

Original article

A disparity in the association of asthma, rhinitis, and eczema with allergen-specific IgE between Finnish and Russian Karelia

Background: A substantial variation in the association of asthma, rhinitis and eczema with elevated serum allergen-specific immunoglobulin E (sIgE) levels between different populations has been reported. Here, we wanted to clarify whether these proportions are different in Finnish and Russian Karelia, and compared the ability of questionnaires, skin prick tests (SPT) and sIgE measurements to detect atopic conditions in these adjacent areas with different living conditions.

Methods: Randomly selected schoolchildren, aged 6–16 years, and their mothers from Finland ($n = 344$ children, 344 mothers) and Russia (427 and 284 respectively) participated. SPTs and sIgE measurements to common inhalant and food allergens were performed. The occurrence of asthma, rhinitis, eczema and related symptoms was assessed with an International Study of Asthma and Allergies in Childhood-based questionnaire. Correlation between SPT and sIgE was estimated using the Spearman correlation coefficient.

Results: The rate of positive sIgE results was significantly higher in Finland among both mothers and children. Seventy-seven per cent of Finnish children and 43% of Russian children with asthma were sIgE positive. The respective figures for hay fever were 94% and 67%, and for eczema 68% and 41%. This discrepancy was similar but of lower magnitude among mothers. The overall occurrence of asthma, rhinitis and eczema was very low in Russian Karelia. The correlation between SPT and sIgE results was generally good.

Conclusion: Asthma, rhinitis and eczema in Russian Karelia are not only rare but also, to a large extent, have no sIgE component. Therefore, the ability of questionnaires to detect sIgE-mediated atopic conditions in this area of Russia is poor.

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A considerable worldwide variation in the prevalence of asthma, rhinitis and eczema has been reported among children (1) and adults (2); the highest figures occurring in the English-speaking, affluent countries. The European Community Respiratory Health Survey has provided evidence of substantial variability of immunoglobulin-E (IgE)-associated (atopic) asthma between countries and even between areas in the same country, e.g. 20% in Tartu, Estonia and 80% in Barcelona, Spain. By using an algorithm, overall, 30–50% of adult asthma was associated with IgE, the proportion being dependent on the asthma criteria in question (3). Earlier studies have reached a similar conclusion (4). For eczema, association with IgE has also varied greatly between studies (5).

Skin prick tests (SPT) and measurement of allergen-specific serum immunoglobulin E (sIgE) concentrations are the standard methods to detect IgE-mediated sensitization to different allergens. Questionnaire-based data have been validated for detecting symptoms and diagnoses, e.g. asthma, in epidemiological studies among Western populations (6, 7), but the data have not usually been compared with sIgE measurements or SPTs. It must be kept in mind, however, that these two tests detect only the atopic sensitization of a subject. Therefore, they are good markers for strongly atopy-associated conditions, such as hay fever, but less so for asthma, of which a large proportion has a non-atopic etiology. For asthma, a marker with better clinical reliability is bronchial hyper-responsiveness.

We have earlier shown that SPT positivity and occurrence of atopic conditions were significantly higher among Finnish children and their mothers compared with their Russian counterparts, irrespective of similar

Abbreviations: SPT, skin prick test; sIgE, allergen-specific serum immunoglobulin E; ISAAC, International Study of Asthma and Allergies in Childhood.

geo-climatic and vegetative conditions of the areas (8). The two areas differ fundamentally in lifestyle and living conditions. Factors involved in the reduced risk of atopy in Russian Karelia include heavy exposure to saprophytes in soil and vegetation (9).

Here we report the association of sIgE measurements to respiratory and other symptoms in Finnish and Russian Karelia, and the correlation between sIgE measurements and SPTs.

