Pediatr Allergy Immunol 2005: 16: 315–320

PEDIATRIC ALLERGY AND IMMUNOLOGY
DOI: 10.1111/j.1399-3038.2005.00276.x

Modest increase in seasonal allergic rhinitis and eczema over 8 years among Estonian schoolchildren

Annus T, Riikjärv M-A, Rahu K, Björkstén B. Modest increase in seasonal allergic rhinitis and eczema over 8 years among Estonian schoolchildren.
Pediatr Allergy Immunol 2005: 16: 315–320. © 2005 Blackwell Munksgaard

We studied time trends in the prevalence of asthma and allergic diseases in Estonian children born before and after the collapse of the Soviet Union, as this event markedly altered the lifestyle in Estonia. Two identical cross-sectional studies were performed as part of phase I and phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Children, aged 6–7 yr (n = 3070 in 1993–94 and 2383 in 2001–02) and 13–14 yr (n = 3476 and 3576, respectively), completed ISAAC core-written questionnaires, and 13–14-yr olds (n = 3427 and 3259, respectively) also video questionnaires. The prevalence of respiratory symptoms was mostly similar in the two studies. Despite this, the prevalence of diagnosed asthma increased. This was probably due to modified diagnostic criteria and increased awareness. Furthermore, the prevalence of rhinitis during the pollen season increased, e.g., rhinitis in May from 1.7% to 3.5%; sex-adjusted prevalence odds ratio (POR) 2.09 (95% confidence interval 1.47–2.96) in 6–7-yr olds, and from 2.6% to 5.5%; POR 2.22 (1.72–2.87) in 13–14-yr olds. The prevalence of flexural dermatitis also increased from 12.0% to 13.5%; POR 1.20 (1.02–1.41) in 6–7-yr olds, and from 7.7% to 9.4%; POR 1.26 (1.07–1.50) in 13–14-yr olds. The increase was similar in children born before and after the regaining of Estonian independence, indicating that the influence of factors related to a Western lifestyle and affecting the prevalence of allergic symptoms is not restricted to infancy, but may be operative throughout childhood.

Triine Annus[1,2], Mall-Anne Riikjärv[2], Kaja Rahu[3,4] and Bengt Björkstén[5]

[1]Tartu University Children's Hospital, Tartu, Estonia, [2]Tallinn Children's Hospital, Tallinn, Estonia, [3]Department of Epidemiology and Biostatistics, National Institute for Health Development, Tallinn, Estonia, [4]Estonian Centre of Excellence in Behavioural and Health Sciences, Tallinn, Estonia, [5]Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Key words: asthma; allergic rhinitis; eczema; time trend; International Study of Asthma and Allergies in Childhood

Dr Triine Annus, Tallinn Children's Hospital Central Policlinic, Ravi 27, 10138 Tallinn, Estonia
Tel.: +372 6207 347
Fax: +372 6207 324
E-mail: triine.annus@mail.ee

Accepted 21 February 2005

The prevalence of asthma and allergic diseases has increased markedly in industrialized countries (1) where these diseases are significantly more common than in developing countries, as shown by the International Study of Asthma and Allergies in Childhood (ISAAC) (2, 3). These findings indicate a relationship between lifestyle in affluent industrialized countries and the risk of allergy.

The fall of the socialist system in Eastern European countries has resulted in marked environmental changes and a rapidly altered lifestyle. Therefore, an increase in the prevalence of asthma and allergic diseases would be expected. Indeed, studies from East Germany have revealed a rapid rise in the prevalence of asthma and allergies after the reunification of Germany (4, 5), while no such increase was found among Estonian schoolchildren between 1992 and 1997 (6). The difference between the two countries may be due to the fact that the reunification of Germany rapidly resulted in pronounced changes, while in Estonia, the transition was slower due to severe economic constraints.

It is suggested that the environmental risk factors associated with asthma and allergies are particularly important during the first years of life (7, 8). Therefore, we hypothesized that the increase in the prevalence of asthma and allergic diseases would be more pronounced in children

who were born in Estonia well after the beginning of the political and economical changes than in children born during the time of the Soviet Union (SU). The aim of the present study was to compare the time trends in the prevalence of asthma and allergic diseases in Estonian schoolchildren born before and after the collapse of the SU.

