Allergic sensitization trends in Albanian children from 2000 to 2012

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Abstract

Aim: Allergic sensistization diplays an increasing rate all over the world but, recent studies report no further increase in asthma in countries with a high prevalence, except for the Eastern European countries where westernization is still continuing. The aim of this study was to assess the atopy prevalence in 2012, its risk factors, and time trends of allergic sensitization in Albanian schoolchildren.
Methods: The Standardized International Study of Asthma and Allergies in Childhood (ISAAC) core and risk factors questionnaires were used to survey 3161 children 10-11 year old selected randomly among all schools of Tirana. Also an 8-airborne allergen skin prick test (SPT) was administered to a subsample of 1071 children to assess define the prevalence of allergy. These data were compared with the ISAAC Phase Two in Tirana.
Results: An increase over the 12-year interval for all individual allergens, except olive was found in our current study. The proportion of children reacting to at least one allergen rose from 15% in 2000 to 24.3% in 2012 (OR=1.83), with a highly statistically significant change. During the same period, there was an increase in the prevalence of current wheeze (4.4% to 5.1%, OR=1.18) and symptoms of hay fever (2.7% to 4.9%, OR=1.91), but there was no change in eczema symptoms.
Conclusion: The prevalence of allergic sensitization increased significantly in Albanian children from 2000 to 2012. There was an increase in the allergic clinical symptoms of Albanian children which was, nevertheless, below the European average, despite substantial changes in the lifestyle factors and the environmental factors.

Keywords: allergic sensitization, atopic disease, epidemiology, school children, skin prick test.

Introduction

The prevalence of allergic diseases for several decades has been in constant increase (1,2), but recent studies report no further increase in asthma in countries with a high prevalence (3) except for the Eastern European countries where westernization is still continuing (4,5). To estimate the prevalence of allergic disease most studies are questionnaire-based, and the increase in asthma may be attributable to increased awareness for these diseases or changed diagnostic criteria (6). Hence, the use of objective measures of allergic sensitization is of great importance. Assessment of skin prick test (SPT) reactivity is a valid and useful method in epidemiologic studies.

Studies evaluating time trends of allergic sensitization in children provide a heterogeneous picture. Studies performed in Australia and European countries (7-11) report a stable prevalence or a decrease, whereas an increase has been reported from Northern Sweden (12), Greenland (13) and Ghana (14). Although some studies have suggested a possible linear dose-response relationship between early life exposure to allergens and the subsequent development of sensitization (15,16), the development of atopic sensitization is the result of a complex interplay of genetic and environmental factors (17-19). The data of ISAAC Phase Two in children of Tirana (1999-2000), showed that the prevalence of allergic sensitization was 15.0% measured by SPT, 2.7% were diagnosed as having asthma, and 4.4% reported wheeze in the last 12 months, hay fever 2.7% and eczema 1.8% (20). A new cohort of the same age, living in the same area was examined in 2011-2012 using same methodology.

The aim of this study was to investigate the prevalence, time trends in the prevalence and risk factor patterns of allergic sensitization among children aged 10 to 11 years in Albania from 2000 to 2012.

Methods

Our study is a part of the Alb-ISAAC 2011-2012, a cross-sectional population-based study. The standardized methodology of ISAAC used in our study (slightly modified), is explained in details elsewhere (21-23).

In August 2011, a random sample of schools was chosen from the list of all the elementary schools of Tirana city (public and non-public), until enrolling the predefined sample of at least 3000 children aged 10-11 years old, in the fifth grade. Children were invited to take part in the study. A written consent for the participation and SPT was obtained from the children's parents. The fieldwork was carried out on schedule, from February to April 2012, the same period as ISAAC Phase Two. The 10-11-year-olds completed the core and risk factors questionnaires, underwent skin examination for flexural atopic dermatitis, and among them, 1263 children were selected randomly for participation to skin prick tests. The study was approved by the National Ethics Committee, the Ministry of Health and the Ministry of Education and Science.

Questionnaire

The ISAAC core questionnaire consisted of three main sections, each involving questions relating to the prevalence and severity of wheezing, rhinitis and eczema, respectively (22,23). These questionnaires were translated and validated in previous phases of ISAAC in Tirana. Additional questions were included aiming at the screening for possible risk factors and evaluate the change in these factors in a 12-year difference. Such questions included family history of allergic diseases, number of siblings and birth order, birth weight, length of breast-feeding, respiratory infections, past or current pets at home, parental smoking, house dampness, and other living condition factors. The questionnaires were distributed by the school teachers. The variable regarding length of breast-

feeding included both exclusive and nonexclusive breast-feeding.

