
Relationship between IgE and specific aeroallergen sensitivity in Alaskan native children

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Background: The relationship between atopic disease and serum IgE levels varies among populations and geographic regions. The close association of atopy with IgE may not occur in subarctic populations as it does in developed countries in temperate climates.

Objective: To evaluate the relationship between total and specific IgE concentrations and clinical atopy in 5- to 8-year-old Alaskan native children.

Methods: Medical record reviews, interviews, physical examinations, serum IgE measurements, and radioallergosorbent testing (RAST) were performed.

Results: The IgE geometric mean was 122.1 IU/mL. Fifty-eight percent of patients had IgE levels greater than 70 IU/mL, and 17% had levels greater than 1,000 IU/mL; 14% had RAST values greater than 0.35 kU/L. Both IgE levels greater than 70 IU/mL and greater than 1,000 IU/mL were associated with RAST values greater than 0.35 IU/L ($P = .004$) and early wheezing ($P = .005$) but not with current wheezing, asthma, eczema, or a history of allergies. A RAST value greater than 3.51 kU/L was associated with eczema ($P = .04$) but not with allergies or wheezing. Children with current wheezing were more likely to have allergies ($P = .03$) but not eczema, an IgE level greater than 70 IU/mL, or a positive RAST value. Children hospitalized with respiratory syncytial virus (RSV) were not more likely than controls to have current wheezing.

Conclusions: Elevated serum IgE concentrations, including levels greater than 1,000 IU/mL, are common among Alaskan native children; positive RAST reactions to aeroallergens are not. The IgE levels do not relate to wheezing, eczema, a history of allergies, or past hospitalization for RSV infection but likely reflect infections other than RSV and environmental factors in subarctic indigenous populations.

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INTRODUCTION

The prevalence of atopic diseases varies widely in different populations and geographic regions.^{1–13} Similarly, the relationship between serum IgE levels and atopic disease also varies throughout the world. Immunoglobulin E is most closely associated with atopic disease in developed countries in temperate climates. In tropical countries, IgE is affected more by environmental and infectious factors, such as helminthic diseases.^{9,11,14,15} In contrast to other regions in the world, less is known about this relationship in subarctic populations.

Levels of IgE have been described in northern countries, including Norway,^{3,12,13} Sweden,^{16,17} and Finland.¹³ In these

westernized developed nations, atopy and IgE are closely associated. In Greenland, people have higher IgE levels than reported in developed countries but much less atopic disease and skin test reactivity to allergens.¹⁸ Between 1999 and 2001, our group¹⁹ studied children who had been hospitalized as infants with respiratory tract infections due to respiratory syncytial virus (RSV) and their age-matched controls to evaluate the long-term impact of RSV on lung health. As part of that study, serum IgE determinations and radioallergosorbent testing (RAST) to aeroallergens were performed, but they have not previously been reported. We hypothesized that Alaskan native children residing in a developed country would have elevated serum IgE levels and sensitization to aeroallergens and that children with elevated IgE levels would be more likely to have active wheezing illnesses. We also compared children whose IgE levels were greater than 1,000 IU/mL with all other children to determine whether elevated IgE levels were associated with atopy.

METHODS

Population

The Yukon Kuskokwim (YK) Delta region encompasses 75,000 square miles of coastal wetlands and tundra, approximately the size of South Dakota. The 2000 population of

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approximately 25,000 comprised primarily Yup'ik Eskimos (85%), who live in 52 villages and the regional town. The flora includes primarily wetland grasses and shrub willow. There are few trees in the delta region. Transportation between villages in the region is by airplane, boat, or snow machine. No roads connect the region to the remainder of the state. The lifestyle of the people living in these villages is primarily local fishing and hunting. Commercial fishing is the main export industry of the area. Most homes are small, and poorly ventilated, and many homes are without running water. The average household size is 6 to 7 persons. Approximately 44% of Alaskan native adults in the region smoke cigarettes,²⁰ and more than 60% of households include a smoker. The Yukon-Kuskokwim Delta Regional Hospital in Bethel, a 50-bed primary care facility, is the only hospital in the region. Children who require tertiary care are transferred to hospitals in Anchorage.