Methods

Subjects

The study design adhered to the ISAAC phase I and phase III protocols (9–11), using data from two identical cross-sectional questionnaire-based prevalence studies 8 yr apart (phase I 1993–94, phase III 2001–02). All Estonian language schools and daycare centers in Tallinn participated in both studies. The studies targeted all children in those two grades with the highest proportion of 6–7- or 13–14-yr-old children.

Questionnaire

The standardized ISAAC core-written questionnaires, inquiring about lifetime and current symptoms and severity of wheezing, rhinitis without a common cold, and eczema, were distributed in schools. The questionnaires were completed by the parents in the younger age group and by the children in the older age group. The data were collected between September and May in both studies. The participation rates were 90.8% (3070/3382) in the younger and 88.7% (3506/3953) in the older age group in 1993–94. In 2001–02 the participation rates were 85.7% (2388/2786) and 93.4% (3605/3860) in the younger and the older age group, respectively. The number of 6–7-yr-old participants decreased over the 8-yr study period due to the fall in birth rate [crude birth rate 16.2 in 1987 and 9.4 in 1995 (12)]. In addition, the 13–14-yr-old children completed the ISAAC video questionnaire presenting asthma symptoms; the participation rate was 87.4% (3454/3953) in 1993–94 and 85.1% (3284/3860) in 2001–02. Respondents who were outside of the 5–9 and 12–15-yr age range were excluded from the analysis, i.e., no children in the younger and 30 in the older age group in 1993–94 and five children in the younger and 29 in the older age group in 2001–02. The distribution of analyzed respondents by age and sex is shown in Table 1.

Table 1. Distribution of respondents by age and sex

	1993–94		2001–02	
Age (yr)	Boys	Girls	Boys	Girls
6–7-yr olds				
5	92 (6.1)	94 (6.1)	22 (1.8)	17 (1.5)
6	672 (44.2)	720 (46.5)	473 (38.6)	461 (39.8)
7	682 (44.9)	692 (44.6)	646 (52.8)	622 (53.7)
8	74 (4.9)	44 (2.8)	83 (6.8)	59 (5.1)
Total	1520 (100.0)	1550 (100.0)	1224 (100.0)	1159 (100.0)
13–14-yr olds				
Questionnaire				
12	79 (4.6)	66 (3.7)	129 (7.2)	183 (10.2)
13	679 (39.9)	753 (42.4)	776 (43.6)	868 (48.3)
14	798 (46.9)	819 (46.1)	742 (41.7)	664 (37.0)
15	145 (8.5)	137 (7.7)	133 (7.5)	81 (4.5)
Total	1701 (100.0)	1775 (100.0)	1780 (100.0)	1796 (100.0)
Video questionnaire				
12	76 (4.5)	65 (3.7)	119 (7.3)	177 (10.9)
13	671 (39.9)	741 (42.5)	697 (42.6)	767 (47.2)
14	793 (47.1)	807 (46.2)	698 (42.7)	604 (37.2)
15	142 (8.4)	132 (7.6)	121 (7.4)	76 (4.7)
Total	1682 (100.0)	1745 (100.0)	1635 (100.0)	1624 (100.0)

Values are expressed as n (%).

Statistical analysis

Data were entered and checked for coding errors and inconsistencies using the Microsoft database management system FoxPro 6.0. Statistical analyses were performed using Stata 8.0 statistical package. According to ISAAC recommendations, the prevalence rates based on questionnaire responses were calculated by dividing the number of affirmative responses to each question by the total number of completed questionnaires (conservative prevalence estimates). Missing or inconsistent responses (1.6% and 2.7% in the younger and 2.6% and 3.2% in the older age group in 1993–94 and in 2001–02, respectively) were excluded from bivariate analyses. To compare the differences in prevalence rates between studies, prevalence odds ratios (POR) with 95% confidence intervals (CI) and chi-squared tests were employed. Because of sex-related differences in the prevalence rates and time trends, sex-adjusted estimates of POR were obtained using logistic regression analyses.

Ethical considerations

The study was approved by the Tallinn Medical Research Ethics Committee.