Skin prick test

The sensitivity to eight aeroallergens (house dust mites-Der p1 and Der f1, cat, alternaria alternata, mixed grasses pollen, mixed tree pollen and olive plus parietaria officinalis of local relevance were added) was assessed by skin prick tests with the same methodology and allergens as in ISAAC Phase Two (Soluprick, ALK, Hørsholm, Denmark). The child was considered atopic by a specific allergen if he/she presented a wheal of ≥3 mm after 15 minutes. The SPT were carried out from February to April, both in 2000 and 2012, in the schools by two specifically trained staff following the European Academy of Allergology and Clinical Immunology recommendations (24).

Statistical analysis

The data were double-entered by data input clerks into Epi-Info, a computer program for the capture and processing of epidemiological data. The datasets were then validated and consolidated by a single data manager. Statistical analysis was performed using the statistical software program STATA (STATA Corporation, College Station, TX, USA). Multiple logistic regression analyses were used to estimate the prevalence change of positive SPT from 2000 to 2012. Risk factors for a positive SPT were calculated by using multiple logistic regression analyses and expressed in odds ratios (ORs) with their respective 95% confidence intervals (CIs). The rapidly changing risk factors were tabulated for SPT positive and negative children. The results were presented as ORs and 95% CIs where appropriate.

Results

In the present study a total of 3481 children were invited to take part in the survey. Alb-ISAAC core and risk factor questionnaires were completed from 3161 children (response rate: 90.8%) and allergen skin prick tests (SPT) were performed on a subsample of 1071 children (response rate: 84.7%).

Skin prick test positivity: prevalence, time trends, and associations with symptoms

Table 1 shows the prevalence of positive skin prick reactions (mean wheal diameter of ≥3mm) to any allergen, and to each individual allergen, in Phase Two (1999-2000) and the current survey. There was an increase over the 12-year interval for all individual allergens except olive. The proportion of children reacting to one or more allergens rose from 15% in 1999-2000 to 24.3% in 2011-2012: a highly statistically significant change: OR=1.83, 95%CI=1.46-2.29. The pattern of allergic sensitization was similar except for a greater increasing rate of grasses over the cat allergen. Much of this difference can be attributed to an increase in the percentage of children reacting to house dust mites (*Der p1* from 10.0% to 18.3% and *Der f1 from 4.8% to 16.9%*).

Table 1. Trends in prevalence of SPT positivity in Albanian children

Skin prick tests, 9-11-year-olds	Cases_2	Percent_2	Cases_4	Percent_4	OR	LCL	UCL
Skin prick reaction 3+mm, any allergen	141	15.0	262	24.3	1.83	1.46	2.29
SPT D pteronyssinus	93	10.0	196	18.3	2.03	1.56	2.64
SPT D farinae	45	4.8	181	16.9	4.03	2.87	5.65
SPT Cat fur	34	3.6	55	5.1	1.44	0.93	2.22
SPT Alternaria	8	0.9	33	3.0	3.69	1.69	8.02
SPT Mixed grass pollen	32	3.4	63	5.9	1.77	1.14	2.73
SPT Mixed tree pollen	7	0.7	18	1.7	2.27	0.94	5.46
SPT Olive	21	2.2	20	1.9	0.83	0.45	1.54
SPT Parietaria	7	0.7	10	0.9	1.25	0.47	3.30
Total	936	100.0	1071	100.0			

Table 2 presents the association between skin prick test positivity (to any allergen) and each of the symptoms, in 1999-2000 (upper part) and 2011-2012 (lower part). Although wheeze in the last year and asthma ever were consistently more common among SPT+ children in both surveys, the indicators of more severe wheezing showed a variable pattern. Wheezing ever in the SPT+ group was more common in 2011-2012 compared to 1999-2000. Neither rhinoconjunctivitis symptoms nor eczema symptoms were associated with SPT positivity, although in the more recent survey, a lifetime history of hay fever or allergic rhinitis was more common among the SPT positives.

Visible flexural dermatitis was not associated with SPT positivity in 1999-2000, but was three times more frequent among 10-11-year-olds with positive skin prick tests in 2011-2012.

