennial survey of JC pollinosis randomly sampled 3600 Tokyo residents, of whom 2101 responded. Subsequently, 410 randomly selected from each severity group were examined by otorhinolaryngologists at local health centers in March 2017, peak season for JC pollen; 266 residents were diagnosed with JC pollinosis.

Table S1 shows the characteristics of 2101 randomly selected residents who returned questionnaires. Among 410 participants who

were medically examined by otorhinolaryngologists, 266 (65%) were diagnosed with JC pollinosis based on established diagnostic criteria. Symptoms and signs of allergic rhinitis were more severe in A1973 than in B1972 (Figure S1).

Levels of JC pollen specific IgE, mite specific IgE, and Japanese cypress pollen were significantly higher in A1973 than in B1972 both among the 410 who participated in the medical examination (Figure 1A,C,E) and among the 266 diagnosed with JC pollinosis (Figure 1B,D,F).

The relative risk (RR) of JC pollinosis increased to 1.50 (95% CI, 1.35-1.67; $P = 0.01$) among A1973 participants born in March (peak month of JC pollen spread) (Figure 2A), but remained unchanged in B1972 born in March (Figure 2B) ($P_{\text{interaction}} < 0.0001$). The rate similarly increased among A1973 born in December to 1.34 (95% CI, 1.11-1.62; $P = 0.04$), but also remained unchanged in B1972 ($P_{\text{interaction}} = 0.04$). Birth month and levels of JC pollen sensitization were analyzed using ordered logistic regression in A1973 (Figure S2A) and in B1972 (Figure S2B). Being born in March conferred prominent risk compared with all other months in A1973 (OR, 6.94; 95% CI, 1.63-29.6; $P = 0.009$), but not in B1972.

This post hoc study of the fourth survey in Tokyo added evidence to support the notion that signs and symptoms of patients with JC pollinosis are more severe among individuals born after (age, <45 years; A1973) than before or during the afforestation period. In addition, levels of JC pollen specific IgE were higher in A1973 than B1972, both in the 410 who participated in the medical examination and the 266 diagnosed with JC pollinosis.

The present study found that risk of JC pollinosis and scores for sensitization to JC pollen were the highest among A1973 born in March, which is the peak time for JC pollen dissemination and the appearance of JC pollinosis. Moreover, these findings were evident in A1973 born after afforestation, but not in B1972 born before or during afforestation. Interaction by generation was statistically significant ($P_{\text{interaction}} < 0.0001$). These results may support our hypothesis that exposure to large amounts of JC pollen during the neonatal period may trigger sensitization and JC pollinosis later in life. In addition, being born not only March but also in December confers risk of JC pollinosis, and being born in January confers risk of JC pollen sensitization. These may suggest that the sensitive period is not only in the neonatal period but also during early infancy.

On the other hand, a quite different hypothesis can also be considered. Immigrant children born in Italy have a lower prevalence of rhinitis due to sensitization to grass than native-born Italian