Children in this region experience extremely high rates of lower respiratory tract infection hospitalizations (248 per 1,000 infants per year) (Arctic Investigations Program [AIP], Centers for Disease Control and Prevention [CDC], unpublished data, 2005) and RSV hospitalizations (156 per 1,000 infants per year).²¹ Wheezing is common in young children from the YK Delta,¹⁹ and asthma hospitalization rates in newborn to 4-year-old Alaskan native children are higher than in the US general population; however, asthma hospitalizations are lower than in the United States for children 4 years and older.²² Potential aeroallergens differ from those in other regions of the United States. Cockroaches are not endemic to Alaska; however, despite the dry cold environment, dust mites are present in bedding because of the high humidity in bedding (J.D., oral communication). The most important grass and tree allergens are timothy perennial rye and shrub willow. Several unusual parasites have been known to infect people in Alaska; however, stool surveys suggest that the overall parasite burden is low in Alaska relative to other states.²³ Helminths are not endemic to Alaska. Although anisakiasis,²⁴ cestodiasis,²⁵ amebiasis, giardiasis, trichinosis,²⁶ and echinococcus²⁷ infections are reported, most are rare.

Study Design

We studied a cohort of children aged 5 to 8 years who had been enrolled during the first 2 years of life as either patients or control subjects in an epidemiologic study of RSV hospitalizations among YK Delta children between 1993 and 1996.^{21,22} A case was defined as a first hospitalization in a child younger than 2 years with laboratory-confirmed RSV infection. Controls were selected from a master list of YK Delta children. Controls could not have had an acute respiratory tract infection hospitalization during the year of the patient's hospitalization. Control matching was performed using a caliper method based on the patient's date of birth and village or subregion of residence.

The present study was approved by the Yukon-Kuskokwim Health Corp Health Board and Human Studies Committee, the Alaska Area Institutional Review Board, and the CDC

Institutional Review Board. Individuals enrolled in the 1993 to 1996 case-control study (now 5–8 years of age) were visited in their home village by a research team between September 1, 1999, and September 30, 2001. A study team interviewed parents regarding the patient's medical history (including medical conditions, family history of allergies and asthma, household characteristics, and respiratory symptoms) using a standardized questionnaire. Data on respiratory and allergic rhinitis symptoms were collected using the standardized International Study of Asthma and Allergies in Children questionnaire.²⁸ Data were also collected about cough in the past year ("In the past year, has your child had daily cough, cough with mucus, cough longer than 3 months, cough at night, cough with exercise, or 4 or more illnesses with cough?"), allergies ("Does your child have any allergies? Has your child taken any allergy medicine in the past year? Does your child have eczema or a chronic rash?"), and physician-diagnosed asthma. Clinic visits and respiratory hospitalizations were reviewed for respiratory and allergy-related illnesses using a standard medical record abstraction form at village clinics, Yukon-Kuskokwim Delta Regional Hospital, and the Alaska Native Medical Center in Anchorage.

Each participant underwent a physical examination by a research team physician, blood sample collection, and pulmonary function testing by a respiratory therapist. Total IgE was measured using immediate-response mobile analysis (Coat-A-Count Total IgE IRMA; Diagnostic Products Corp, Los Angeles, CA) at the CDC's AIP laboratory; values greater than 1,000 IU/mL were confirmed by Quest Diagnostics Inc (Seattle, WA). Allergen specific IgE antibody was measured for household pets (dog epithelia and dog and cat dander), molds (*Alternaria alternata*, *Penicillium notatum*, *Aspergillus fumigatus*, and *Cladosporium herbarium*), house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and outdoor aeroallergens (willow, perennial rye, sheep sorrel, and timothy grass) by means of RAST at Quest Diagnostics Inc. Allergens for RAST were based on the prevalent potential allergens in this region in consultation with a pediatric allergist (J.D.). Values of RAST for individual antigens less than 0.35 kU/L are considered class 0, with antibody undetected; RAST values of 0.35 to 0.70 kU/L are considered class 1, or low level of allergen specific IgE; and RAST values greater than 3.5 kU/L are considered class 3 or above, corresponding to high levels of allergen specific IgE.