Methods

Study areas and subjects

The study was carried out in autumn 2003 in North Karelia, Finland, and in Pitkäranta District, the Republic of Karelia, Russia. The Republic of Karelia (presently an autonomous republic of the Russian Federation) was part of the Soviet Union until the communist system was overthrown in 1991. To date, the cultural, political and socio-economic differences between these bordering areas are fundamental. In Finland, the way of life is westernized and the rate of affluence is high. In Pitkäranta, on the contrary, the lifestyle is traditional, and the living conditions are very simple; the economic gap between these areas is considered one of the widest in the world. Both populations are racially white. Subject characteristics are presented in Table 1.

Randomly selected school children, aged 6–16 years, and their mothers were recruited from 24 schools in Finland and 11 schools in Russia. A total of 546 child–mother pairs from Finland and 550 of those from Russia were enrolled. Data obtained by a questionnaire were available from 413 (75.6%) children and from 409 (74.9%) mothers in Finland and from 448 (81.5%) children and 439 (79.8%) mothers in Russia. We report here the data from 344 children and 344 mothers in Finland and 427 children and 284 mothers in Russia who also participated in the SPT and sIgE measurements. The study protocol was approved by the Ethics Committee of the Helsinki University Central Hospital, and written informed consent was obtained from all participants.

Questionnaire

The questionnaire used in this study was an extended phase I of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire including items on demographic factors, home/living characteristics, and on occurrence of atopic disease in children and their parents. The questionnaire was translated into local languages (Finnish and Russian), and the caregiver filled it out together with the child before the study visit. In this paper we focus on 12 questions: wheezing ever, wheezing during the last 12 months, asthma ever, physician-diagnosed asthma ever, use of asthma medication during the last 12 months, sneezing/runny/blocked nose not associated with flu or common cold ever (rhinitis), sneezing/runny/blocked nose not associated with flu or common cold during the last 12 months (rhinitis), hay fever ever, physician-diagnosed hay fever ever, itchy rash during the last 12 months, atopic eczema ever and physician-diagnosed atopic eczema ever.

Serum IgE measurements

Circulating IgE antibodies against nine common pollen and animal allergens (birch, timothy grass, mugwort, horse, cat, dog, *Dermatophagoides pteronyssinus*, *D. farinae*, and *Cladosporium*) and six

Table 1. Subject characteristics, self-reported conditions, and occurrence of atopy determined by sIgE and SPTs

	Finland	Russia	P-value*
Children (n)	344	427	
Mothers (n)	344	284	
Mean age (SD)			
Children	11.3 (2.5)	11.5 (2.6)	
Mothers	40.8 (5.1)	35.7 (6.5)	
Gender, children, M/F	170/174	211/216	
sIgE positivity, n (%)			
Children	168 (48.8)	84 (19.7)	<0.001
Mothers	87 (25.3)	45 (15.9)	0.004
SPT positivity, n (%)			
Children	147 (42.7)	66 (15.5)	<0.001
Mothers	119 (34.6)	51 (18.0)	<0.001
Wheezing ever, n (%)			
Children	110 (32.0)	104 (24.4)	0.019
Mothers	122 (35.5)	76 (26.8)	0.020
Asthma ever, n (%)			
Children	31 (9.0)	7 (1.6)	<0.001
Mothers	38 (11.1)	6 (2.1)	<0.001
Rhinitis ever, n (%)			
Children	166 (48.5)	114 (26.8)	<0.001
Mothers	238 (69.4)	114 (40.1)	<0.001
Hay fever ever, n (%)			
Children	55 (16.0)	5 (1.2)	<0.001
Mothers	69 (20.1)	10 (3.6)	<0.001
Atopic eczema ever, n (%)			
Children	130 (37.8)	31 (7.3)	<0.001
Mothers	86 (25.0)	23 (8.2)	<0.001
sIgE positive, no abovementioned symptoms (% of sIgE positive subjects)			
Children	35 (20.8)	38 (45.2)	<0.001
Mothers	6 (6.9)	17 (37.8)	<0.001
SPT positive, no abovementioned symptoms (% of SPT positive subjects)			
Children	22 (15.0)	27 (40.9)	<0.001
Mothers	10 (8.4)	23 (45.1)	<0.001

sIgE, allergen-specific immunoglobulin E; SPT, skin prick test.