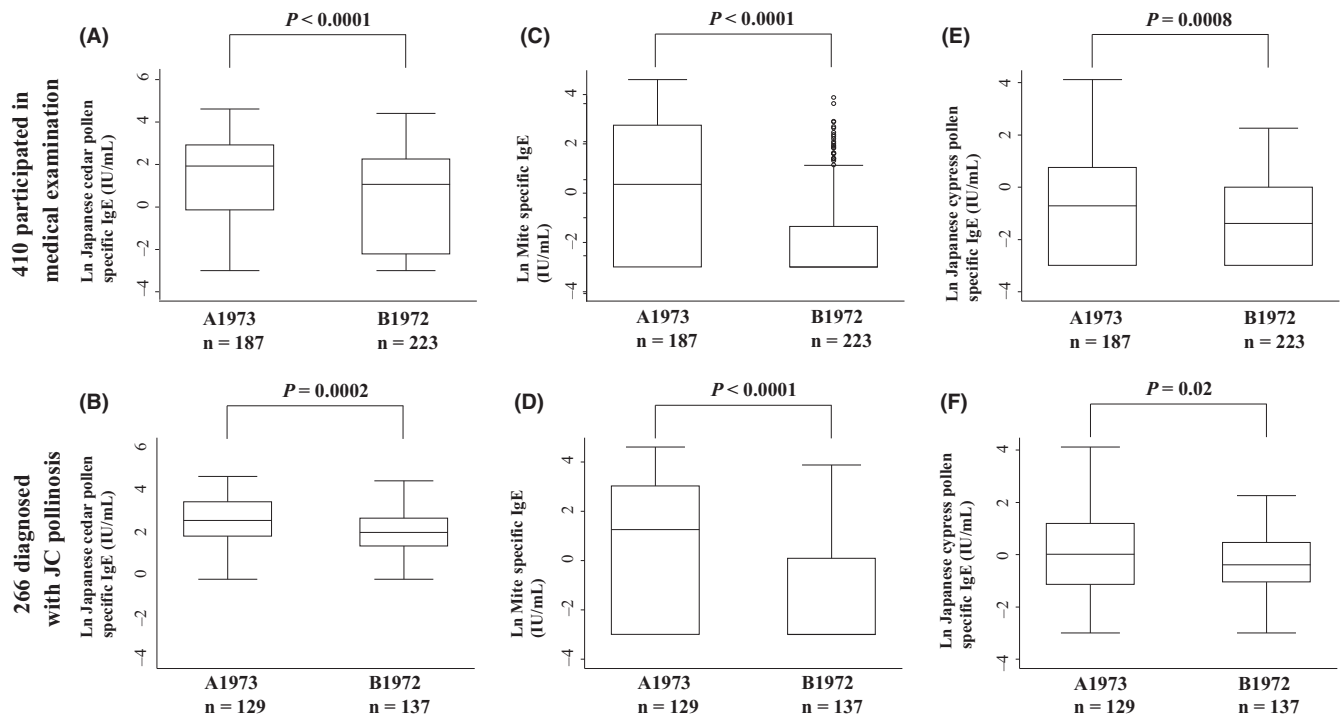


FIGURE 1 Comparisons of specific IgE to various antigens between generations born in or after 1973 (A1973) and in or before 1972 (B1972). Levels of Japanese cedar pollen (JC pollen) specific IgE in the 410 who participated in the medical examination (A); levels of Japanese cedar pollen (JC pollen) specific IgE in the 266 diagnosed with JC pollen (B); levels of mite specific IgE in the 410 who participated in the medical examination (C); levels of mite specific IgE in the 266 diagnosed with JC pollen (D); levels of Japanese cypress pollen specific IgE in the 410 who participated in the medical examination (E); levels of Japanese cypress pollen specific IgE in the 266 diagnosed with JC pollen (F); P values were calculated using Mann-Whitney tests. Levels of IgE were transformed by natural logarithm

