

Allergic diseases, skin prick test responses, and IgE levels in North Karelia, Finland, and the Republic of Karelia, Russia

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Background: There is growing evidence to show that atopic diseases are more common in Western Europe than in the former socialist countries of Eastern Europe.

Objective: The aim of this study was to assess whether a similar difference exists between the most eastern province of Finland and a neighboring western district of Russia.

Methods: A random sample of 25- to 54-year-old subjects was taken from the population registers in the North Karelia Province in eastern Finland and from the Pitkäranta district across the border in the western part of Russia. Participants filled out a questionnaire on atopic and allergic symptoms and participated in a clinical study, which included skin prick tests with 11 airborne allergens and IgE measurements.

Results: Self-reported hay fever, allergic eye symptoms, atopic eczema, and asthma were much more common in Finland than in Russia. In Finland 34.2% and in Russia 21.8% had at least one positive skin prick test reaction. In Finland 21.5% but in Russia only 15.8% had at least one elevated allergen-specific IgE value of the 5 values measured. From 6% to 47% of the differences in self-reported symptoms between the countries were explained by atopy, as measured by means of skin prick testing or specific IgE values.

Conclusions: A major difference in clinical allergic diseases and signs of symptoms was observed between the 2 geographically adjacent areas. This suggests that the difference in clinical allergy and atopic disposition is related to the differences in lifestyle and environmental factors. (*J Allergy Clin Immunol* 2002;109:643-8.)

Key words: Atopy, epidemiology, Finland, IgE, Russia, skin prick test

Atopy and asthma are significant public health problems in industrialized countries. The estimated prevalence of asthma in Finland is 4% to 5% among school-aged children, and the lifetime incidence has been

Abbreviation used

HEP: Histamine equivalent prick

estimated to be 5% to 10%.¹ Large differences have been observed in atopy and asthma between countries. Symptoms are increasing with urbanization, with industrialization, and with increasing standard of living.²⁻⁵ There is growing awareness that atopy and asthma prevalence are on the increase in the developed countries. The evidence is mainly based on hospital or clinical records and self-reported symptoms.⁶⁻⁹ An increase in specific IgE levels or skin prick test reactivity has been reported in children in Japan and Switzerland.^{10,11} However, in 3 Australian areas few changes were observed in skin prick test positivity rates despite major increases in the incidence of asthma.^{12,13} On the other hand, an increase in the prevalence of atopy and hay fever has been observed in the eastern part of Germany, which was not accompanied by any increase in asthma.¹⁴ This suggests that the trends in atopy and asthma do not always occur concurrently.

Several environmental causes have been proposed to account for this increase. It has been suggested that smoking and air pollution from traffic and industry are the main causes of the increase, although others have pointed to prenatal factors, such as mothers' smoking.¹⁵ The role of infections in the cause is more controversial: on the one hand, infections may increase asthma, but on the other hand, it has been suggested that the control of infectious diseases and the increase in general hygiene in the past decades may have increased atopy.¹⁶

A few epidemiologic studies have indicated that atopy and asthma are more prevalent in Western Europe than in Eastern Europe or in the former Soviet Union countries. Among 9- to 11-year-old schoolchildren, the prevalence of asthma diagnosed by a physician, hay fever, bronchial hyperresponsiveness, and positive skin prick test responses was much higher in West Germany than in East Germany.^{17,18} Among 10- to 12-year-old schoolchildren, the prevalence of positive skin test responses was much higher in Sweden than in Poland and Estonia.^{19,20} In the International Study of Asthma and Allergy in Children, atopic symptoms were most common in Finland and Sweden, followed by Estonia, Latvia, and Poland, with the lowest prevalence being found in Albania, Romania, Russia,

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TABLE I. Allergic diseases in North Karelia, Finland, and in the Republic of Karelia, Russia

	Finland (n = 787), %	Russia (n = 385), %	P value (χ^2 test)
Hay fever (ever)	21.9	4.2	.001
Hay fever (in the past 12 mo)	17.9	2.3	.001
Hay fever (diagnosed by physician)	8.1	1.6	.001
Allergic eye symptoms (ever)	23.7	3.9	.001
Allergic eye symptoms (in the past 12 mo)	16.4	2.3	.001
Allergic eye symptoms (diagnosed by physician)	7.4	1.3	.001
Atopic eczema (ever)	28.1	11.6	.001
Atopic eczema (in the past 12 mo)	14.7	4.4	.001
Atopic eczema (diagnosed by physician)	17.7	7.9	.001
Asthma (ever)	5.8	2.1	.005
Asthma (diagnosed by physician)	5.5	1.6	.002

