

Atopic sensitization among children in an Arctic environment

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Summary

Background Asthma has been reported to be rare among Inuits, but so far total and specific IgE levels have never been determined in arctic populations.

Objective To determine the prevalence of atopy in children living in an arctic environment, and to examine whether atopy and total IgE levels were associated with parental place of birth, as a measure of ethnicity, and travel history.

Material and Methods All schoolchildren in Sisimiut, a community on the West coast of Greenland, were screened for atopy. Blood samples were analysed for total IgE and for specific IgE against inhalant and food allergens. Information on place of birth of children and their parents was obtained from national registries. Information on travel history was obtained from self-administered questionnaires.

Results A total of 1031 schoolchildren aged 5 to 18 years had a blood sample drawn (85% of available children for the study). Of these, 151 (14.6%) children were sensitized to at least one inhalant allergen and 42 (4.1%) to at least one food allergen. Sensitization to grass was most common, whereas sensitization to mugwort, birch, animal-dander and house-dust mite was infrequent. Children whose parents were both born abroad had a higher risk of sensitization to inhalant allergens compared with children born of Greenlandic parents (OR = 8.6, 95% CI 2.8–27.1). Furthermore, children who had been abroad had a higher risk of sensitization towards pollen (OR = 1.6, 95% CI 1.0–2.5) and animal-dander (OR = 2.1, 95% CI 1.0–4.6) after adjustment for confounders. Both atopic and non-atopic children demonstrated high levels of total IgE (medians of 251 and 58 kU/L).

Conclusions Compared with European findings Greenlandic children have high levels of total IgE but a low prevalence of allergic sensitization towards inhalant allergens. This may be due to a low genetic susceptibility to atopy and less allergen exposure, as well as to living conditions in an arctic environment.

Keywords allergic sensitization, allergy, arctic, atopic sensitization, atopy, children, epidemiology, Greenland, IgE, Inuit

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Introduction

The frequency of atopic diseases displays wide geographical and ethnic variations [1]. Allergic diseases appear most common in countries with a westernized lifestyle [2,3], where also more recent evidence for an increase in prevalence has been particularly pronounced [4–6]. Through the last 50 years the native population in Greenland has been highly influenced by western civilization, which may lead to a change in their disease pattern. Such a change has been observed in other arctic populations where the prevalence of 'western diseases' such as adiposity, diabetes mellitus type 2 and certain cancers is increasing [7–9].

The frequency of hospital admissions because of asthma has previously been reported to be very low among Inuits in Greenland and Canada [10,11], and Inuit schoolchildren living in northern Quebec in Canada have been found to have a very low prevalence of skin prick test positivity and exercise-induced asthma (5%) [12], but an increasing rate of hospitalizations because of asthma has been observed among American Alaskan native children in the last decades [13]. In contrast, a relatively high prevalence of atopic diseases has been found among Russian and Norwegian populations in the arctic areas [14]. The exact prevalence of allergic sensitization and of atopic diseases is not known in Greenland. The objective of this study was to describe the distribution of specific IgE towards a panel of inhalant and food allergens in Greenlandic children, and also to examine whether atopy and total IgE levels were associated with parental place of birth, as a measure of ethnicity, and travel history.

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Materials and methods

Subjects

This cross-sectional study took place in November 1998 in Sisimiut, the second largest town in Greenland, located on the western coast just north of the Arctic Circle. The town has 5445 inhabitants and 11% of the population comes from other countries, primarily from Denmark, as Greenland has been a part of Denmark since 1721. The main occupations are related to fishing and the fish industry. The climate is arctic, with average monthly temperatures ranging from -14 to 6°C and an average humidity of 80%. All schoolchildren in the Sisimiut community were invited to participate in the study. These children attended four schools, two in Sisimiut and two in the neighbouring settlements Sarfannguaq and Itilleq. Children had a venous blood sample drawn and answered a self-administered questionnaire with their parents regarding socio-demographic variables, travel history and other variables. Information on place of birth of the children and their parents was obtained by linking the unique identification number given to all Danish and Greenlandic citizens with the Civil Registration System. This registry has been described in detail elsewhere [15].