Japanese Cedar Pollinosis

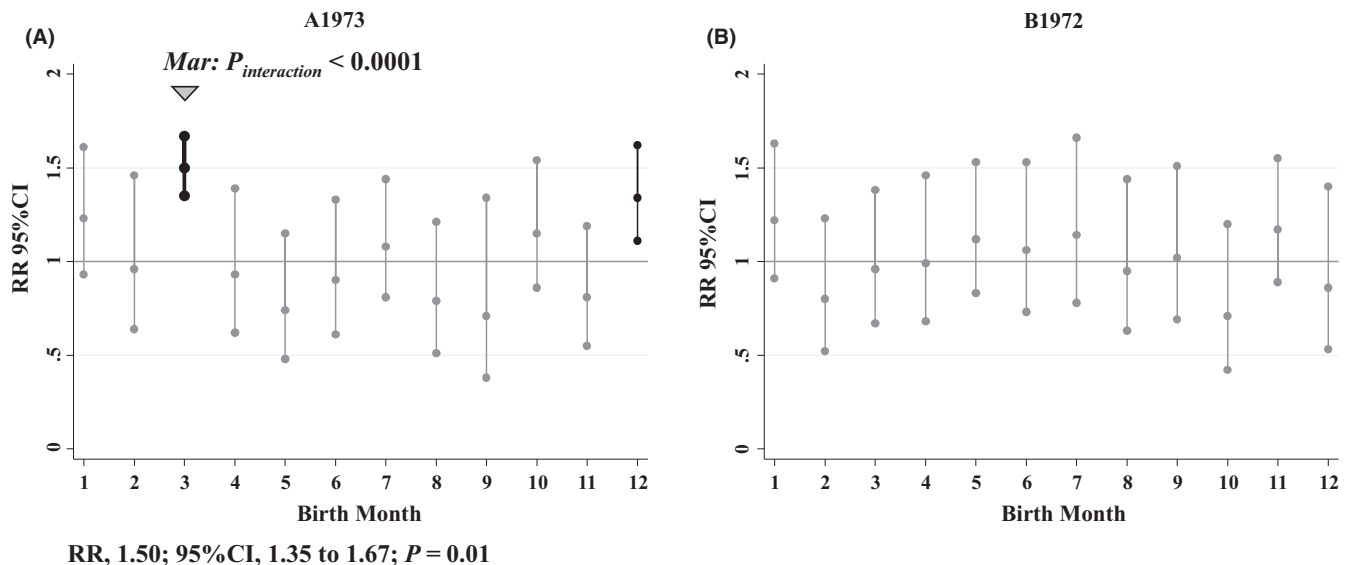


FIGURE 2 Risk ratios with 95% CI of Japanese cedar pollinosis and birth month between January and December. A, age-group born in or after 1973 (A1973); B, age-group born in or before 1972 (B1972). Black bold bars, significant RR; gray bars, nonsignificant RR (with 95% CI crossing 1). P values are calculated using chi-squared tests. P for interaction was calculated as a test of homogeneity between A1973 and B1972

children,⁴ and a parental atopic predisposition might be not only inherited, but also enhanced in the next generation. The present study cohort included three generations, and the prevalence of the

most severe symptoms of allergic rhinitis was 15% in those aged 25–49, 6.0% in those aged 50–75, and 1.7% in those aged >75, suggesting that sensitivity to allergens increases over generations.

In conclusion, we found that (a) signs and symptoms of JC pollinosis were more severe; (b) levels for JC pollen specific IgE and mite specific IgE were higher in A1973 than in B1972 with JC pollinosis; and (c) being born in March conferred risk of JC pollinosis and sensitization to JC pollen in A1973.

We would like to advise the Japanese government that it is not too late to start action to substitute Japanese cedar trees with other trees to increase diversity. We hope that other countries do not repeat the same mistakes as Japan.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTION

Urashima M, Asaka D, Endo T, and Kojima H involved in the conception and design of the study. Asaka D, Endo T, Omae S, Sugimoto N, Takaishi S, Mitsuyoshi R, Nakayama T, Nagakura H, and Endo T involved in the acquisition of data. Urashima M, Akutsu T, and Tachimoto H analyzed and interpreted the data. Urashima M drafted the article. All the other authors critically revised the article for important intellectual content. All authors approved the final version of the manuscript to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary file

Title:

Japanese cedar pollinosis in Tokyo residents born after massive national afforestation policy

Table S1. First cohort of 2,101 participants randomly sampled from registration in Tokyo.

Variable	A1973 n=948 (45.1%)	B1972 n=1,153 (54.9%)	Total n=2,101	<i>P</i>
Age (y)				
Median (25-75%)	27 (13-36)	63 (53-75)	47 (29-66)	-
Range	1-44	45-102	1-102	
Male, n (%)	456 (48)	530 (46)	986 (47)	0.33 [*]
Severity [§] n (%) [†]				OR, 1.60; 95%CI, 1.42-1.95 <0.001 [‡]
Asymptomatic	311 (33)	479 (42)	790 (38)	
Mild	169 (18)	261 (23)	430 (21)	
Moderate	195 (21)	220 (19)	415 (20)	
Severe	146 (16)	123 (11)	269 (13)	
Most severe	121 (13)	70 (6)	191 (9)	
Drug usage for allergic rhinitis, n (%)	69 (7)	68 (6)	137 (7)	0.20 [*]

*Chi-square test. [†]Total is not always 100% due to rounding. [‡]Ordinal logistic regression.