TABLE II. Positive skin prick test responses (wheal ≥ 3 mm in diameter) in North Karelia, Finland, and in the Republic of Karelia, Russia

	Finland (n = 770), %	Russia (n = 381), %	P value (χ^2 test)
Birch	12.3	5.5	.001
Timothy grass	10.3	5.3	.004
Mugwort	7.8	9.2	.419
Cat	12.7	5.5	.001
Dog	12.9	3.7	.001
Horse	2.9	1.6	.184
Cow	2.6	0.5	.016
<i>Alternaria alternata</i> (mold)	2.2	1.6	.487
<i>Cladosporium herbarum</i> (mold)	3.3	2.1	.242
<i>Dermatophagoides pteronyssinus</i> (dust)	7.0	5.7	.411
Cockroach	7.2	7.3	.971
Any positive response to pollen	18.4	12.6	.012
Any other positive response	27.3	15.8	.001
Any positive response	34.2	21.8	.001

Georgia, and Uzbekistan.²¹ Differences between the areas were less pronounced in children 6 to 7 years of age than in 13- to 14-year-old children.

The aim of this article is to describe allergic diseases, positive skin prick test reactions, and IgE values to common inhalant allergens in the most eastern province of North Karelia in Finland and in the nearby district of Pitkäranta in Russia. The areas are geographically close to each other but differ in cultural, economic, and lifestyle conditions. This represents a unique possibility to study the possible effect of the western lifestyle on the prevalence of atopy.

METHODS

The National FINRISK Study has been carried out at 5-year intervals to monitor noncommunicable disease risk factors in Finland. Risk factor surveys were started to evaluate the North Karelia Project in 1972.²² It was continued as the FINMONICA study related to the World Health Organization MONICA project. Since 1992,

the aim of the surveys has been to monitor and investigate risk factors at a national level.²³ The long-term goal is to obtain comparable data on symptoms and biologic markers on the trend of these diseases. In 1992 and 1997, the same survey team, using the same protocol, performed the survey in the Republic of Karelia in Russia. In 1997, the survey included 5 areas in Finland, and a new atopy, allergy, and asthma component was added.

The Finnish study area, North Karelia, is the most eastern province of the country. About 30% of the 180,000 inhabitants live in the capital of the province. Sixty-four percent of the working population is employed in the service industries, 23% in manufacturing and construction, and 12% in agriculture and forestry. The Russian study area, Pitkäranta district, is located in the Republic of Karelia. The size of the population is 27,500, 50% of whom live in the capital of the province. About 50% of workers are employed in industry or construction, 30% in the service industries, and 10% in forestry and agriculture.

This report is based on an additional survey that was carried out in 1998 on a subsample of adults aged 25 to 55 years who had participated in the risk factor survey in 1997 in North Karelia province in Finland and in Pitkäranta district in the Republic of Karelia in Russia. The original FINRISK sample in 1997 included 1500 subjects from North Karelia in Finland and 750 subjects from Pitkäranta district in Russia. The sample was randomly drawn from the population registers and stratified on the basis of 10-year age groups and sex. In 1997, 1070 (71%) subjects participated in North Karelia and 560 (75%) in Pitkäranta, and in the additional survey in 1998, the respective numbers were 790 (53%) in North Karelia and 387 (52%) in Pitkäranta.