Blood sampling and laboratory analysis

Venous blood samples were drawn in EDTA tubes. After centrifugation, plasma was frozen at -20°C and transported at this temperature to Copenhagen. Plasma samples were analysed for total IgE with the UniCAP[®] total IgE and for specific IgE with Phadiatop[®] and fx5 comprising the following inhalant and food allergens: grass (Timothy, g6), mugwort (w6), birch (t3); *Cladosporium herbarum* (m2); house-dust mite (*Dermatophagoides pteronyssinus*, d1); cat (e1), dog (e2), horse (e3); egg (f1), milk (f2), fish (f3), wheat (f4), peanut (f13) and soy (f14). Blood samples positive for Phadiatop[®] or fx5 tests were quantitatively analysed for specific IgE to the same allergens with the Pharmacia UniCAP[®]. The results of total and specific IgE were quantitative and expressed in kU/L. The lowest detectable value for total IgE was 2 kU/L, with no upper limit. The highest detectable value for specific IgE was 100 kU/L, with no lower limit. The inhalant allergens were divided into three major groups: pollen (grass, birch and mugwort); animal-dander (dog, cat and horse); and house-dust mite. Atopy was defined as specific IgE towards at least one inhalant or one food allergen. The cut-off for a positive reaction was set at ≥ 0.7 kU/L.

Statistical analysis

We could not obtain a normal distribution of the IgE values after log transformation; therefore, IgE levels were expressed as medians with 25th and 75th percentiles. Differences in total IgE according to atopy and ethnicity were tested using the Wilcoxon test and according to age using the Kruskal–Wallis test. Logistic regression was used to examine associations between atopic sensitization towards different allergens and different combinations of parents' birthplace (Greenland/Greenland, Greenland/missing, Greenland/abroad, abroad/abroad) and travel history, adjusting for gender, age group (5 to 6, 7 to 8, 9 to 10, 11 to 12, 13 to 14, 15 to 18), and mother's education (8 years of primary school/unskilled worker, 12 years of primary school, skilled worker, baccalaureate/higher education). Logistic

regression analysis was carried out using PROC GENMOD in SAS version 6.12. Homogeneity of levels in the logistic regression analyses was tested using Wald's test.

Results

Of the 1213 children attending the four schools, 1068 (88%) children returned the questionnaire and 1031 (85%) had a blood sample drawn. We identified all children between 7 and 15 years of age living in the Sisimiut community at 1 November 1998 in the Civil Registration System. By subtracting children in this age group who took part in the study, we could identify those who did not take part in the study. These children did not differ from participating children according to age and sex, but children with both parents born abroad were not as well represented in the study as Greenlandic children.

Table 1 presents the distribution of children sensitized to inhalant and food allergens according to background variables. Overall, 151 (14.6%) children were sensitized to at least one inhalant allergen and 42 (4.1%) to at least one food allergen. Sensitization to inhalant and food allergens was significantly associated with age but not with sex. The prevalence of allergic sensitization was higher in children born abroad, in children with both parents born abroad, in children with uneducated mothers, and in children who had travelled abroad.

Table 2 presents the prevalence of atopic sensitization towards inhalant and food allergens in children born in Greenland with Greenlandic parents and in children where either the child or one of its parents was born abroad. Overall, 13.9% of Greenlandic children were sensitized towards at least one inhalant allergen. Eleven per cent of Greenlandic children were sensitized to grass, often with very high titres of specific IgE (16% reached the maximum detectable value of 100 kU/L, with a median value of 5.9 kU/L). Altogether, 3.9% of Greenlandic children were sensitized towards a food allergen. Sensitization towards wheat, peanut and soy was most frequent and among Greenlandic children almost 50% of those sensitized to either wheat, peanut or soy had higher IgE levels towards pollen. The prevalence of allergic sensitization to all allergens was higher in children where either the child itself or one of its parents was born abroad compared with Greenlandic children.

The level of total IgE varied from 2 kU/L to 8290 kU/L. Children of more than 15 years of age had lower IgE levels compared with the other age groups, but in the other age groups there was no association between age and level of total IgE, nor were there any differences in IgE level according to sex. Overall, the median IgE level was 70 kU/L (25th, 75th centiles: 27, 222). Non-atopic children had a median IgE level of 58 kU/L (25th, 75th centiles: 24, 166) and atopic children 251 kU/L (25th, 75th centiles: 93, 643). The median IgE level in Greenlandic non-atopic children aged 5 to 15 years was 61 kU/L (25th, 75th centiles: 25, 195). Figure 1 presents the distribution of the IgE values in children born in Greenland with Greenlandic parents and others according to atopy status. There was no difference in IgE level between children born in Greenland with Greenlandic parents and others, but the level in the atopic and non-atopic group was significantly different ($P < 0.001$).