[§]Based on responses to questionnaire. A1973, younger age group born in or after 1973; B1972, older age group born in or before 1972.

Characteristics of the participants

Table S1 shows the characteristics of 2,101 randomly selected residents who returned questionnaires. Their overall median age was 47 (range, 1-102) years. The median age of the A1973 and B1972 groups was 27 and 63 years, respectively. The ratio of males was

47% and did not significantly differ between the groups. The severity of allergic rhinitis between February and April 2016 determined from questionnaire responses was significantly worse in A1973 than B1972 (OR, 1.60; 95%CI, 1.42-1.95; $P < 0.001$). The prevalence of “most severe” symptoms, as well as sum of “most severe” and “severe”, were significantly higher in A1973 than in B1972 ($P < 0.0001$ for both). The ratio of individuals taking medicine for allergic rhinitis was 7% and did not significantly differ between the groups. The prevalence of the most severe symptoms decreased with increasing generation: 15.3% in those aged 25-49 years, 6.0% in those aged 50-75 years, and 1.7% in those aged >75 years (not listed in Table S1).

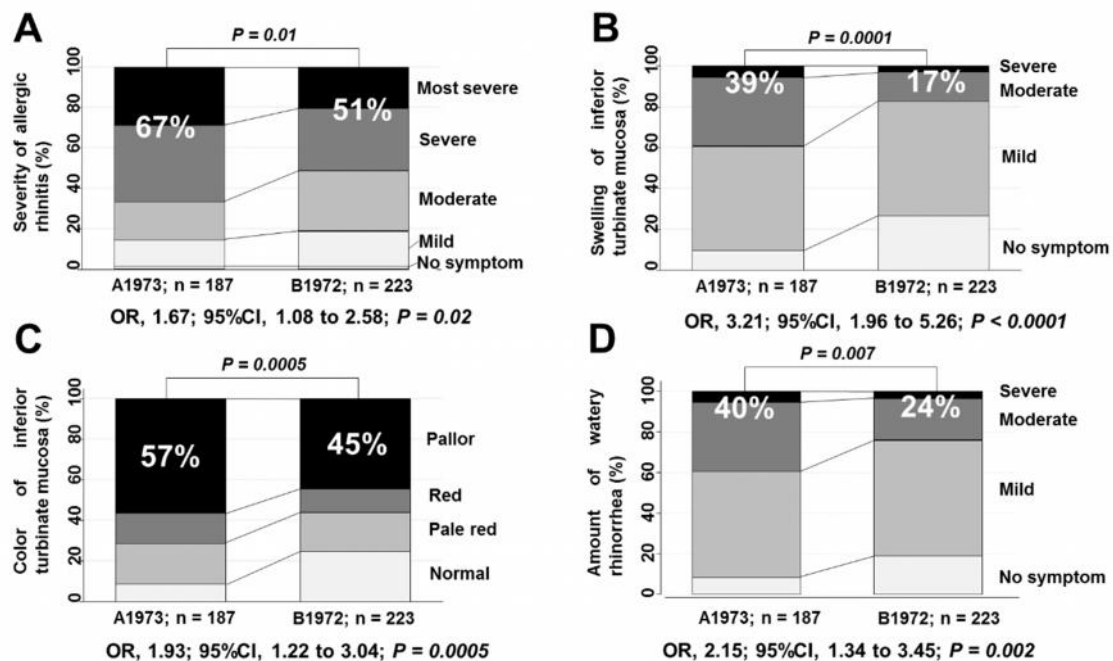


Figure S1. Distribution and symptomatic severity of allergic rhinitis between Tokyo residents born in or after 1973 (A1973) and in or before 1972 (B1972).