*Chi-square test for the difference between the countries.

common food allergens [cow's milk, hen's egg, fish (cod), soy, wheat, peanut] were measured using a radioallergosorbent test (UniCAP 1000 v.2; Pharmacia Upjohn, Uppsala, Sweden). Concentrations of 0.35 kU_A/l or higher were considered positive. Results concerning *D. farinae*, *Cladosporium*, and soy allergens were not included in the final analyses as SPT for these allergens were not performed. The study subject was defined atopic by the sIgE if having one or more positive results out of the 12 allergens included.

Skin prick tests

Skin prick tests were performed during the study visit as described in detail earlier (8). Briefly, both the child and the mother were tested using a standard set of airborne (birch, timothy grass, mugwort, cat, dog, horse, cow, and *D. pteronyssinus*; Solu-Prick SQ ALK A/S, Copenhagen, Denmark) and food allergens [fish (cod), egg, wheat, cow's milk, peanut and hazelnut]. A positive (histamine dihydrochloride 10 mg/ml) and a negative (solvent) control were used throughout the study. A wheal with diameter of 3 mm or more was considered a positive result. Cow dander and hazelnut allergens were excluded from the final analyses as sIgE measurements for these allergens were not performed. The study subject was defined

atopic by the SPT, if having one or more positive results out of the 12 allergens included.

Statistical analysis

Analyses were performed using the SAS program, version 8.2 (SAS Institute Inc., Cary, NC). Categorical data were compared using the chi-square test and logistic model and continuous data by the analysis of variance. Correlations were assessed using the Spearman rank correlation method. All analyses were adjusted for age. A two-tailed P -value < 0.05 was considered significant.

Results

In Finland, 48.8% of the children had at least one positive sIgE result, whereas in Russia the respective figure was 19.7% ($P < 0.001$). Of the mothers 25.3% and 15.9% were sIgE positive in Finland and Russia, respectively ($P = 0.004$). Sensitization rates to all 12 allergens were significantly higher among Finnish children and their mothers compared with their Russian counterparts, except to mite (children and mothers) and mugwort (mothers only), to which the sensitization rates were comparable on both sides of the border. Children in Finland had markedly higher atopy rates both by sIgE and SPTs than their mothers, whereas in Russia, such a concordant trend was not observed (Table 1).

Proportions of positive sIgE results among those study subjects who reported symptoms or diagnoses of asthma, rhinitis, or eczema are given in Table 2. These symptoms and diagnoses in Russia were not only found to be generally rare both among children and mothers (Table 2, (8)) but, contrary to Finland, a great proportion of them had no sIgE component. Figure 1 shows the association of self-reported symptoms (rhinitis ever, wheezing ever, asthma ever, hay fever ever, and atopic eczema ever) with sIgE status among the studied

children. The differences were most striking for rhinitis, which was associated with sIgE only in a quarter of the cases among Russian children but in two-thirds of the cases among their Finnish counterparts ($P < 0.001$). Less than a half of the asthmatic children in Russia had positive sIgE, whereas in Finland, more than 75% of the asthmatic children were sIgE positive (not statistically significant due to the low prevalence of asthma in Russia). Among mothers, the difference in the sIgE association of symptoms was most pronounced for wheezing of which 18% was associated with sIgE in Russia, compared with 39% in Finland ($P = 0.015$). Disparities were also significant for rhinitis; 33% of the Finnish mothers who had ever had rhinitis were sIgE positive compared with 22% of those in Russia ($P = 0.039$). Other statistically significant disparities were not observed due to the low prevalence of the reported symptoms in Russia (Table 2).