Results

The prevalence and severity of most of the questionnaire-reported asthma symptoms were similar in the two studies performed 8 yr apart (Table 2). The only significant increase was seen for lifetime prevalence of wheezing among

Table 2. Prevalence rates, sex-adjusted prevalence odds ratios (POR) and 95% confidence intervals (CI) of allergic symptoms among 6–7- and 13–14-yr-old Estonian children (2001–02 vs. 1993–94)

	6–7-yr olds				13–14-yr olds			
	1993–94 (N = 3070)	2001–02 (N = 2383)	Adjusted POR (95% CI)	p	1993–94 (N = 3476)	2001–02 (N = 3576)	Adjusted POR (95% CI)	p
Asthma								
Lifetime prevalence								
Wheezing	582 (19.0)	541 (22.7)	1.25 (1.10–1.43)	0.001	661 (19.0)	719 (20.1)	1.07 (0.95–1.20)	0.291
Diagnosed asthma	43 (1.4)	98 (4.1)	3.42 (2.38–4.92)	<0.001	113 (3.3)	169 (4.7)	1.55 (1.22–1.98)	<0.001
12-month prevalence								
Wheezing	285 (9.3)	230 (9.7)	1.05 (0.87–1.26)	0.615	297 (8.5)	330 (9.2)	1.09 (0.93–1.29)	0.286
≥4 attacks	45 (1.5)	48 (2.0)	1.39 (0.92–2.09)	0.118	54 (1.6)	74 (2.1)	1.36 (0.95–1.94)	0.090
Exercise-induced wheezing	50 (1.6)	47 (2.0)	1.21 (0.81–1.81)	0.344	321 (9.2)	322 (9.0)	0.96 (0.82–1.13)	0.665
Speech-limiting wheezing	22 (0.7)	19 (0.8)	1.11 (0.60–2.05)	0.744	46 (1.3)	43 (1.2)	0.91 (0.60–1.39)	0.674
Sleep-disturbing wheezing	142 (4.6)	113 (4.7)	1.03 (0.80–1.33)	0.817	111 (3.2)	109 (3.0)	0.96 (0.73–1.26)	0.764
Night cough	360 (11.7)	323 (13.6)	1.18 (1.00–1.38)	0.049	505 (14.5)	418 (11.7)	0.77 (0.67–0.89)	<0.001
Rhinitis								
Lifetime prevalence								
Rhinitis	461 (15.0)	436 (18.3)	1.27 (1.10–1.46)	0.001	1170 (33.7)	1236 (34.6)	1.04 (0.94–1.15)	0.438
12-month prevalence								
Rhinitis	357 (11.6)	311 (13.1)	1.15 (0.97–1.35)	0.101	811 (23.3)	875 (24.5)	1.07 (0.96–1.20)	0.215
Rhinoconjunctivitis	119 (3.9)	112 (4.7)	1.22 (0.94–1.59)	0.139	184 (5.3)	261 (7.3)	1.41 (1.16–1.72)	<0.001
Interference with activities	248 (8.1)	205 (8.6)	1.07 (0.88–1.30)	0.474	499 (14.4)	625 (17.5)	1.27 (1.11–1.44)	<0.001
Eczema								
Lifetime prevalence								
Itchy rash	519 (16.9)	525 (22.0)	1.40 (1.22–1.61)	<0.001	529 (15.2)	691 (19.3)	1.34 (1.18–1.52)	<0.001
12-month prevalence								
Itchy rash	388 (12.6)	407 (17.1)	1.44 (1.24–1.67)	<0.001	362 (10.4)	532 (14.9)	1.51 (1.31–1.74)	<0.001
Flexural rash	367 (12.0)	322 (13.5)	1.20 (1.02–1.41)	0.025	267 (7.7)	335 (9.4)	1.26 (1.07–1.50)	0.006
Sleep-disturbing rash	94 (3.1)	86 (3.6)	1.19 (0.88–1.60)	0.249	85 (2.4)	96 (2.7)	1.11 (0.83–1.50)	0.476

Values are expressed as n (%).