Table 3 presents the adjusted risk of atopic sensitization towards inhalant allergens according to parent's place of birth and travel history. Sensitization towards inhalant allergens

Table 1. Distribution of children sensitized to inhalant and food allergens according to background variables ($n = 1031$)

Variables	Participants ($n = 1031$)		Inhalant allergens overall($n = 151$)		Food allergens overall($n = 42$)	
	n	%	n	%	n	%
Age (yr)						
5–6	95	9.2	6	6.3	2	2.1
7–8	216	21.0	22	10.2	6	2.8
9–10	209	20.3	27	12.9	11	6.3
11–12	168	16.3	29	17.3	11	6.5
13–14	176	17.1	36	20.5	11	6.2
15–18	167	16.2	31	18.6	1	0.6
Gender						
Boys	524	50.8	81	15.5	23	4.4
Girls	507	49.2	70	13.8	19	3.7
Place of birth						
Greenland	990	96.0	138	13.9	40	4.0
Abroad	40	3.9	13	32.5	2	5.0
Missing	1	0.1	0		0	
Mother's place of birth						
Greenland	985	95.5	140	14.2	37	3.8
Abroad	45	4.4	11	24.4	5	11.1
Missing	1	0.1	0		0	
Father's place of birth						
Greenland	869	84.3	120	13.8	35	4.0
Abroad	69	6.7	17	24.6	3	4.3
Missing	92	9.0	14	15.2	4	4.3
Mother's education						
8th grade/unskilled worker	234	22.7	41	17.5	8	2.4
9th–12th grade	239	23.2	38	16.0	12	5.0
Skilled worker	282	27.4	29	10.3	16	5.7
Baccalaureate/higher education	115	11.2	16	13.9	3	2.6
Missing	161	15.6	27	16.7	3	1.9
Travel history						
Never abroad	525	50.9	64	12.2	17	1.6
Ever abroad	504	48.9	87	17.3	25	2.4
Missing	3	0.3	0		0	

overall was significantly associated with parental place of birth, and the risk of sensitization to pollen and animal dander was significantly higher in children who had travelled abroad.

Discussion

We found that children living in Greenland had a low prevalence of sensitization to inhalant allergens compared with European findings. In a study performed among 500 Danish schoolchildren aged 7 to 16 years, where atopy was measured with skin prick test including the same allergens, the prevalence of sensitization to inhalant allergens was twice as high as among Greenlandic children [16]. This difference may be even larger, as Phadiatop[®] has a higher sensitivity than skin prick test to diagnose atopic disease [17].

Eighty per cent of the Greenlandic schoolchildren sensitized to an inhalant allergen were sensitized to grass, whereas only 7.0% and 13.0% were sensitized to birch and mugwort, respectively. There are no trees in Sisimiut but so-called dwarf birch, which are small bushes, do exist in this area and so do mugwort and grass. Pollen measurements have never been performed in this area of Greenland but in Iceland, also located in the North

Atlantic, mean grass pollen levels are generally high, whereas birch pollen levels are low compared with pollen levels in Scandinavian countries (mean grass and birch pollen levels of 2688 and 199 per m³ in Reykjavik, and of 1217 and 6117 per m³ in Uppsala in the period 1988 to 1992) [18]. If pollen levels show a similar distribution in Greenland this would be consistent with our finding of grass as the major cause of allergic sensitization.

We also observed a low prevalence of sensitization to animal dander. The prevalence of sensitization to cat and dog in the Danish study was 7% and 9.3%, respectively [16], which is almost three times higher than among the Greenlandic children. This may be explained by the fact that dogs are never and cats only rarely kept as indoor pets in Greenland. In Sisimiut, Greenlandic dogs are used for dog sledging and are kept outside throughout the year. This is why allergen exposure is probably less intensive.

The prevalence of sensitization to house dust mite in Greenland was four times lower than in Denmark, whereas sensitization to *Cladosporium herbarum* was about the same. The low air humidity in Greenland may lead to low indoor levels of house dust mite, as has been observed in Northern Norway [19].

We found a high frequency of sensitization to wheat, peanut and soy. Cross-reactivity between wheat and grass pollen has previously been reported [20], and as sensitization towards wheat, peanut and soy was highly correlated and almost 50%

Table 2. Prevalence of atopic sensitization towards inhalant and food allergens in children born in Greenland with Greenlandic parents and in children where either the child or one of its parents was born abroad ($n = 1031$)

	Greenlanders ($n = 827$)		Others ($n = 204$)	
	n	%	n	%
Inhalant allergens				
Overall	115	13.9	36	17.7
Grass	91	11.0	30	14.7
Birch	8	1.0	5	2.5
Mugwort	15	1.8	6	2.9
Dog	21	2.5	9	4.4
Cat	18	2.2	6	2.9
Horse	7	0.9	5	2.5
House-dust mite	31	3.7	9	4.4
<i>Cladosporium herbarum</i>	10	1.2	8	3.9
Food allergens				
Overall	32	3.9	10	4.8
Egg	3	0.4	1	0.5
Milk	3	0.4	2	1.0
Fish	5	0.6	2	1.0
Peanut	20(11*)	2.4	7(1*)	3.4
Wheat	19(7*)	2.3	6(0*)	2.9
Soy	17(11*)	2.1	5(1*)	2.5
Sensitized to only one allergen	77	9.3	21	10.3

*Children where specific IgE levels towards grass, birch and mugwort were lower than specific IgE levels towards peanut, wheat and soy.

of the cases had higher IgE levels against pollen, allergenic cross-reactivity with pollen may explain this finding.