The atopy, asthma, and allergy component of the National FINRISK Study in 1997 included a self-administered questionnaire, as well as an assay of IgE concentrations in serum. The measurements included total IgE and specific IgE for 5 common inhalant allergens. In 1998, the additional survey participants filled out a more detailed questionnaire on symptoms and diseases. Studies of skin sensitivity are feasible in epidemiologic surveys and are generally acceptable to the public. They give a semiquantitative measure of sensitization and are relatively cheap to perform. The skin prick testing was carried out with Soluprick solutions (ALK and Vivodiagnostik) and steel lancets with 1-mm points used to prick the volar surface of the forearms of patients, according to the procedure described by Dreborg.²⁴

A standard list of 11 airborne allergens stored in glycerin and PBS was used throughout the survey. All allergens came from a single batch. The allergens used in all areas included birch (10 histamine equivalent prick [HEP]), timothy grass (10 HEP), mugwort (10 HEP), cat (10 HEP), dog (10 HEP), horse (10 HEP), cow (1:100), *Alternaria alternata* (5 mg/mL), *Cladosporium herbarum* (5 mg/mL), *Dermatophagoides pteronyssinus* (10 HEP), *Dermatophagoides farinae* (10 HEP), and cockroach (1:100), with a

TABLE III. Percentage of high total IgE values (≥ 110 IU/L) and specific IgE values (≥ 0.35 IU/L) in North Karelia, Finland, and in the Republic of Korea, Russia

	Finland (n = 772), %	Russia (n = 385), %	P value (χ^2 test)
Total IgE	37.8	43.6	.033
Birch	7.8	2.1	.001
Timothy	8.6	3.9	.003
<i>Cladosporium herbarum</i>	1.9	0.5	.058
<i>Dermatophagoides pteronyssinus</i>	10.4	11.7	.49
Cat	6.1	2.1	.003
No positive response	78.5	84.2	.03
One positive response	13.7	12.7	
Two positive responses	4.2	2.1	
Three positive responses	2.3	0.8	
Four or 5 positive responses	1.3	0.3	

positive control (histamine dihydrochloride, 10 mg/mL) and a negative control (solvent) and no duplicate testing. The size of the wheal after 15 minutes was determined by measuring the diameter in 2 perpendicular directions and then halving the sum. The reaction was regarded as positive if the wheal diameter was 3 mm. Fifteen Finns and 3 Russians were omitted because the negative control solution caused a 1-mm positive reaction.

Serum-specific and total IgE levels were measured with the Pharmacia CAP System. Specific IgE was measured against birch, timothy grass, cat, *C herbarum*, and *D pteronyssinus*. Although total IgE has poor sensitivity and specificity for clinical atopy, it has been considered in some studies to be the single best predictor of asthma.²⁵

The statistical analyses were carried out with the SAS program by using the χ^2 test, *t* test, and logistic regression model. The mean age of participants was 39.7 years in Russia and 40.8 years in Finland. The age standardization did not have any meaningful effect on results. Hence only the nonstandardized results are presented.

RESULTS

Symptoms of allergic diseases were more common in North Karelia in Finland than in Pitkäranta in Russia (Table I). A lifetime history of hay fever was reported by 21.9% of Finns and 4.2% of Russians. Hay fever during the past 12 months was 8 times more common in Finland, and hay fever diagnosed by a physician was 5 times more common in Finland. A similar difference between the countries was observed in allergic eye symptoms. Atopic eczema was more common in Finland: 28.2% reported having eczema at some time in Finland and 11.6% in Russia. In Finland 5.5% of subjects reported having asthma diagnosed by a physician compared with 1.6% in Russia.

The most common positive skin prick test responses in Finland were to birch, timothy, cat, and dog. The prevalence varied from 10.2% to 12.9% in Finland and from 3.7% to 5.5% in Russia. In Russia the most common positive reaction was to mugwort (9.2%). Of the 11 tested allergens, 34.2% of Finns and 21.8% of Russians had at least one positive skin prick test response (Table II). This difference between countries was observed in all of the tested allergens except mugwort. The prevalence of high total serum IgE values was statistically significantly higher in Russia than in Finland (Table III).

The median levels of IgE were 34 IU/L in Finland and 38 IU/L in Russia. However, in Finland the prevalence of positive specific IgE levels was higher for birch, timothy, and cat, which correspond to the difference observed in skin prick tests. Also, the prevalence of Finnish subjects having one or several positive values was significantly higher compared with their Russian counterparts. However, no difference was observed for house dust mite, which may be due in part to the larger wheal diameters among the positive skin prick test responses in Russia (Table II).

The association between symptoms and any positive skin prick test responses and any high specific IgE values is shown in Table IV. The odds ratios were rather similar for hay fever and eye symptoms in Finland and Russia. There was a difference between the countries with respect to atopic eczema. In Finland there was a positive association between symptoms and skin prick test responses and high IgE values, whereas in Russia no such association was found. For asthma, the associations were less clear, but this may be due to the small number of asthmatic subjects in Russia. In Finland both skin prick test response and specific IgE positivity doubled the risk of asthma, but in Russia only specific IgE was associated with more asthma.