Table 2. Relationship between SPT positivity and symptoms in Albanian children

Symptom questionnaire, 9-11-year-olds, Phase II (1999-2000)	SPT+ N	SPT+ cases	SPT+ %	SPT- N	SPT- cases	SPT- %	OR	LCL	UCL
Wheeze ever	134	18	13.43	778	87	11.18	1.23	0.72	2.12
Wheeze in the past 12 months	134	11	8.21	777	28	3.60	2.39	1.16	4.93
4 or more attacks of wheeze in the past 12 months	133	2	1.50	775	3	0.39	3.93	0.65	23.74
Sleep disturbance from wheeze, 1 or more nights a week in the past 12m	133	2	1.50	773	2	0.26	5.89	0.82	42.15
Speech limited by wheeze in the past 12 months	133	1	0.75	773	1	0.13	5.85	0.36	94.08
Asthma ever	132	9	6.82	774	15	1.94	3.70	1.59	8.65
Wheeze during or after exercise in the past 12 months	131	8	6.11	759	25	3.29	1.91	0.84	4.33
Night cough in the past 12 months	132	16	12.12	759	58	7.64	1.67	0.93	3.00
Nose symptoms ever	133	39	29.32	767	221	28.81	1.03	0.68	1.54
Nose symptoms in the past 12 months	133	29	21.80	766	129	16.84	1.38	0.88	2.17
Nose and eye symptoms in the past 12 months	133	7	5.26	763	54	7.08	0.73	0.32	1.64
Nose symptoms affecting activities a lot in the past 12 months	132	2	1.52	761	13	1.71	0.89	0.20	3.97
Hayfever ever	129	1	0.78	766	25	3.26	0.23	0.03	1.72
Rash ever	130	11	8.46	766	70	9.14	0.92	0.47	1.79
Rash in the past 12 months	130	8	6.15	766	59	7.70	0.79	0.37	1.69
Flexural rash in the past 12 months	130	6	4.62	765	47	6.14	0.74	0.31	1.77
No clearance of rash in the past 12 months	130	3	2.31	764	16	2.09	1.10	0.32	3.84
Sleep disturbance from rash, 1 or more nights a week in the past 12 months	129	1	0.78	760	6	0.79	0.98	0.12	8.22
Eczema ever	132	3	2.27	770	14	1.82	1.26	0.36	4.43
Visible flexural dermatitis on skin examination	138	3	2.17	771	20	2.59	0.83	0.24	2.85
Symptom questionnaire, 9-11-year-olds, Phase IV (2011-2012)	**SPT+ N**	**SPT+ cases**	**SPT+ %**	**SPT- N**	**SPT- cases**	**SPT- %**	**OR**	**LCL**	**UCL**
Wheeze ever	251	49	19.52	828	116	14.01	1.50	1.04	2.17
Wheeze in the past 12 months	251	20	7.97	828	40	4.83	1.71	0.98	2.98
4 or more attacks of wheeze in the past 12 months	251	1	0.40	828	4	0.48	0.45	0.05	4.30
Sleep disturbance from wheeze, 1 or more nights a week in the past 12m	251	1	0.40	828	5	0.60	0.37	0.04	3.38
Speech limited by wheeze in the past 12 months	251	2	0.80	828	2	0.24	2.06	0.27	15.80
Asthma ever	251	15	5.98	828	19	2.29	2.72	1.36	5.43
Wheeze during or after exercise in the past 12 months	251	13	5.18	828	13	1.57	3.42	1.57	7.48
Night cough in the past 12 months	251	31	12.35	828	80	9.66	1.33	0.85	2.06
Nose symptoms ever	251	73	29.08	828	218	26.33	1.15	0.84	1.57
Nose symptoms in the past 12 months	251	65	25.90	828	183	22.10	1.23	0.89	1.70

Symptom questionnaire, 9-11-year-olds, Phase IV (2011-2012)	SPT+ N	SPT+ cases	SPT+ %	SPT- N	SPT- cases	SPT- %	OR	LCL	UCL
Nose and eye symptoms in the past 12 months	251	26	10.36	828	53	6.40	1.74	0.96	3.15
Nose symptoms affecting activities a lot in the past 12 months	251	1	0.40	828	10	1.21	0.29	0.04	2.31
Hayfever ever	251	19	7.57	828	29	3.50	2.24	1.24	4.07
Rash ever	251	14	5.58	828	43	5.19	1.07	0.58	2.00
Rash in the past 12 months	251	12	4.78	828	31	3.74	1.28	0.65	2.54
Flexural rash in the past 12 months	251	5	1.99	828	18	2.17	0.46	0.11	1.91
No clearance of rash in the past 12 months	251	7	2.79	828	26	3.14	0.81	0.13	4.91
Sleep disturbance from rash, 1 or more nights a week in the past 12 months	251	1	0.40	828	5	0.60	0.62	0.06	6.17
Eczema ever	251	3	1.20	828	13	1.57	0.75	0.21	2.67
Visible flexural dermatitis on skin examination	251	13	5.18	828	14	1.69	3.16	1.47	6.82