Table 3. Twelve-month prevalence rates, prevalence odds ratios (POR) and 95% confidence intervals (CI) of asthma symptoms from the video questionnaire among 13–14-yr-old Estonian children (2001–02 vs. 1993–94)

	Boys				Girls			
	1993–94 (N = 1682)	2001–02 (N = 1635)	POR (95% CI)	p	1993–94 (N = 1745)	2001–02 (N = 1624)	POR (95% CI	p
Wheezing at rest	26 (1.5)	33 (2.0)	1.31 (0.78–2.21)	0.303	45 (2.6)	39 (2.4)	0.93 (0.60–1.44)	0.756
Exercise-induced wheezing	55 (3.3)	111 (6.8)	2.17 (1.56–3.02)	<0.001	130 (7.5)	107 (6.6)	0.88 (0.68–1.15)	0.350
Sleep-disturbing wheezing	13 (0.8)	19 (1.2)	1.51 (0.74–3.07)	0.253	27 (1.5)	27 (1.7)	1.07 (0.62–1.84)	0.799
Sleep-disturbing cough	54 (3.2)	81 (5.0)	1.58 (1.11–2.25)	0.011	155 (8.9)	148 (9.1)	1.03 (0.81–1.30)	0.813
Severe wheezing	10 (0.6)	12 (0.7)	1.24 (0.53–2.88)	0.618	22 (1.3)	35 (2.2)	1.73 (1.01–2.95)	0.047

Values are expressed as n (%).

6–7-yr-old children, whereas the prevalence of current night cough decreased in the older age group. When boys and girls were analyzed separately, the results were similar, except for the 12-month prevalence of ≥4 attacks of wheezing among 13–14-yr olds, which increased in boys, i.e., from 1.1% to 2.3% (POR 2.23, 95% CI 1.25–4.14), but not in girls, i.e., from 2.0 to 1.8 (POR 0.92, 95% CI 0.55–1.52). However, the prevalence of current asthma symptoms derived from the video questionnaire increased in boys, reaching statistical significance for exercise-induced wheeze and sleep-disturbing cough (Table 3). In girls, severe wheeze was the only increasing symptom from the video.

Compared with the prevalence of wheeze and cough, there was a marked increase in the prevalence of diagnosed asthma (Table 2). The rise was more pronounced in the younger age group and among boys, i.e., from 1.4% to 5.1% (POR 4.18, 95% CI 2.51–7.18) in 6–7-yr-old boys, from 1.4% to 3.1% (POR 2.63, 95% CI 1.49–4.77) in 6–7-yr-old girls, from 3.7% to 6.0% (POR 1.71, 95% CI 1.23–2.40) in 13–14-yr-old

boys, and from 2.8% to 3.5% (POR 1.35, 95% CI 0.91–2.01) in 13–14-yr-old girls. There was also an increase in the proportion of children with diagnosed asthma among 6–7-yr-old boys with current wheeze, i.e., from 9.4% in the first study to 29.7% in the second study (POR 4.16, 95% CI 2.08–8.61). Similar trends were recorded in the other groups, i.e., from 8.7% to 17.6% (POR 2.29, 95% CI 0.96–5.67) in younger girls, from 15.2% to 23.1% (POR 1.70, 95% CI 0.88–3.32) in older boys and from 13.3% to 16.6% (POR 1.28, 95% CI 0.68–2.44) in older girls, respectively.

There was a moderate increase in symptoms of rhinitis, reaching statistical significance for lifetime prevalence among 6–7-yr olds (Table 2). In the older age group there was an increase in the prevalence of rhinoconjunctivitis and severe rhinitis, interfering with daily activities.

The peak season of nasal symptoms changed significantly in both age groups. When the prevalence of rhinitis was determined separately for each month of the last year, rhinitis was markedly more common in the winter months than in the summer months in the first study. In the second study, the prevalence of spring and summer rhinitis increased, while a decrease was observed for the proportion of 6–7-yr-old children who reported having nasal symptoms in November and December (Fig. 1). The changes were similar in boys and girls (data not shown).