The odds ratios between the countries for atopic symptoms varied from 2.9 for asthma to 9.1 for hay fever (Table V). After adjusting these odds ratios according to whether there was a positive skin prick test response or any high specific IgE values, the odds ratios declined by only 6% to 47%. The result was essentially the same if the 11 skin prick tests and 5 specific IgE values were used independently in the analyses. Hence most of the differences in self-reported allergic diseases between the countries could not be explained by atopy.

DISCUSSION

In the present study, self-reported symptoms, those diagnosed by a physician, or both for the following diseases were more common in Finnish North Karelia than

TABLE IV. Percentage of self-reported allergic disease with positive and negative skin prick test response and association of diseases with skin prick test responses measured as odds ratios separately in North Karelia, Finland, and in the Republic of Karelia, Russia

	Finland			Russia		
	Negative SPT response (n = 509), %	Positive SPT response (n = 266), %	OR (95% CI)	Negative SPT response (n = 298), %	Positive SPT response (n = 84), %	OR (95% CI)
Hay fever (ever)	13.0	40.3	4.5 (3.2-6.4)	2.4	10.7	5.0 (1.8-13)
Hay fever (in the past 12 mo)	10.0	33.8	4.6 (3.1-6.7)	0.7	8.3	13.5 (2.7-67)
Hay fever (diagnosed by physician)	3.1	18.1	6.8 (3.8-12)	1.0	3.6	3.64 (0.7-18)
Allergic eye symptoms (ever)	13.8	42.4	4.61 (3.3-6.6)	2.7	8.3	3.3 (1.2-9.0)
Allergic eye symptoms (in the past 12 mo)	8.9	31.2	4.6 (3.1-6.9)	0.7	8.3	13 (2.7-66)
Allergic eye symptoms (diagnosed by physician)	2.6	16.3	7.3 (3.8-14)	0.7	3.6	5.48 (3.8-14)
Atopic eczema (ever)	24.2	36.9	1.8 (1.3-2.5)	11.9	9.64	0.79 (0.3-1.8)
Atopic eczema (in the past 12 mo)	11.3	22.0	2.2 (1.5-3.3)	5.1	2.4	0.46 (0.1-2.0)
Atopic eczema (diagnosed by physician)	13.2	27.1	2.5 (1.7-3.6)	8.8	4.8	0.52 (0.2-1.5)
Asthma (ever)	4.18	9.3	2.3 (1.3-4.3)	2.0	2.4	1.17 (0.2-5.9)
Asthma (diagnosed by physician)	4.0	8.9	2.3 (1.3-4.4)	1.4	2.4	1.8 (0.3-9.9)

SPT, Skin prick test; OR, odds ratio.

TABLE V. Odds ratios for comparisons of the occurrence of atopic symptoms between North Karelia, Finland, and the Republic of Karelia, Russia

	Unadjusted OR*	Adjusted OR†	Change in odds, %	Adjusted OR‡	Change in odds, %
Hay fever (ever)	6.5	5.6	16	5.9	11
Hay fever (in the past 12 mo)	9.1	7.7	17	8.6	6
Hay fever (diagnosed by physician)	5.6	4.5	24	4.1	33
Allergic eye symptoms (ever)	7.6	6.7	14	6.9	11
Allergic eye symptoms (in the past 12 mo)	8.3	7.1	16	7.3	14
Allergic eye symptoms (diagnosed by physician)	6.1	4.5	31	3.7	47
Atopic eczema (ever)	3.0	2.9	5	2.7	15
Atopic eczema (in the past 12 mo)	3.7	3.4	11	3.2	19
Atopic eczema (diagnosed by physician)	2.5	2.3	13	2.1	27
Asthma (ever)	2.9	2.6	16	2.4	26
Asthma (diagnosed by physician)	3.7	3.2	19	2.9	30

Odds ratios are unadjusted and adjusted by means of skin prick test responses and specific IgE levels.

*Unadjusted.

†Adjusted for any skin prick test reaction (yes/no) and any specific IgE level (yes/no).