Risk factor prevalence and time trends

The prevalence of risk factors for asthma and allergic diseases, ascertained using the same questionnaire in ISAAC Phase Two (1999-2000) and the current survey (2011-2012) was obtained and the statistically significant changes are as follows (those with odds ratios >2.0 or <0.5 are asterisked):

Statistically significant *increases* in:

a) the proportion of infants breastfed for 6 months or more
b) family size, both older and younger siblings
c) exposure to day care, kindergarten or nursery school (*)
d) exposure to pet birds
e) use of gas for cooking and heating, replacing electricity and other fuels (*)
f) air conditioning, both now and in the first year of life (*)
g) loose carpets in the child's bedroom, replacing bare floors and fitted carpets
h) sealed-unit double glazing and secondary glazing (*)
i) use of synthetic fibre pillows and feather pillows, replacing other pillow types (*)
j) use of synthetic quilts and feather quilts replacing other forms of bedding (*)
k) frequency of consumption of fish, and decreased consumption meat (*)
l) frequency of green vegetable consumption at least daily
m) frequency of consumption of burgers (*)
n) frequency of consumption of fresh fruit juice (*)

Statistically significant decreases in:

o) prevalence of parental asthma and eczema
p) lifetime history of pertussis vaccination (*)
q) lifetime history of measles and BCG vaccinations
r) lifetime history of pertussis illness and measles illness (*)
s) lifetime history of worm infestation
t) bedroom sharing, both now and in the first year of life
u) exposure to pet dogs and cats, both now and in the first year of life
v) current exposure to smoking in the household
w) home dampness
x) frequency of consumption of fizzy drinks (*)

Associations of changing risk factors with skin test positivity

The "asterisked" risk factors were tabulated for SPT positive and SPT negative children in Table 3. None of these rapidly changing risk factors were significantly associated with allergic sensitization either in 1999-2000, or in 2011-2012.

Table 3. Relationship between SPT positivity and changing risk factors

Risk factor questionnaire, 9-11-year-olds, Phase II (1999-2000)	SPT+ N	SPT+ exposed	SPT+ %	SPT- N	SPT- exposed	SPT- %	OR	LCL	UCL
Child care, kindergarten or nursery school	127	90	70.87	734	537	73.16	0.89	0.59	1.35
Pertussis vaccination ever	119	93	78.15	672	542	80.65	0.86	0.53	1.38
Pertussis illness ever	126	35	27.78	696	208	29.89	0.90	0.59	1.38
Measles illness ever	127	48	37.80	701	254	36.23	1.07	0.72	1.58
Cook with gas now	125	22	17.60	727	140	19.26	0.90	0.55	1.47
Air conditioned home now	127	7	5.51	732	48	6.56	0.83	0.37	1.88
Sealed unit double-glazing in child's bedroom now	129	5	3.88	730	50	6.85	0.55	0.21	1.40
Synthetic fibre pillow now	129	26	20.16	730	149	20.41	0.98	0.62	1.57
Feather quilt now	128	15	11.72	727	91	12.52	0.93	0.52	1.66
Eats fish once a day or more	120	1	0.83	684	14	2.05	0.40	0.05	3.09
Eats burgers once a day or more	122	7	5.74	696	41	5.89	0.97	0.43	2.22
Drinks fruit juice once a day or more	123	38	30.89	702	226	32.19	0.94	0.62	1.42
Drinks fizzy drinks once a day or more	123	27	21.95	703	117	16.64	1.41	0.88	2.26
Risk factor questionnaire, 9-11-year-olds, Phase IV (2011-2012)	**SPT+ N**	**SPT+ exposed**	**SPT+ %**	**SPT- N**	**SPT- exposed**	**SPT- %**	**OR**	**LCL**	**UCL**
Child care, kindergarten or nursery school	251	232	92.43	828	744	89.86	1.38	0.82	2.32
Pertussis vaccination ever	251	106	42.23	828	318	38.41	1.17	0.88	1.56
Pertussis illness ever	251	51	20.32	828	163	19.69	1.04	0.73	1.48
Measles illness ever	251	31	12.35	828	123	14.86	0.81	0.53	1.23
Cook with gas now	251	138	54.98	828	491	59.3	0.84	0.63	1.11
Air conditioned home now	251	131	52.19	828	384	46.38	1.26	0.95	1.67
Sealed unit double-glazing in child's bedroom now	251	54	21.51	828	202	24.4	0.85	0.60	1.19
Synthetic fibre pillow now	251	108	43.03	828	329	39.73	1.15	0.86	1.52
Feather quilt now	251	85	33.86	828	279	33.7	1.01	0.75	1.36
Eats fish once a day or more	251	9	3.59	828	39	4.71	0.75	0.36	1.58
Eats burgers once a day or more	251	26	10.36	828	85	10.27	1.01	0.64	1.61
Drinks fruit juice once a day or more	251	120	47.81	828	404	48.79	0.96	0.72	1.28
Drinks fizzy drinks once a day or more	251	31	12.35	828	102	12.32	1.00	0.65	1.54