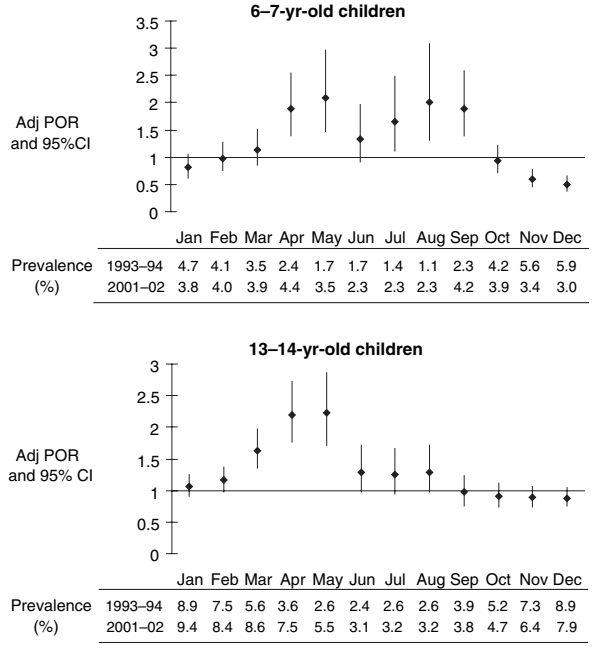

Fig. 1. Twelve-month prevalence rates, sex-adjusted prevalence odds ratios (adj POR) and 95% confidence intervals (CI) of seasonal rhinitis in 6–7- and 13–14-yr-old Estonian schoolchildren (2001–02 vs. 1993–94).

The prevalence of lifetime and current symptoms of eczema increased in both age groups (Table 2). The rise was similar in both sexes (data not shown). However, the increase in severe, sleep-disturbing rash was not statistically significant. Among 13–14-yr-old girls with current itchy rash, the proportion of those complaining about disturbed sleep fell from 23.8% to 15.4% (POR 0.59, 95% CI 0.37–0.93).

The 12-month prevalence of at least one symptom of potentially allergic origin (wheeze, rhinoconjunctivitis, and/or flexural itchy rash) increased among girls, i.e., from 20.2% to 23.6% (POR 1.26, 95% CI 1.04–1.52) in 6–7-yr olds and from 19.5% to 23.6% (POR 1.30, 95% CI 1.10–1.54) in 13–14-yr olds. This was not the case in boys, i.e., 22.0% in the first and 23.3% in the second study (POR 1.13, 95% CI 0.94–1.36) in the younger boys and 15.8% and 17.5% (POR 1.14, 95% CI 0.95–1.37) in the older boys, respectively.

Discussion

Using identical methods in two studies 8 yr apart, we found a modest increase in the prevalence of allergic disorders among Estonian schoolchildren. The increase was more pronounced for symptoms of eczema, while most of the asthma symptoms did not change, nor did the prevalence of rhinitis. However, a marked change occurred in the seasonal variation of rhinitis. In the first study, the prevalence of rhinitis was three to four times higher in the winter months than in the summer months. This was in concordance with the results of the ISAAC phase I study from other post-socialist Eastern European countries, where the peak incidence of nasal symptoms was recorded during the winter months, while in Sweden and Finland the highest figures were recorded in April–July (13). Over an 8-yr period, the prevalence of rhinitis in Estonian children decreased in the winter months, while the prevalence of spring and summer rhinitis increased. The increase coincides with the pollen season of the main allergenic plants in Estonia, i.e., alder and hazel in March and April, birch in May, grasses in June and July, and mugwort in August and September. The change in the prevalence of seasonal rhinitis is not explained by the season of the collection of the data, as this was done in the same months in both studies. These findings, together with the rise in rhinoconjunctivitis, indicate a true increase in the prevalence of allergic rhinitis while non-allergic rhinitis seems to decrease.

Our results are similar to those reported in some studies from the former East Germany where an increasing prevalence of hay fever but not of asthma was observed 4–5 yr after the reunification of Germany (4, 14). However, other studies showed a parallel increase in asthma and the other allergic symptoms among East German children (5). Interestingly, a recent ISAAC phase III study from Hong Kong also found an increase in rhinitis and eczema, but not in asthma (15). It has been hypothesized that environmental factors may influence the risk of asthma and hay fever at different ages (4) and that a rising trend in the prevalence of asthma may take longer time (16). Remarkable economic changes took place in Estonia between 1993 and 2001, e.g., average monthly gross wages increased from 68 to 353 EUR and per capita gross domestic product in current prices from 976 to 4520 EUR, respectively (17, 18). However, the living conditions are still not comparable with those in Western Europe. For example, Estonian homes are significantly more crowded (19) and have higher endotoxin levels in house dust (20) than Swedish homes. The markedly slower transition to a Western lifestyle may explain the less pronounced increase in allergic diseases and the lack of change in the prevalence of wheezing in Estonian children compared with East German children.