We may not have tested for all relevant allergens in this area of Greenland. However, in the European Community Respiratory Health Survey study the prevalence of specific IgE towards house-dust mite (*Dermatophagoides pteronyssinus*), grass (Timothy), *Cladosporium herbarum*, cat and a local allergen was measured in 17 countries around the world [21], and the addition of a local allergen did not greatly affect the prevalence of atopy. The four allergens tested for accounted for 96% of the variance in the prevalence of atopy, defined as a response to any of these four allergens or the local allergen. The cut-off for specific IgE was set to ≥ 0.7 kU/L to avoid inclusion of less specific reactions. The change of the cut-off from ≥ 0.35 kU/L to ≥ 0.7 kU/L reduced the prevalence of sensitization to inhalant allergens overall only marginally from 15.4% to 14.6%, whereas the prevalence of sensitization to food allergens overall was reduced from 4.9% to 4.1%.

Wide differences in IgE levels in adult populations have been observed [21]. Greenlandic children had high IgE levels and the values had a wide range. Backer et al. found a geometric mean of IgE of 18 kU/L (± 2 SD 1–327) in Danish children aged 8 to 15 years with no atopic symptoms and negative skin prick test [22], which was markedly lower than the non-atopic Greenlandic children aged 5 to 15 years in our study. In theory, this difference could be due to the different definitions of atopy in the studies. However, the IgE level in the atopic Greenlandic children was also markedly higher. The fact that IgE levels between children born in Greenland with Greenlandic parents and others did not differ suggests that exposures in the Greenlandic environment may be responsible for the high levels of IgE. Infestation with parasites is associated with high levels of total IgE, but apart from reports of cases with human trichinellosis, we have not been able to find any literature on the prevalence of human infestation with parasites in arctic areas.

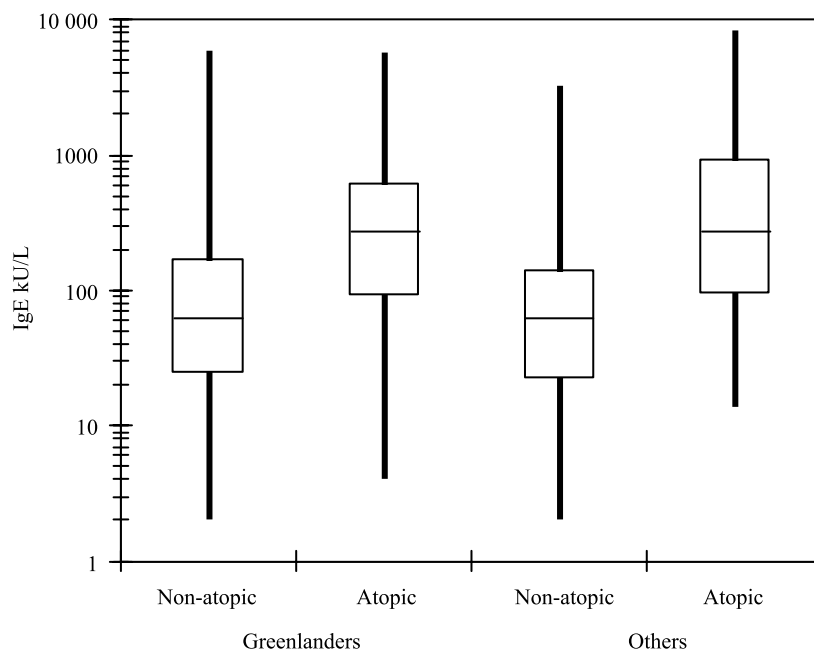


Fig. 1. Twenty-fifth, fiftieth and seventy-fifth percentiles, and minimum and maximum values of IgE in children born in Greenland to Greenlandic parents and others according to atopy status.