A. Severity of allergic rhinitis. **B.** Swelling of inferior turbinate mucosa. **C.** Color of inferior turbinate mucosa. **D.** Amount of watery rhinorrhea. Odds ratios (OR), 95% confidence intervals (95%CI), and P values determined using ordered logistic regression.

Severity of JCPollinosis

Among 410 participants who were medically examined by otorhinolaryngologists, 266 (65%) were diagnosed with JCPollinosis based on established diagnostic criteria. The severity of symptoms and signs were compared between A1973 and B1972 (Fig. S1). Symptoms of allergic rhinitis based on Japanese guidelines were worse in A1973 than B1972 (OR, 1.67; $P=0.02$ ordered logistic regression). Significantly more A1973 than B1972 had 'most severe' plus 'severe' symptoms (67% vs. 51%, $P=0.01$; Fig. S1A). Swelling of the inferior turbinate mucosa was more serious in A1973 than in B1972 (OR, 3.21; $P<0.0001$): Severe plus moderate symptoms were significantly more prevalent in A1973 than B1972 (39% vs. 17%, $P=0.0001$; Fig. S1B). The color of the inferior turbinate mucosa indicated more serious in A1973 than in B1972 (OR, 1.93; $P=0.0005$). Pallor was significantly more prevalent in A1973 than B1972 (57% vs. 45%, $P=0.049$; Fig. S1C). Volumes of watery rhinorrhea were larger (OR, 2.15; $P=0.002$) and the prevalence of 'severe' plus 'moderate' volumes was higher (40% vs. 24%; $P=0.007$) in A1973 than in B1972 (Fig. S1D).

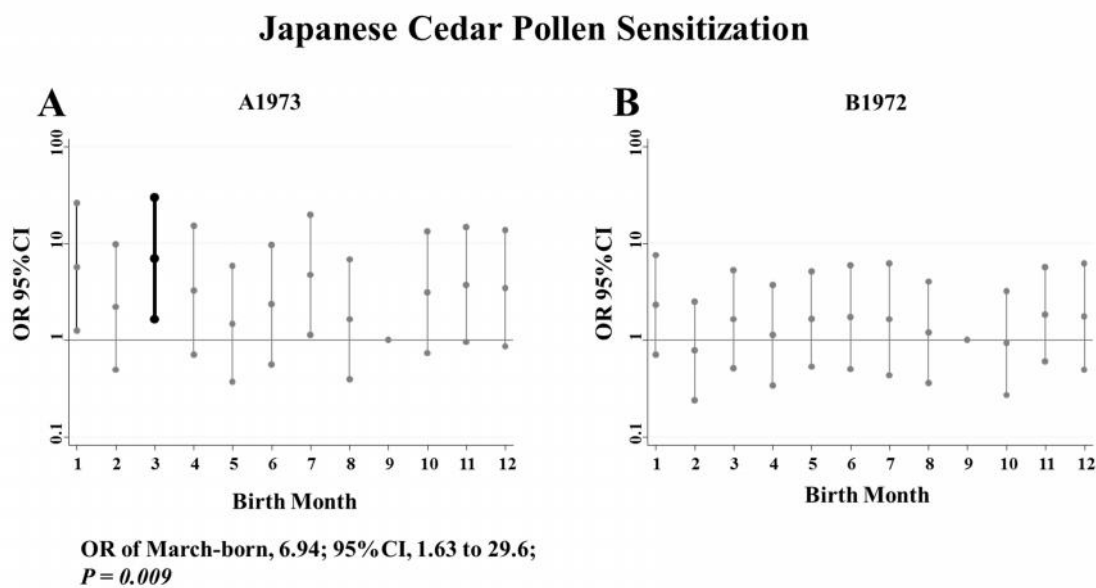


Figure S2. Sensitization to Japanese cedar pollen and birth month between January and December.

A, age group born in or after 1973 (A1973); **B**, age group born in or before 1972 (B1972). Risk in September is set as reference (OR=1). Black bold bars, significant OR; gray bars,

non-significant OR (with 95%CI crossing 1). OR, 95%CI, and P values calculated using ordered logistic regression. Y axes are transformed with $\log_{10}$. OR, odds ratio(s).