An alternative explanation to the absence of an increase in wheezing may arise from a possible change in the proportions of different phenotypes of asthma. If non-allergic wheezing has decreased in Estonian children to a similar extent as non-allergic rhinitis, while allergic wheezing has increased, the overall prevalence of wheezing could remain unchanged. Furthermore, a slight rise in asthma among Estonian boys cannot be excluded, as the prevalence of symptoms according to the video questionnaire tended to increase in boys.

In contrast to reported wheezing, the prevalence of diagnosed asthma increased markedly. This finding is probably due to an increased awareness and to changes in diagnostic procedures, rather than a genuine increase in prevalence. This is also suggested by the significantly increased proportion of diagnosed asthma among children with current wheeze. Virus-related wheezing episodes in young children are increasingly labeled as asthma, which may explain the more pronounced inconsistency between the time trends of reported wheezing and diagnosed asthma in the younger age group. Independent of the reasons, an increased awareness leads to improved asthma management and thus to a better controlled disease (21, 22), which also may partly explain the absence of a parallel increase in asthma-like symptoms and diagnosed asthma. Our findings underline the importance of exploring prevalence of symptoms rather than diagnosis in epidemiological surveys and studies of time trends.

The increase in allergy-related symptoms was more pronounced among girls in both age groups. Previous trend studies have also found a greater increase in asthma and allergies among girls compared with boys (23–25), suggesting that girls may be more susceptible to environmental risk factors. However, the increase in the prevalence of diagnosed asthma was higher in boys in our study and the proportion of children with diagnosed asthma among wheezers was higher in boys than in girls. Similar findings have been reported in the ISAAC studies from Belgium and Germany, where asthma symptoms were more common in girls, whereas the prevalence of diagnosed asthma was higher among boys (23, 26). These observations may reflect either under-reporting of symptoms by boys or under-diagnosis of asthma in girls as reported in several studies among schoolchildren (27, 28).

In a previous study of Estonian schoolchildren, using data from 1992–93 and 1996–97, we found no increase in the prevalence of atopic sensitization, asthma and allergic diseases (6). The children, studied in 1996–97, had spent their first 4–5 yr of life under Soviet conditions, and were exposed to a changing lifestyle only during the following 6 yr. The absence of the increase in the prevalence of allergic diseases in that study could indicate that the environmental changes during the first years of Estonian independence were too modest to affect the risk of allergy. Alternatively, it could support the notion that the first years of life are crucial for the development of allergy (7, 8). This hypothesis, however, has been challenged recently. The available evidence does not support the critical importance of early life immune deviation in preventing the development of allergy (29).

The first phase of the present study was performed 2 yr after the restitution of independence, while the second took place 10 yr after the beginning of the changes toward western living conditions. Thus, the younger participants in the second phase of the study were born well after the beginning of changes, whereas the older children spent their first 3–4 yr of life in the SU. However, the increase in allergic symptoms was similar in both age groups indicating that the environmental factors related to the development of allergy may be operative throughout childhood.

In conclusion, the prevalence of allergic disorders has increased slightly among Estonian schoolchildren during the years following the collapse of the SU. As the increase is similar in children born before and after the beginning of changes, the influence of potential risk factors related to a Western lifestyle seems not to be restricted to infancy.

Acknowledgments

This study was supported by grants from the Swedish Heart and Lung Association and the Swedish Foundation for Allergy and Caring Sciences. The research of K.R. was financed by the Estonian Ministry of Education and Science (target funding 01921112s02).