Serum cotinine concentrations were measured using high-pressure liquid chromatography at the CDC's National Center for Environmental Health Tobacco Exposure Biomarkers Laboratory (Atlanta, GA).^{29,30} The lower limit of detection for this assay is 0.05 ng/mL. Serum IgG antibodies to *Helicobacter pylori* were measured by means of enzyme immunoassay at the AIP using high-molecular-weight cell-associated protein antigen (HM-CAP; Enteric Products Inc, Stony Brook, NY) as described by Evan et al.³¹

Pulmonary function testing before and after standard stepping exercise was performed on every child who could com-

ply with this procedure using a pneumotach-based portable digital spirometer (Schiller America, Tustin, CA). This spirometer meets American Thoracic Society guidelines for the measurement of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and forced expiratory flow between 25% and 75%.³²

Definitions

We evaluated the cohort for current wheezing and a history of allergies at the time of physical examination. Current wheezing was defined as wheezing in the past year as determined by interview, review of outpatient visits in the medical record, or wheezing on physical examination. Allergies were defined as a positive response to the question "Does (name) have any allergies?" on parent interview. Eczema was defined by a positive response on parent interview, stigmata of eczema on physical examination, or a diagnosis of eczema at any past outpatient visit in the medical record.

Statistical Analysis

Associations of demographic, atopic, and environmental factors with elevated IgE levels greater than 70 IU/mL and greater than 1,000 IU/mL and elevated RAST levels were made using χ^2 or Fisher exact tests as appropriate. Total IgE concentrations are expressed as geometric means. Median IgE concentrations were compared using a rank sum test. *T* tests and analyses of variance were performed on log-transformed IgE concentrations. All *P* values are 2-sided.

RESULTS

Between 1993 and 1996, 204 patients hospitalized with RSV were recruited and matched to 338 control subjects in the RSV case-control study.²² The present follow-up study includes 192 participants aged 5 to 8 years (86 patients hospitalized with RSV and 106 control subjects) who were younger than 2 years at the time of RSV infection and had IgE testing at follow-up. This represents approximately 8% of all YK Delta children 5 to 8 years of age in southwestern Alaska. Demographic characteristics of patients and controls at follow-up compared with the original cohort have been described elsewhere.¹⁹

The geometric mean for total IgE concentration in the present study children was 122.1 IU/mL (Fig 1). Median total IgE levels were not significantly different in patients hospitalized for RSV vs controls (80 vs 93.2 IU/mL; *P* = .55), but both groups were higher than the median (19 IU/mL) and 95th percentile (70 IU/mL) based on 125 healthy children aged 3 to 9 years reported as a reference in the Diagnostic Products Corp product information.

Fifty-eight percent of all the participants had IgE levels greater than 70 IU/mL, and 17% had IgE levels greater than 1,000 IU/mL (Fig 1). In contrast to the high total IgE concentrations, only 14% of the participants had RAST values greater than 0.35 kU/L and only 7% had RAST values greater than 3.5 kU/L to 1 or more common aeroallergens (Fig 2). For patients and controls, the prevalence of sensitization (any positive RAST value) to specific allergens varied from 0%

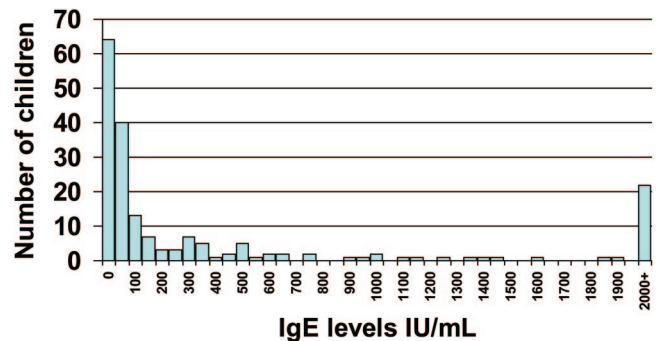


Figure 1. Distribution of total IgE concentrations in the study participants.

for *A alternata*, *C herbarium*, *P notatum*, dog epithelia, and sheep sorrel to 10.5% for *D pteronyssinus* (Fig 2).