‡Adjusted for all 11 skin prick tests and all 5 high specific IgE values.

in Russian Karelia, Pitkäranta, as determined by means of skin prick testing and specific serum IgE level measurement: hay fever, atopic eye symptoms, atopic eczema, and asthma. These areas are geographically adjacent. However, in social, political, economic, and lifestyle terms they represent 2 different worlds. This suggests that differences in lifestyle and standard of living between the countries can influence the prevalence of atopy. The genetic background of the populations are very different, and its effect cannot be ruled out.

Similar differences have been observed in children in West and East Germany: Both atopic sensation measured as a positive skin prick test response and reported asthma, as well as hay fever and eye symptoms, were more common in the West Germany than in East Germany. Also, Swedish schoolchildren more often had positive skin prick test responses than their Polish counterparts. Our data confirm that this phenomenon exists also in

other areas between Eastern and Western Europe, and thus it seems to be linked with the western lifestyle.

It has been proposed that air pollution may cause asthma. It is evident that asthmatic patients have increased respiratory reactivity to air pollution. It is not clear whether air pollution can cause asthma or atopy. The fact that atopy was less prevalent in East Germany, which had a much higher level of air pollution, than in West Germany argues against the hypothesis that increased air pollution, at least classical mass pollutants like SO₂, plays a major role in the increase in atopy or in the differences between the countries. In the present study both areas have very low pollution levels, and it is unlikely that 2 neighboring communities would be exposed to very different levels of airborne pollutants. Hence it is very unlikely that air pollution can account for the observed differences. However, we do not have pollution measurements from the study areas.

There is also evidence that the prevalence of atopic diseases is on the increase, at least in western countries. These 2 findings suggest that the increase in atopy is related in some way to the modern western lifestyle. A recent article by Matricardi et al²⁶ suggested that atopy and respiratory allergy are less frequent in subjects exposed to orofecal and foodborne microbes, but no association was found between markers of airborne viral infections. Similar analyses are being examined from our data set.

Only less than one fifth of the difference in self-reported symptoms between the countries was explained by atopy, as assessed by means of skin prick tests or specific IgE values. This is due to the fact that symptoms were reported in Finland more than 10 times more often than in Russia, but positive skin prick test responses were only 2 times more common. Our findings support the conclusion that the prevalence of atopy can only partly explain differences in the prevalence of allergic diseases, particularly asthma. For example, Peat et al²⁷ found little or no association between the prevalence of atopy and diagnosed asthma in different parts of Australia. Similarly, Leung and Ho²⁸ report large differences in asthma prevalence in Hong Kong, Malaysia, and San Bu, China, where atopy prevalence was similar. In southwest Ethiopia²⁹ asthma prevalence was lower, but atopy was higher in a rural than in an urban area. In the European Community Respiratory Health Survey the prevalence of atopy³⁰ appears to be associated with the prevalence of subjects reporting asthma attacks at the country level. However, this association is mainly driven by the English-speaking countries, and other European countries show only a weak association.

However, some studies carried out in Europe point to an association between the prevalence of atopy and asthma.^{31,32} This is especially true for studies comparing Eastern and Western Europe.³³ In Finland 47% of those who had positive skin prick test responses for at least one pollen reported that they had hay fever, whereas in Russia the respective prevalence was only 13%. This suggests that either the awareness of allergic diseases is at a lower level in Russia or that they experience less severe symptoms or that some factors in Russia protect them from symptomatic allergic disease. However, we do not have any information of the severity of symptoms in the present study. Cross-cultural comparisons of self-reported allergic symptoms and even diagnoses made by physicians should be interpreted cautiously. However, in the present study the associations between atopy and symptomatic allergic disease were very similar in the 2 areas studied. The effect of age on symptoms, skin prick test responses, and IgE levels were similar in both countries.

The difference in specific IgE values was much smaller between the countries, and the total IgE value was higher in Russia than in Finland. This suggests that in Russia the immune system reacts more against other agents than is the case in Finland.

In summary, our data confirm that there is a difference between Eastern and Western Europe in terms of atopy and allergic diseases. Only a minor part of the difference

in allergic diseases could be explained by the difference in atopy. Further analyses are needed from this data set and from other studies to clarify which factors are responsible for this difference.