METHODS

Survey

The Review Board of the Tokyo Metropolitan Institute of Public Health approved this post-hoc study of the fourth decennial survey of 3,600 Tokyo residents that aimed to determine the prevalence of JCPollinosis in 2017. The residents were randomly sampled from registrants in Akiruno City (1,200, 2.0% of the resident population), Chofu City (1,200, 2.5% of the resident population), and Ota-ku (1,200, 1.9% of the resident population) in Tokyo, and 3,523 were surveyed by mailouts between November and December, 2016. The survey addressed symptoms of allergic rhinitis such as repetitive sneezing, rhinorrhea, nasal blockade and itchy eyes, between February and April 2016. The response rate was 60.1% (2,116 residents). We excluded those whose data we were unable to attend the medical examination to assess the severity of allergic rhinitis in 2,101 residents based on the 2016 Japanese guidelines.¹⁵ The residents were then sub-grouped according to the severity of allergic rhinitis and randomly sampled again (most severe, n=186; severe, n=217; moderate, n=217; mild, n=215; asymptomatic, n=215) and also grouped equally (n=350) according to area of residence. Finally, 1,050 residents were invited, from whom 410 participated in medical examinations.

Medical examination

Otorhinolaryngologists interviewed these 410 residents at local health centers during March 2017, which is the peak season for JCPollinosis and conducted nasal speculum examinations. Blood was also sampled to measure IgE specific for pollen from the Japanese cedar (*Cryptomeria japonica*), Japanese cypress (*Chamaecyparis obtusa*), orchard grass (*Dactylis glomerata*), ragweed (*Ambrosia artemisiifolia*) and for mites (*Dermatophagoides pteronyssinus*) using capsulated hydrophilic carrier polymer-radioallergosorbent tests (CAP-RAST).

Outcomes

JCPollinosis was defined as follows: JCPollen-specific IgE ≥ 0.7 IU/mL, signs and symptoms of allergic rhinitis or resorting to medicines to relieve symptoms of allergic rhinitis. The

results showed that 266 (64.9%) residents were diagnosed with JCPollinosis and that 23 (5.6%) were sensitized. That is, they had JCPollen-specific IgE ≥ 0.7 IU/mL but no signs or symptoms of allergic rhinitis or were not using medicines to relieve symptoms of allergic rhinitis. The remaining 121 residents had neither criterion for JCPollinosis or sensitization.

Post hoc analyses

The Tokyo Government Office permitted the authors to use the survey data of 2,101 participants and the medical data of 410 of them for post hoc analyses. All personal information about the participants was anonymous.

Statistical analysis

Categorical variables were assessed using chi-squared tests to determine significant differences between A1973 and B1972. Risk ratios (RR) and 95% confidence intervals (95%CI) were calculated to determine associations between birth month and risk of JCPollinosis. Judged from questionnaire responses, the severity of allergic rhinitis (most severe, severe, moderate, mild, asymptomatic) swelling (severe, moderate, mild, none) and the color (pallor, red, pale red, normal) of the inferior turbinate mucosa, amounts of watery rhinorrhea (severe, moderate, mild, none) and IgE scores for JCPollen antigen (<0.35 , 0; ≥ 0.35 , 1+; ≥ 0.70 , 2+; ≥ 3.5 , 3+; ≥ 17.5 , 4+; ≥ 50 , 5+, and ≥ 100 IU/mL, 6+; respectively) and birth month were assessed using ordinal logistic regression and odds ratio (OR) and 95%CI. Antigen-specific IgE was compared between A1973 and B1972 using Mann-Whitney tests. The strength of associations between serum levels of JCPollen- and other antigen-specific IgE was analyzed using Spearman rank correlations with linear regression. All data were statistically analyzed using Stata version 14.0 software (StataCorp, College Station, TX, USA). Values with $P < 0.05$ were considered significant.