Concentrations of IgE greater than 70 IU/mL were more common in children with 1 or more positive RAST values greater than 0.35 kU/L or RAST values greater than 3.51 kU/L (Table 1). An IgE level greater than 70 IU/mL was also significantly associated with a history of wheezing at the outpatient visit in the first 2 years of life (*P* = .005) but not with current wheezing, productive cough, eczema, asthma diagnosis, history of allergies, family history of asthma or allergies, current household factors (animals in house, smoker in house, wood-burning stove, ≥ 7 persons in the house, running water, and flush toilets), serum cotinine level, or positive *H pylori* serology (Table 1). Values of IgE greater than 1,000 IU/mL were also associated with any RAST value greater than 0.35 and 3.5 kU/L but not with current wheezing or eczema (Table 1). Low IgE levels were associated with eating prechewed food (by parents) (*P* = .04) and smokers in the household (*P* = .002). Any RAST value greater than 3.51 kU/L, but not RAST values greater than 0.35 kU/L, was associated with eczema (*P* = .04), fewer than 5 rooms in the house, running water in the house, and flush toilets in the house.

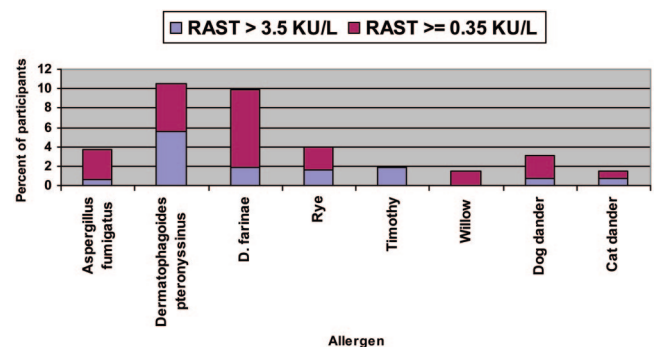


Figure 2. Sensitization to inhalant allergens on radioallergosorbent testing (RAST) at 5 to 8 years of age among patients and controls. None of the study participants had positive RAST values for *Alternaria alternata*, *Cladosporium herbarium*, *Penicillium notatum*, dog epithelia, or sheep sorrel.

Table 1. Relationship Between Total IgE Concentration and Atopic and Environmental Factors in 192 Participants at 5 to 8 Years of Age*

Factor	IgE level, IU/mL			P value for trend
	≤70	>70 to ≤1,000	>1,000	
Any RAST >3.51 kU/L (class 3)	0/72	2/67 (3)	10/28 (36)	<.001
Any RAST [mt]0.35 kU/L (class 1)	3/72 (4)	7/67 (10)	13/28 (46)	<.001
Fed prechewed food in infancy	35/73 (48)	26/75 (35)	9/31 (29)	.04
Smoker in household at time of patient illness	55/75 (73)	37/76 (49)	17/31 (55)	.002
Current wheezing	28/81 (35)	40/79 (51)	12/32 (38)	.40
Eczema	13/81 (16)	17/79 (22)	7/32 (22)	.39
History of allergy	14/77 (18)	25/78 (32)	6/31 (19)	.46
Wheeze at clinic visit at age <2 y	70/81 (86)	76/79 (96)	32/32 (100)	.005
<i>Helicobacter pylori</i> IgG positive	54/81 (67)	39/78 (50)	24/32 (75)	.52

Abbreviation: RAST, radioallergosorbent testing.

* Data are given as number/total number (percentage) of participants. There were no associations between IgE and sex, breastfed in infancy, more than 5 rooms in the house, shared rooms in infancy, productive cough, family member with asthma or allergies, diagnosed as having asthma, animal in household, smoking in household, wood-burning stove, more than 7 persons in the household, more than 5 children in the household, running water in the house, flush toilets in the house, or severe dental caries.

The number of children with reproducible artifact-free spirometric results was limited owing to the age of those studied. Among children with acceptable technique, the mean FEV₁/FVC was 89.5% for 38 children with IgE levels less than 70 IU/mL, 89.8% for 40 children with IgE levels of 70 to less than 1,000 IU/mL, and 87.5% for 14 children with IgE levels of at least 1,000 IU/mL. These results, and mean and median values for FVC, FEV₁, and forced expiratory flow between 25% and 75%, were not different among the groups.