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Correction

With regard to the article entitled "Exposure to endotoxin decreases the risk of atopic eczema in infancy: A cohort study," which appeared in the November 2001 issue of *The JACI* (Gehring et al. 2001;108:847-54), the authors submit the following remarks:

Our questionnaire comprised 2 questions on doctor-diagnosed eczema, one referring to atopic eczema and the other referring to "eczema (not specified)" (for the exact wording, see Appendix 2 as corrected below). By mistake, we substituted the data pertaining to doctor-diagnosed "eczema (not specified)" for the data pertaining to doctor-diagnosed atopic eczema and therefore presented results for the former instead of results for the latter. Thus the term *atopic eczema* must be replaced by the term *eczema (not specified)* throughout the article.

The correct prevalence of doctor-diagnosed atopic eczema was 116/1754 (6.2%) at the age of 6 months and 198/1728 (11.5%) at the age of 12 months (see Table I as corrected below). Only 13 of the parents reported doctors' diagnoses of both atopic eczema and nonatopic eczema at the age of 6 months, and only 52 of the parents reported doctors' diagnoses of both atopic eczema and nonatopic eczema at the age of 12 months. The corrected results for the multiple regression analysis for both atopic eczema and "eczema (not specified)" are presented in Table IV as corrected below. No protective effect of exposure to endotoxin in the 5th quintile and doctor-diagnosed eczema can be found for the first 6 months of life. No difference was found between children of atopic parents and children of nonatopic parents (data not shown).

Accordingly, the conclusions that we reported must be modified as follows: Exposure to high concentrations of endotoxin very early in life might protect against the development of "eczema (not specified)" within the first 6 months of life along with an increased prevalence of nonspecific respiratory diseases. Exposure to high concentrations of endotoxins does not protect against the development of atopic eczema.

TABLE I (CORRECTED). Description of the study population

	Frequency	
	n/N	Percent
Age of 6 mo		
Dermatologic symptoms and diseases*		
Doctor-diagnosed atopic eczema	116/1754	6.2
Doctor-diagnosed eczema (not specified)	169/1868	9.1
Age of 12 mo		
Dermatologic symptoms and diseases*		
Doctor-diagnosed atopic eczema	198/1728	11.5
Doctor-diagnosed eczema (not specified)	287/1809	15.9

*Lifetime prevalence.

TABLE IV (CORRECTED). Multiple logistic regression between symptoms and diseases and endotoxin in dust from mothers' mattresses: adjusted* odds ratios and 95% CIs

	1st quintile ≤824 EU/g		2nd quintile 824-1973 EU/g		3rd quintile 1973-4365 EU/g		4th quintile 4365-10163 EU/g		5th quintile >10163 EU/g	
	OR		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age of 6 mo										
Dermatologic symptoms and diseases										
Doctor-diagnosed atopic eczema	1		1.08	(0.58; 2.03)	1.38	(0.75; 2.52)	1.15	(0.62; 2.15)	1.15	(0.61; 2.14)
Doctor-diagnosed eczema (not specified)	1		1.09	(0.68; 1.74)	0.96	(0.59; 1.56)	0.83	(0.51; 1.37)	0.50†	(0.28; 0.88)
Age of 12 mo										
Dermatologic symptoms and diseases										
Doctor-diagnosed atopic eczema	1		0.82	(0.52; 1.32)	0.88	(0.55; 1.40)	0.89	(0.56; 1.41)	0.96	(0.60; 1.53)
Doctor-diagnosed eczema (not specified)	1		1.17	(0.79; 1.74)	1.10	(0.74; 1.65)	1.13	(0.76; 1.68)	0.87	(0.57; 1.32)

OR, Odds ratio.

*Adjusted for the following: place of residence; sex; parental atopy; parental education; smoking during pregnancy; breast-feeding; keeping of dog, cat, hamster/rabbit/guinea pig, and other pets; mite (Der p 1 + Der f 1) and cat allergens in mother's mattress dust. † $P < .05$. ‡ $P < .01$.

APPENDIX 2 (CORRECTED)

Outcome variable	Question
Doctor-diagnosed atopic eczema	Did a doctor diagnose an allergic or atopic eczema in your child in the past 6 months?
Doctor-diagnosed eczema (not specified)	Did a doctor diagnose an eczema (not specified) in your child in the past 6 months?