

Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren

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Summary

Background The prevalence of asthma and allergic diseases is significantly lower in post socialist Eastern Europe than in Western industrialized countries. The reason for this difference is largely unknown. Different types of childhood wheezing could be related to different risk factors. **Objective** To compare the prevalence of respiratory symptoms, asthma and atopic diseases among Estonian and Swedish schoolchildren and to evaluate characteristics for wheezing in the two countries.

Methods In a prevalence study, population-based random samples of 10–11-year-old schoolchildren in Tallinn ($n = 979$), Estonia and in Linköping ($n = 911$) and Östersund ($n = 1197$), Sweden were studied by a parental questionnaire and skin prick tests (SPT). All 275 children with wheeze in the past 12 months and 710 randomly selected controls within the original cohorts were invited to a case-control study involving a parental questionnaire, examination for flexural dermatitis and bronchial challenge with hypertonic saline. The study adhered to the International Study of Asthma and Allergies in Childhood (ISAAC) Phase II protocol.

Results The prevalence of current wheezing was similar (8–10%) in the three centres, while diagnosed asthma and atopic symptoms were more common in Sweden and cold-related respiratory symptoms were more prevalent in Estonia. Frequent wheezing was more common in Sweden than in Estonia (but significantly so only in Östersund). Wheezing children in Sweden had a high rate of positive SPT (49% in Linköping and 58% in Östersund) bronchial hyper-responsiveness (BHR) (48% in Linköping and Östersund) and anti-asthmatic treatment (63% in Linköping and 81% in Östersund). In Estonia, the proportion of wheezing children with positive SPT, BHR and anti-asthmatic treatment was only 26%, 13% and 17%, respectively. Domestic crowding was inversely related to wheezing in one of the study areas (Östersund). The mean baseline forced expiratory volume in one second (FEV_1) was higher in Estonia than in Sweden, both in wheezing and non-wheezing children.

Conclusions Our study suggested that although wheezing symptoms were equally common in Estonia and Sweden, they were less severe in Estonia. More frequent symptoms and a high rate of atopy, BHR and anti-asthmatic medication characterized wheezing children in Sweden. In contrast, BHR, atopy and medication were uncommon among wheezing children in Estonia.

Keywords: schoolchildren, wheezing, allergic diseases, International Study of Asthma and Allergies in Childhood (ISAAC), risk factors, bronchial challenge

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Introduction

The prevalence of asthma and allergic diseases has increased markedly in Western industrialized countries over the past few decades [1]. There is also a substantial (20- to 60-fold) world-wide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and eczema, as shown by the International Study of Asthma and Allergies in Childhood (ISAAC) [2]. In this study, the prevalence of current wheezing varied in schoolchildren from 33% to 2%, with declining prevalence from North to South and from West to East in Europe [2].

The striking geographical differences and the short period over which these changes have occurred have brought attention to environmental factors, which might explain the difference. Suggested factors include indoor climate [3], family size [4], childhood infections [5], exposure to tobacco smoke [1]. None of these factors can explain the geographical differences, however. Furthermore, recent studies suggest that there are different types of childhood wheezing, which could be related to different risk factors [6].

The prevalence of asthma, allergic diseases and atopic sensitization is significantly lower in Estonia than in Sweden, both among schoolchildren [7] and young adults [8,9], while the risk factors are largely similar [10,11].

The aim of this study, which was undertaken as part of ISAAC Phase II study, was to compare the prevalence of respiratory symptoms, asthma and atopic diseases among Estonian and Swedish schoolchildren and to assess some potential risk factors and characteristics for wheezing in the two countries.

Methods

Study area

The studies were conducted in Tallinn, which is the capital of Estonia, and in two towns in Sweden, e.g. Linköping and Östersund. Tallinn (420 470 inhabitants in 1997) is situated in northern Estonia on the coast of the Baltic Sea (latitude 59 °), Linköping (132 089 inhabitants in 1997) is a university town in southern Sweden (latitude 58 °) and Östersund (59 188 inhabitants in 1997) is an administrative centre in northern Sweden (latitude 61 °). The climate is maritime in Tallinn and Linköping and continental in Östersund. The annual mean temperatures are 4.8 °C, 6.1 °C, and 2.5 °C, and the annual precipitation 609, 517, and 484 mm in Tallinn, Linköping, and Östersund, respectively.

Prevalence study

The study design adhered to the ISAAC Phase II protocol

[12]. Clusters of children were randomly selected in each centre for the study, using schools as sampling units. In Tallinn, 20 schools were selected among the Estonian language schools. In Linköping, the survey involved 15 schools and in Östersund, all 25 schools in the area were selected due to the lower population. All 10–11-year-old children in the targeted schools were invited to participate in the initial survey, which included a standardized questionnaire to parents and skin prick test.