Children with current wheezing, regardless of RSV history, were more likely to have reported a history of allergies (33% vs 18%; odds ratio, 2.28; $P = .03$) but were not more likely to have elevated IgE levels, any RAST, eczema, or family members with asthma or allergies (Table 2). Former patients hospitalized with RSV were not more likely than control children to have elevated IgE levels or a positive RAST value (Table 2).

Evidence of infection with *H pylori* was common in children with normal and elevated IgE levels but did not differ between the groups (Table 1). Similarly, the frequency of antibodies to *H pylori* was similar between children with positive and negative RAST values (61% vs 60%; $P > .99$)

and among children with vs without current wheezing (59% vs 63%; $P = .70$) (Table 3).

DISCUSSION

Alaskan native children residing in rural Alaska have high levels of total IgE but a low prevalence of allergic sensitization to inhalant allergens. In this population, total and specific IgE levels are not associated with asthma, a history of allergies, or eczema. In this respect, Alaskan native children are similar to people in Russia, eastern Europe,^{11,13} Greenland,¹⁸ and rural nonindustrialized countries^{1,4,9} and contrast with populations in many western countries.^{2,3,13,33}

Table 3. Relationship of Current Wheezing to Atopy and Total or Allergen Specific IgE*

	Current Wheezing		P value
	Yes	No	
IgE >70 IU/mL	51/79 (65)	60/113 (53)	.15
IgE >1,000 IU/mL	12/79 (15)	20/113 (18)	.83
Any RAST >0.35 kU/L	5/67 (7)	18/100 (18)	.07
Any RAST >3.51 kU/L	2/67 (3)	10/100 (10)	.13
Allergy (by interview)†	25/75 (33)	20/111 (18)	.03
Any eczema‡	14/79 (18)	23/113 (20)	.79
Family member with asthma (by interview)	23/77 (30)	21/111 (19)	.12
Family member with allergies (by interview)	31/75 (41)	39/110 (35)	.51
<i>Helicobacter pylori</i> IgG antibodies	46/78 (59)	71/113 (63)	.70

Abbreviation: RAST, radioallergosorbent testing.

* Data are given as number/total number (percentage) of participants.

† Allergy was defined as a positive response to the question "Does (name) have any allergies?" on parent interview.

‡ Eczema was defined by a positive response on parent interview, a diagnosis on physical examination, or a diagnosis at any past outpatient visit in the medical record.

Table 2. Comparison of IgE and RAST Results in Patients With RSV and Their Controls at 5 to 8 Years of Age*

	Patients with RSV	Control subjects	Relative risk (95% CI)
IgE >70 IU/mL	49/86 (57)	62/106 (58)	0.97 (0.70–1.33)
IgE >1,000 IU/mL	13/86 (15)	19/106 (18)	0.89 (0.57–1.40)
IgE, median, IU/mL	80	93.2	.54†
Any RAST >0.35 kU/L	6/72 (8)	17/95 (18)	0.57 (0.28–1.16)
Any RAST >3.51 kU/L	2/72 (3)	10/95 (11)	0.37 (0.10–1.32)

Abbreviations: CI, confidence interval; RAST, radioallergosorbent testing; RSV, respiratory syncytial virus.

* Data are given as number/total number (percentage) of participants except where indicated otherwise.

† Rank sum P value.

Two previously published studies from Tucson, AZ,²⁸ and Sweden¹⁶ have reported IgE, atopy, and early childhood infections in children in a longitudinal prospective manner. The Alaskan native children had higher IgE concentrations than similar-aged children from studies in Sweden and Arizona. However, in contrast to these studies, high IgE concentrations among Alaskan native children did not correlate with current wheezing. The present study children had significantly higher IgE concentrations (geometric mean, 122.1 vs 36.3 IU/mL) and a higher proportion of IgE levels greater than 1,000 IU/mL (16% vs 3.2%) than children in the Tucson Childhood Respiratory Study (Ann Wright, unpublished data, 2006). Despite high IgE concentrations, only 14% of our study children had 1 or more positive RAST values compared with 41.7% of Swedish children.¹⁶ Also, in contrast to children in Sweden and Tucson,^{16,17,34} the present study children with current wheezing were not more likely to have elevated total or specific IgE levels compared with nonwheezing children. Alaskan native children with wheezing visits in the first 2 years of life were more likely to have high IgE levels at 5 to 8 years old than children without early wheezing visits. However, in contrast to Swedish children,¹⁶ our children with severe RSV prompting hospitalization were not more likely than control children to have elevated IgE levels or asthma at follow-up.