Conversely, when occurrence of asthma, rhinitis, and eczema was stratified according to sIgE status to measure the ability of questionnaires for detecting sIgE-associated conditions, similar substantial differences between the countries were found. In Finland, as expected, a significantly higher proportion of all sIgE-positive subjects reported asthma, rhinitis, eczema, and related symptoms. The association was strongest for rhinitis and hay fever both among Finnish children and their mothers ($P < 0.001$ for the difference between sIgE-positive and -negative subjects, both for children and mothers). By contrast, in Russia, the difference in occurrence of asthma, rhinitis and eczema between sIgE-positive and -negative subjects was mostly nonsignificant both among children and their mothers (data not shown). Only hay fever ever, itchy rash, and diagnosed atopic eczema were significantly more common in Russian children who were sIgE positive than those who were not. In Russian mothers only rhinitis ever and diagnosed hay fever were

Table 2. Proportions of sIgE-positive subjects of those reporting a given symptom or disease in Finland and Russia

	Children			Mothers		
	Finland, n/N (%)	Russia, n/N (%)	P -value	Finland, n/N (%)	Russia, n/N (%)	P -value
Wheezing (last 12 months)	34/52 (65)	15/51 (29)	<0.001	23/58 (40)	8/36 (22)	0.211
Wheezing ever	69/110 (63)	23/104 (22)	<0.001	74/122 (39)	14/76 (18)	0.015
Asthma ever	24/31 (77)	3/7 (43)	0.077	20/38 (53)	2/6 (33)	0.372
Physician-diagnosed asthma	23/30 (77)	3/7 (43)	0.088	20/38 (53)	2/6 (33)	0.372
Use of asthma medications (last 12 months)	21/27 (78)	3/5 (60)	0.286	16/25 (64)	1/4 (25)	0.111
Rhinitis (last 12 months)	105/153 (69)	27/104 (26)	<0.001	73/218 (33)	20/98 (20)	0.018
Rhinitis ever	111/166 (67)	27/114 (24)	<0.001	78/238 (33)	25/114 (22)	0.039
Hay fever ever	51/55 (93)	3/5 (60)	0.073	33/69 (48)	4/10 (40)	0.437
Physician-diagnosed hay fever	30/32 (94)	2/3 (67)	0.146	21/33 (64)	3/5 (60)	0.917
Itchy rash (last 12 months)	50/78 (64)	14/41 (34)	0.002	30/81 (37)	6/37 (16)	0.091
Atopic eczema ever	80/130 (62)	9/31 (29)	<0.001	34/86 (40)	4/23 (17)	0.082
Physician-diagnosed atopic eczema	62/91 (68)	7/17 (41)	0.033	26/64 (41)	1/9 (11)	0.088

n , number of sIgE positive subjects out of those reporting the disease/symptom; N , number of study subjects reporting the disease/symptom; P -value is age adjusted and is calculated for the difference between the countries. sIgE, allergen-specific immunoglobulin E.