The questionnaires, inquiring about symptoms of wheezing, rhinoconjunctivitis and eczema, were distributed in the winter 1996/1997. The response rate was 85% (979/1158) in Tallinn, 82% (911/1115) in Linköping, and 86% (1197/1390) in Östersund.

Skin prick tests were carried out according to the ISAAC Phase II protocol with standardized extracts (Soluprick SQ, ALK, Hørsholm, Denmark) of *Dermatophagoides pteronyssinus*, *D. farinae*, cat and dog dander, birch pollen, timothy pollen, and *Alternaria tenuis*. Extracts of the same batch were used in all three towns. All field workers performed a series of SPTs with histamine before the onset of the study, until the coefficient of variation was less than 20%. The quality of the test was checked during the field work according to the ISAAC manual [12]. The tests were carried out in 1997, before the pollen season. The percentage of children participating in the SPTs was 56% (643/1158) in Tallinn, 77% (859/1115) in Linköping and 71% (992/1390) in Östersund.

Case-control study

All children with a history of wheeze in the past 12 months, as reported in the parental questionnaire, and a random sample of non-wheezing children from the original cohorts were invited to a case-control study, which included a parental questionnaire, examination for flexural dermatitis and bronchial challenge with hypertonic saline. This study was conducted outside the pollen season in 1998 in all the three centres. The participation rates and anthropometric data are shown in Table 1. The bronchial challenges of wheezers and non-wheezers were evenly distributed over the study period in Tallinn and Östersund. In Linköping, however, 75% of the wheezing children were challenged between February and April in 1998 whereas 94% of the non-wheezers were challenged between September 1998 and February 1999, which explains the differences in their heights and weights.

The parental questionnaire focused on lifestyle and home environment, including size and type of the dwelling, exposure to environmental tobacco smoke, home dampness, family size, and childhood infections. It also comprised asthma management and current treatment.

Examination for flexural dermatitis was performed

Table 1. Case control study: Participation rate and anthropometric data

	Tallinn		Linköping		Östersund	
	Wheezing	Non-wheezing	Wheezing	Non-wheezing	Wheezing	Non-wheezing
Invited	81	259	72	207	122	244
Questionnaire on risk factors	67 (83%)	227 (88%)	62 (86%)	143 (69%)	109 (89%)	170 (70%)
Baseline spirometry	56 (69%)	188 (73%)	59† (82%)	125 (60%)	109‡ (89%)	171† (70%)
Bronchial challenge*	56 (69%)	184 (73%)	56 (81%)	117 (57%)	77 (63%)	135 (55%)
Bronchial challenge or reversibility test	56 (69%)	188 (73%)	58 (81%)	118 (57%)	94 (77%)	139 (57%)
Mean age (SD)§	12.3 (0.5) years	12.2 (0.5) years	12.3 (0.7) years	12.8 (0.6) years	12.2 (0.6) years	12.3 (0.6) years
Male/female	25/31	75/113	27/32	68/57	63/46	87/84
Mean height (SD)§	156 (7.8) cm	155 (7.5) cm	154 (6.9) cm	158 (8.0) cm	154 (7.3) cm	155 (8.0) cm
Mean weight (SD)§	43.7 (9.2) kg	43.2 (9.1) kg	47.8 (10.6) kg	49.3 (11.9) kg	46.4 (10.6) kg	44.8 (9.0) kg

*The challenge was terminated after a fall in FEV₁ > 15% or after a total inhalation time of 15.5 min.

†One child with FEV₁ at baseline < 75%.

‡Four children with FEV₁ at baseline < 75%.

§SD, standard deviation.

according to an illustrated manual [12]. The presence or absence of signs of dermatitis were recorded for any of the following areas [1]: around the eyes [2], around the sides and front of the neck [2], fronts of elbows [3], the wrists [4], behind the knees, and [5] fronts of ankles.

Bronchial responsiveness was assessed by changes in forced expiratory volume in one second (FEV₁) after inhalation of 4.5% hypertonic saline according to the ISAAC protocol [12]. Children were asked to withhold short-acting bronchodilators for 6 h and long-acting bronchodilators for 12 h prior to test. Baseline and postchallenge FEV₁ were measured by MasterScope Version 4.3 (Jäger, Würzburg, Germany). For the baseline FEV₁, the best of three measurements was chosen. The children inhaled 4.5% saline solution nebulized via an ultrasonic nebulizer DeVilbiss Ultraneb 2000 (DeVilbiss, Somerset, WI, USA) during progressively increasing inhalation periods of 0.5, 1, 2, 4, and 8 min. Bronchial hyper-responsiveness (BHR) was defined as a decline in FEV₁ of 15% or greater as compared with the baseline during the challenge after the total cumulative inhalation time of 15.5 min or less. If the baseline FEV₁ was less than 75% of predicted, a bronchial reversibility test was performed instead of a challenge. A positive reversibility test was defined as an increase of FEV₁ of 15% or more after two inhalations of 200 µg Salbutamol. The field

workers for BHR study were trained at the ISAAC Western Europe centre in Munich and used the same equipment in each town.