Discussion

Our study found a statistically significant increase from 15.0% to 24.3% in the prevalence of allergic sensitization in 10-11 year-olds in Tirana from 2000 to 2012. This major increase in the prevalence was attributed more to the increase of the sensitization to house dust mite allergens, specifically Dermatophagoideus pteronnyssinus and Dermatophagoideus farinae. Also, an important finding was the increase of sensitization to Alternaria, perhaps due to climate changes and also to more isolated home environments. Although it is an outdoor mould, it was found in large quantities inside the houses too (25). Despite the large increase in the prevalence of allergic sensitization, the increase in the prevalence of symptoms of asthma, rhinitis, or eczema was not at the same rate and remained still below the European average prevalence, which may be explained by the reduction in well-known risk

factors for asthma such as parental smoking, or home dampness. Also, studies suggest that atopy could be a risk factor *per se* (26), but recently atopy is considered to have different phenotypes (17) and a SPT positivity does not always predicts if a child will develop allergic disease (27). These results emphasize the difference and discrepancy between allergic sensitization and allergic disease. Our findings partially converge with the study by Rönmark et al. (12) when it comes to allergic sensitization, although the prevalence of allergic diseases had changed in Albania. The studies evaluating time trends of allergic sensitization in children show diverging results (7-11,13,14). While most studies from westernized countries showed that after thirty years of increasing prevalence of sensitization and allergies a plateau or a decrease in the prevalence is currently observed, in our study there was evidence of a significant increase in sensitization to all common allergens in the area. Another study form the former East Germany reported conflicting results as the prevalence of any allergen decreased, whereas "strong sensitization", defined as RAST _17.5 kU_L21, increased (4).
In addition, similar to many less affluent centres in ISAAC Phase Two (28-30), the association between skin test positivity and symptoms of asthma, rhinitis or eczema, or flexural dermatitis on examination, is weaker than seen in more affluent countries. Perhaps, our findings are indirectly in line with the hygiene hypotheses (31,32). According to this hypothesis, allergic sensitization should be related to lack of infections and microbial products in early age (33) due to a shift in the balance of TH cells toward TH2 cells. Parallel to the increase in allergic sensitization, we found fewer smoking parents, and an increase in breast-feeding. The decrease in respiratory infections was mainly attributable to a decrease in pertussis and measles infections, although the prevalence of pertussis vaccination has fallen too. Theoretically, vaccination in general could result in increased risk for allergic sensitization which cannot explain the increase in our study, although a double-blind study performed in Sweden (34) and a large population study in England (35) did not show any association between immunization to pertussis and allergic sensitization or allergic disease. None of these changing risk factors were significantly associated with allergic sensitization.
In conclusion, this analysis of two large cross-sectional studies of schoolchildren of the same age in the same city, Tirana, performed 12 years apart with identical methods and a high participation rate found a significant increase in the prevalence of allergic sensitization measured by SPT. In parallel, there is an increase in the prevalence of allergy symptoms, but not at the same rate as the other European countries, perhaps as a result of a lower environmental tobacco smoke, and respiratory infections. Although there was not a big increase in symptoms of allergy, the large increase in sensitization may predict a continuous increase in clinical manifestations of allergic diseases in the preteenage and teenage years.

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