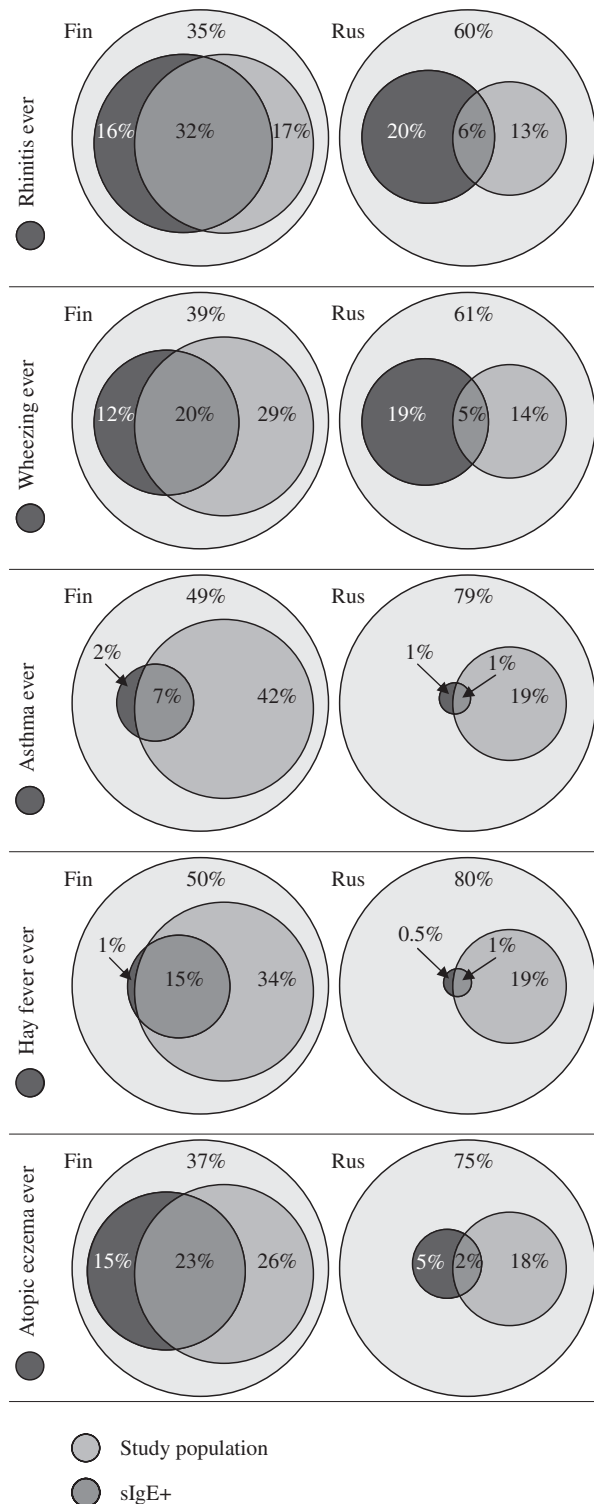


Figure 1. Venn diagram of the association of allergen-specific serum immunoglobulin E (sIgE) status with positive answers to 'rhinitis ever', 'wheezing ever', 'asthma ever', 'hay fever ever', and 'atopic eczema ever' among studied children. Fin = Finland, Rus = Russia, sIgE+ = at least one positive allergen-specific IgE test result out of the 12 allergens included. Study population: $n = 344$ (Finland), $n = 427$ (Russia).

more common in sIgE-positive subjects (data not shown). When the data were stratified according to SPT status, the results were similar (data not shown).

The correlation between SPTs and sIgE measurements was generally good. Particularly high correlation coefficients were found for airborne allergens, whereas for food allergens, the correlations were weaker. Overall, sensitization rates to the used fish (cod) allergen were, for some reason, very low. Cod is not used widely in the study areas, and it is probable that the used cod-allergen is unable to detect sensitization to other species of fish. The sIgE test was generally found to give more positive results than the SPT among children in both countries, whereas among mothers, the opposite trend emerged. The overall Spearman correlation coefficient between these two tests was 0.73 ($P < 0.001$) and 0.70 ($P < 0.001$) for children in Finland and Russia, respectively, and for mothers 0.65 ($P < 0.001$) and 0.55 ($P < 0.001$), respectively (Table 3).

Discussion

We have previously shown that the occurrence of asthma, rhinitis and eczema using an ISAAC-based questionnaire is, overall, very low in Russian Karelia (8). This study further highlights that a substantial proportion of these symptoms are not associated with elevated sIgE levels. As a consequence, the concordance between questionnaires and sIgE measurements in detecting atopic diseases in Russian Karelia is poor. Our results are in line with those published earlier showing that the proportion of subjects with negative SPT and sIgE test results among all those reporting asthma, rhinitis, eczema, or related symptoms is higher in Eastern Europe compared with Western countries (3, 10). Studies from Estonia and Sweden have also showed that sIgE antibodies in Estonian children, contrary to Swedish children, are poorly related to allergic diseases. Irrespective of lower SPT positivity, sIgE antibodies were more common in Estonia than in Sweden, and even asymptomatic children in Estonia had sIgE antibodies (11, 12). Although the ultimate causes for these phenomena are unknown, living conditions and lifestyle are likely to be involved.