Table 3. Odds ratios and 95% confidence intervals for atopic sensitization towards inhalant allergens according to parents' place of birth and travel history (*n* = 869)

	<i>n</i> (cases)	Inhalant allergens overall	Pollen	Animal dander	House dust mite
Parents' place of birth*					
Greenland/Greenland	193 (70)	1	1	1	1
Greenland/abroad	79 (12)	1.2 (0.6–2.4)	1.3 (0.7–2.6)	0.9 (0.3–2.9)	0.7 (0.2–3.3)
Greenland/missing	75 (12)	1.4 (0.7–2.7)	1.2 (0.6–2.6)	1.6 (0.5–5.0)	1.9 (0.6–5.9)
Abroad/abroad	14 (7)	8.6 (2.8–27.1)	5.0 (1.5–16.3)	1.5 (0.2–12.8)	8.3 (1.4–47.5)
		<i>P</i> < 0.005	<i>P</i> = 0.10	<i>P</i> = 0.85	<i>P</i> = 0.13
Travel History†					
Never abroad	446 (56)	1	1	1	1
Ever abroad	424 (68)	1.2 (0.8–1.9)	1.6 (1.0–2.5)	2.1 (1.0–4.6)	1.1 (0.5–2.3)

P-values test for homogeneity. * Adjusted for age group, gender, mother's education and travel history. † Adjusted for age group, gender, mother's education and parents' place of birth.

We found that the risk of sensitization overall was significantly associated with ethnic background, as children whose parents were both born abroad had an eightfold higher risk of sensitization to inhalant allergens. The Inuit population of Greenland has for a number of years to a certain extent been mixed with Danes. We defined ethnicity in genetic terms and used biological parents' place of birth as a proxy measure of ethnicity. To investigate whether this indeed is a valid measure of genetic constitution, we identified all children born in Greenland after the year 1990 in the Civil Registration System. For these children we could obtain almost complete information on place of birth of parents and grandparents. Among children with both parents born in Greenland, 96% of the grandparents were born in Greenland. In children where only one parent was born in Greenland, 56% of the grandparents were born in Greenland. Finally, only 4% of the grandparents were born in Greenland if both parents were born abroad. Thus, we feel confident that parents' place of birth is a valid measure of biological ethnicity in Greenland. However, we did not have exact information on how long the families had lived in Greenland. Thus, the high risk could both be due to an increased genetic susceptibility in children whose parents were born abroad, but it could also be a result of exposure to 'western lifestyle risk factors' before moving to Greenland.

We found that children with both parents born abroad were not as well represented in the study as Greenlandic children. In general, higher participation rates among Greenlanders than Danes have consistently been observed in previous studies in Greenland, irrespective of study objectives [23–25]. We believe that the difference in participation rates among children with a foreign ethnic background and Greenlandic children reflects this phenomenon and does not result in selection bias related to atopy. Furthermore, a number of sensitized children might not have allergic symptoms, which also reduces the risk of selection bias. However, even in a worst-case scenario where all non-participating children of parents born abroad would be non-sensitized, the prevalence of atopic sensitization among these children would still be higher than among the other groups of children.

Children who had been abroad had a significantly higher risk of sensitization to pollen and animal dander after adjustment for confounders. The most obvious interpretation of this finding is that children have been exposed to higher levels of allergen abroad. However, even though we have adjusted for ethnic

background, other lifestyle factors associated with going abroad could also influence the susceptibility to atopic sensitization in this subgroup.

The low prevalence of atopy among Inuits may be explained both by low exposure to allergens and by Inuits being genetically less susceptible to atopy than Danes. Both hypotheses are in agreement with our findings. However, other environmental factors may be involved. Recently, attention has been drawn to the possible protective effect of infections in early childhood on the development of allergic disease [26,27]. The frequency of acute respiratory tract infections during early childhood is very high in Greenland [24], which could protect these children from allergic diseases. Another interesting possible protective factor in the Greenlandic lifestyle is the large consumption of fish, which contains high levels of ω -3 fatty acids. Studies have shown that Greenlanders have higher n-3/n-6 polyunsaturated fatty acids ratios compared with Danes [28], and ω -3 fatty acids are thought to have an anti-inflammatory and immunomodulating effect [29]. Accordingly, consumption of high levels of fish has been associated with higher FEV₁ (forced expiratory volume in one second) [29], and a decreased risk of asthma [30]. A study among schoolchildren also found that children with allergic disease had a higher n-3/n-6 ratio compared with non-allergic children [31]. Whether the protective role of childhood infections or of ω -3 fatty acids plays any role in the development of atopy in this population remains to be clarified.

In conclusion, compared with European findings Greenlandic children have generally high levels of total IgE but a low prevalence of allergic sensitization towards inhalant allergens. This may be due to a low genetic susceptibility to atopy and to less allergen exposure, as well as to living conditions in an arctic environment.

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