The present results more closely reflect data reported among Inuit children in Canada and native Greenlandic children.^{18,35} All 3 groups reside in arctic or subarctic rural environments and are indigenous in ethnicity. Among 7- to 13-year-old Inuit children, the rate of positive skin test reactions to aeroallergens was 5.5% (28/509) and was unrelated to airway reactivity.³⁵ In Greenland, 14.6% of children had 1 or more positive RAST values to aeroallergens and 4.1% to food allergens (egg, milk, fish, wheat, peanut, and soy).³⁶ Greenlandic children born to Greenlandic parents had an 8-fold lower rate of specific IgE to inhalant allergens compared with children whose parents were born abroad, despite similar total IgE concentrations.^{18,36} Greenlandic children have crowded living conditions and high rates of respiratory tract infection, similar to the children in the present study. Like our Alaskan native children, Greenlandic native children have high levels of total IgE but a low prevalence of specific IgE to inhalant allergens compared with Danish children,¹⁸ suggesting that risk of sensitization may be associated with ethnic background as well as living conditions and allergen exposure in an arctic environment.

The association between total or specific IgE and asthma and allergic rhinitis is stronger in countries with a western high standard of living lifestyle than in rural areas of Africa, South America, Asia, and western countries with lower standards of living (eg, Russia and Eastern Europe). Vartiainen et al¹³ found a higher total IgE concentration but lower rates of hay fever, eczema, asthma dermatitis, and specific IgE in Russian adults compared with neighboring Finnish adults. These findings suggest that differences in lifestyle and standard of living between countries can affect the prevalence of

atopy and the IgE concentration. In countries with a less westernized lifestyle, high IgE levels may be less affected by atopy or asthma and may be more affected by high rates of viral,³¹ helminth,^{1,5,9,14,37} or bacterial infections³⁸ and by environmental factors such as wood-burning stoves, indoor mold, housing materials, more persons in the household, open-heating facilities, chipboard construction, and cigarette smoke exposure.^{10,11,13,38,39} Helminths are not endemic to Alaska, but as part of this study we evaluated relationships between infections with RSV in infancy and *H pylori* infections in childhood using IgE levels and RAST values. Respiratory syncytial virus had no relationship to total serum IgE or specific IgE to aeroallergens and no relationship to wheezing at 5 to 8 years of age. Past *Helicobacter* infections have been reported to have protective effects against atopy.⁴⁰ *Helicobacter pylori* is common among Alaskan native and Canadian Inuit populations.^{41,42} In the present study population, 60% of the children had IgG antibodies specific to *H pylori*. However, *H pylori* infections in Alaskan native children were related to neither low or high serum IgE nor positive RAST values and did not relate to childhood wheezing on interview, medical record review, or physical examination. Finally, we know of no published data regarding helminthic infections in arctic populations to know whether these infections affect our data.

This study has several limitations. First, the population studied was not a cross-section of the child population but a special group of children identified because of early RSV hospitalization and their age-matched controls, which may affect generalization of the results. However, this study population should be representative of the age cohort in this region, because the total cohort of 542 original case-control participants represents approximately 30% of the age cohort population in this region. Second, we relied on parent recall, physical examination, and medical record review for determination of allergies and recent wheezing history. We also relied on parent recall for determination of household smokers and other household factors. We could not explain the association demonstrated between high IgE levels and not having a smoker in the household. Third, there most likely are other important factors related to IgE concentrations that were not evaluated in this study. Although there was little evidence of food allergies by history or medical record review, we did not perform RAST to evaluate for food allergies.

CONCLUSION

This study population experiences living conditions and disease exposure similar to individuals in Greenland and Eastern European countries rather than in Western European countries or the United States. Compared with European findings, Alaskan native children have a low prevalence of allergic sensitization to inhalant allergens and high levels of total IgE, with no association between IgE levels and asthma or allergy symptoms.

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