References

1. Sly RM. Changing prevalence of allergic rhinitis and asthma. Ann Allergy Asthma Immunol 1999: 82: 233–48.
2. ISAAC. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). Eur Respir J 1998: 12: 315–35.
3. ISAAC. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 1998: 35: 1225–32.
4. von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U. Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. Lancet 1998: 351: 862–6.
5. Heinrich J, Hoelscher B, Frye C, Meyer I, Wjst M, Wichmann HE. Trends in prevalence of atopic diseases and allergic sensitization in children in Eastern Germany. Eur Respir J 2002: 19: 1040–6.
6. Riikjärv MA, Annus T, Bråbäck L, Rahu K, Björkstén B. Similar prevalence of respiratory symptoms and atopy in Estonian schoolchildren with changing lifestyle over 4 yrs. Eur Respir J 2000: 16: 86–90.
7. Björkstén B. Risk factors in early childhood for the development of atopic diseases. Allergy 1994: 49: 400–7.
8. Holt PG. Postnatal maturation of immune competence during infancy and childhood. Pediatr Allergy Immunol 1995: 6: 59–70.
9. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 1995: 8: 483–91.
10. ISAAC Manual, 2nd edn. Auckland/Münster: ISAAC, 1993.
11. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, on behalf of the ISAAC Steering Committee and the ISAAC Phase Three Study Group. ISAAC Phase Three Manual. Auckland: ISAAC, 2000.
12. Population 2001. Tallinn: Statistical Office of Estonia, 2002.
13. Björkstén B, Dumitrascu D, Foucard T, et al. Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. Eur Respir J 1998: 12: 432–7.
14. Weiland SK, von Mutius E, Hirsch T, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. Eur Respir J 1999: 14: 862–70.
15. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (Phase 3 International Study of Asthma and Allergies in Childhood). Pediatr Allergy Immunol 2004: 15: 72–8.
16. Matricardi PM. Prevalence of atopy and asthma in eastern vs. western Europe: why the difference? Ann Allergy Asthma Immunol 2001: 87 (Suppl. 3): 24–7.
17. Statistical Yearbook of Estonia 1994. Tallinn: Statistical Office of Estonia, 1994.
18. Statistical Yearbook of Estonia 2002. Tallinn: Statistical Office of Estonia, 2002.
19. Annus T, Björkstén B, Mai X-M, et al. Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren. Clin Exp Allergy 2001: 31: 1846–53.
20. Böttcher MF, Björkstén B, Gustafson S, et al. Endotoxin levels in Estonian and Swedish house dust and atopy in infancy. Clin Exp Allergy 2003: 33: 295–300.
21. Goldman M, Rachmiel M, Gendler L, Katz Y. Decrease in asthma mortality rate in Israel from 1991–1995: is it related to increased use of inhaled corticosteroids? J Allergy Clin Immunol 2000: 105: 71–4.
22. Kumana CR, Kou M, Lauder IJ, Ip MS, Lam WK. Increasing use of inhaled steroids associated with declining asthma mortality. J Asthma 2001: 38: 161–7.
23. Maziak W, Behrens T, Brasky TM, et al. Are asthma and allergies in children and adolescents increasing? Results from ISAAC phase I and phase III surveys in Munster, Germany. Allergy 2003: 58: 572–9.
24. Venn A, Lewis S, Cooper M, Hill J, Britton J. Increasing prevalence of wheeze and asthma in Nottingham primary schoolchildren 1988–1995. Eur Respir J 1998: 11: 1324–8.
25. Selnes A, Bolle R, Holt J, Lund E. Cumulative incidence of asthma and allergy in north-Norwegian schoolchildren in 1985 and 1995. Pediatr Allergy Immunol 2002: 13: 58–63.
26. Wieringa MH, Weyler JJ, Van Bever HP, Nelen VJ, Vermeire PA. Gender differences in respiratory, nasal and skin symptoms: 6–7 versus 13–14–year-old children. Acta Paediatr 1999: 88: 147–9.
27. Siersted HC, Boldsen J, Hansen HS, Mostgaard G, Hyldebrandt N. Population based study of risk factors for underdiagnosis of asthma in adolescence: Odense schoolchild study. BMJ 1998: 316: 651–5.
28. Kuhni CE, Sennhauser FH. The Yentl syndrome in childhood asthma: risk factors for undertreatment in Swiss children. Pediatr Pulmonol 1995: 19: 156–60.
29. Kemp A, Björkstén B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. Pediatr Allergy Immunol 2003: 14: 74–80.