It is now well recognized that asthma, rhinitis, and eczema each represent an aggregation of several diseases with certain characteristics and symptoms in common (13, 14). Each of these disorders is multitietiological and multifaceted. Attempts to clarify the nomenclature have recently been made (15), and the term 'atopic' has been proposed to be used only in connection with sIgE-mediated conditions. The clarification whether any given disease, such as asthma, rhinitis, or eczema is truly atopic (i.e., associated with sIgE) or not has been considered to be important as it may have implications for treatment and additionally may give clues for etiology, severity, and prognosis of the disease (5, 16, 17).

Table 3. Correlation between sIgE* and SPT* results among children and mothers in Finland and Russia

	Finland				Russia			
	sIgE+ (%)	SPT+ (%)	SCC	P-value	sIgE+ (%)	SPT+ (%)	SCC	P-value
<i>Children</i>								
Tested allergen								
Birch	26.2	26.7	0.88	<0.001	3.8	2.1	0.66	<0.001
Timothy grass	29.1	28.5	0.86	<0.001	5.2	4.9	0.68	<0.001
Mugwort	16.9	7.3	0.50	<0.001	5.2	5.2	0.52	<0.001
Cat	20.6	19.8	0.88	<0.001	4.2	3.8	0.82	<0.001
Dog	25.0	21.5	0.71	<0.001	3.5	2.6	0.37	<0.001
Horse	9.6	6.1	0.66	<0.001	1.2	0.2	0.45	<0.001
<i>D. pteronyssinus</i>	14.2	9.3	0.47	<0.001	11.7	9.1	0.77	<0.001
Fish (cod)	0.0	0.3			0.2	0.2	-0.002	0.961
Hen's egg white	10.8	2.0	0.28	<0.001	2.3	0.9	-0.02	0.756
Wheat	13.4	11.3	0.56	<0.001	3.0	1.2	0.49	<0.001
Cow's milk	13.7	0.3	-0.02	0.691	2.1	0.2	-0.01	0.884
Peanut	15.1	8.1	0.50	<0.001	1.9	0.5	0.24	<0.001
Any	48.8	42.7	0.73	<0.001	19.7	15.5	0.70	<0.001
<i>Mothers</i>								
Tested allergen								
Birch	11.3	14.8	0.70	<0.001	3.2	6.3	0.61	<0.001
Timothy grass	7.9	12.2	0.65	<0.001	2.5	4.6	0.51	<0.001
Mugwort	6.1	9.0	0.56	<0.001	6.0	8.8	0.66	<0.001
Cat	7.3	10.8	0.66	<0.001	2.5	3.9	0.44	<0.001
Dog	7.6	14.5	0.60	<0.001	2.5	5.3	0.37	<0.001
Horse	2.0	4.7	0.46	<0.001	0.7	1.1	-0.01	0.884
<i>D. pteronyssinus</i>	11.1	11.3	0.58	<0.001	8.5	6.7	0.43	<0.001
Fish (cod)	0.3	2.9	-0.01	0.863	0.4	1.4	-0.01	0.905
Hen's egg white	2.9	3.2	0.36	<0.001	0.7	1.4	-0.01	0.866
Wheat	3.8	8.4	0.32	<0.001	0.7	1.4	-0.01	0.866
Cow's milk	2.3	3.2	0.19	<0.001	0.0	1.4		
Peanut	3.8	9.9	0.50	<0.001	0.7	2.1	-0.01	0.836
Any	25.3	34.6	0.65	<0.001	15.9	18.0	0.55	<0.001

SCC, Spearman correlation coefficient (adjusted for age); sIgE+, positive allergen-specific immunoglobulin E test; SPT+, positive skin prick test.

Systematic analyses of published studies from 1980 onward have shown that the role of atopy, as defined above, in the overall burden of asthma (4), rhinitis (18), and eczema (5) may have been overestimated, even in Western countries. Only a partial overlap between clinical diagnoses and the presence of sIgE has been found. For example in Munich, Germany, 50% of schoolchildren with asthma and over 20% of those with hay fever had a negative SPT result (13). In the present study, however, only 23% of children with diagnosed asthma and 9% of those with diagnosed hay fever had a negative SPT result in Finland (data not shown). The prevalence of diagnosed asthma and hay fever was similar both in Germany and Finland, but only 23% of all studied children in Munich had a positive SPT result (13) compared to 43% in Finland.

As regards atopy in Finland and Russia, nearly half of the children in Finland were sIgE positive compared with 20% in Russia. Although the rate of positive sIgE results was high among Finnish children, this is neither unexpected nor exceptional based on some recent European birth cohort studies (19–21). As regards mothers, 25% in Finland and 16% in Russia were sIgE positive. Gener-

ational analyses showed that disparities in atopy prevalence during the last few decades between Finland and Russia have not decreased, rather increased, indicating that no signs of westernization, using atopy as a proxy, are yet discernible in Russian Karelia (8).

Interestingly, irrespective of substantial disparities in sensitization rates to most allergens tested and in the occurrences of asthma, rhinitis, and eczema between Finland and Russia, sensitization rates to house dust mite were similar among children and mothers in both countries. This casts doubt over the possibility that sensitization to house dust mite is necessarily associated with the development of atopic diseases in all populations. A link between sIgE, which can only be a marker of exposure, and clinical disease has been difficult to prove as there is no gold standard for this respect (16). It has been suggested that the association of dust mite sensitization with the increase in asthma prevalence and severity may be explained by the combined effects of westernization: improved control of infectious diseases, decreased physical activity, and increased exposure to indoor allergens (22).

Good correlation between SPT and sIgE has been reported previously from several laboratories in Europe

and USA (16, 23–25), in line with the present study. On the other hand, skin testing and sIgE measurements may not always be interchangeable. In addition to indicating the presence of sIgE, SPT also reflects mast cell integrity and vascular and neural (end-organ) responsiveness (26). Especially with food, a child's sIgE levels for a certain allergen (especially cow's milk) may be high without clinical allergy. Diagnosing food allergy in young patients should therefore never be based solely on sIgE measurements.

It is likely that both population susceptibility to atopic sensitization and end-organ responsiveness (27) differ between Finnish and Russian Karelians. The etiology of asthma, rhinitis, and eczema in Russian Karelia may include factors such as viral and other infections, indoor tobacco smoke, high indoor humidity and mold growth, and outdoor chemical irritants (mainly from pulp industry) (17, 28, 29). There may also be remarkable cultural differences in attitudes toward symptoms and diagnoses such as wheezing and asthma. This may, at least in part, explain some of the disparities in the association of the symptoms with serum markers of atopy. If, for example, the prevalence of chronic airway infections is high,

symptoms of wheezing may be considered trivial, and the diagnosis of asthma may be delayed or even missed. Attitudes may differ both among the common people and healthcare workers. In addition the availability and quality of medical care may play a role, especially when diagnoses are considered. For all these reasons, questionnaire-based data from populations of different cultures cannot be directly compared to map the prevalence of, for example, asthma and allergy.

We conclude that substantial proportions of asthma, rhinitis, and eczema in Russian Karelia were not truly atopic (i.e., associated with elevated sIgE levels), suggesting a largely different etiology of these disorders in these two neighboring areas. The correlation between SPTs and sIgE measurements was generally good, and particularly so for airborne allergens.

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