Statistical analysis

Data entry, checking for coding errors and inconsistencies and calculation of prevalence rates were performed using the microsoft database management system FOX.PRO. Prevalence rates based on questionnaire responses were calculated by dividing the number of affirmative responses by the number of those who answered the respective question. Statistical analyses were performed using statistical software program STATA. To compare the differences in prevalence rates between groups, Chi-squared tests and odds ratios (OR) with 95% confidence intervals (CI) were employed. Univariate variance analyses was used to determine adjusted differences in baseline FEV₁ mean value between the groups. The analyses of variance was also used to obtain an estimate of the predicted value for the individuals. There was no adjustment for multiple comparisons.

Ethical considerations

The study was approved by the institutional review boards

of Tallinn Institute of Experimental and Clinical Medicine, and Linköping and Umeå Universities. A written parental consent was obtained separately for each element of the study.

Results

Questionnaire-reported symptoms of rhinoconjunctivitis and eczema, as well as at least one positive SPT were more common in the two Swedish towns than in Tallinn (Table 2). On the other hand, cold related cough and phlegm were reported more frequently in Estonia.

The prevalence of current and ever wheezing were similar in the two countries. The prevalence of children with disturbed sleep or speech limitations due to wheezing were also similar in the three study centres (data not shown). However, frequent wheezing (at least four attacks during the last year), was more likely in Sweden (but significantly so only in Östersund).

The parents' replies to the risk factor questionnaire in the case control study illustrate some of the major differences in the living conditions between Estonia and Sweden (Table 3). Children in Tallinn more frequently lived in blockhouse apartments with three rooms or less. Furthermore, exposure to indoor dampness, condensation on the

windows in the sleeping room and current maternal smoking were more common in Tallinn. In contrast, most of the Swedish children lived in one-family houses with more than three rooms and mostly less than one person per room. Whooping cough and exposure to maternal smoking during pregnancy were more common in Sweden.

There was no strong relationship between wheezing status and current home environment, neither in Estonia, nor in Sweden. The only exception was domestic crowding (= 1 person per room), which was related to a decreased risk of wheezing, but significantly so only in Östersund. However, one third of the children with wheezing and one fourth of the children without wheezing had lived less than five years in the current dwelling (similar in the three study areas).

Wheezing was strongly associated with atopic symptoms and positive SPT in both countries (Table 4). However, the proportion of children with rhinoconjunctivitis or positive SPT was much lower in Estonia than in Sweden, both in wheezing and non-wheezing children. Furthermore, diagnosed asthma and anti-asthmatic medication was less likely in Estonia (Table 5).

Wheezing was significantly associated with BHR in all the three towns, yet the proportion of a positive bronchial challenge was much higher in Sweden than in Estonia

Table 2. Prevalence rates and crude odds ratios (OR) of atopic symptoms and positive skin prick tests among Estonian (Tallinn) and Swedish (Linköping and Östersund) children

	Tallinn	Linköping		Östersund	
	Prevalence	Prevalence	Crude OR* (95% CI)	Prevalence	Crude OR* (95% CI)
Allergic rhinoconjunctivitis					
Ever	208/962 (21.6%)	199/882 (22.6%)	1.1 (0.8–1.3)	287/1187 (24.2%)	1.4 (0.9–1.4)
12-month prevalence	60/962 (6.2%)	124/878 (14.1%)	2.5 (1.8–3.5)	146/1184 (12.3%)	2.1 (1.5–2.9)
Wheezing					
Ever	196/963 (20.4%)	216/910 (23.7%)	1.2 (1.0–1.5)	267/1188 (22.5%)	1.1 (0.9–1.4)
12-month prevalence	81/963 (8.4%)	72/910 (7.9%)	0.9 (0.7–1.3)	122/1192 (10.2%)	1.2 (0.9–1.6)
≥ 4 attacks per year	14/80 (17.5%)	18/70 (25.7%)	1.6 (0.7–3.6)	52/121 (43%)	3.5 (1.8–7.0)
Ever asthma	24/957 (2.5%)	86/900 (9.6%)	4.1 (2.5–6.7)	129/1186 (10.9%)	4.7 (3.0–7.6)
Cough and phlegm (12-month prevalence)					
With colds	395/958 (41.2%)	222/903 (24.6%)	0.5 (0.4–0.6)	338/1189 (28.4%)	0.6 (0.5–0.7)
Without colds	53/952 (5.6%)	49/895 (5.5%)	1.0 (0.7–1.5)	59/1169 (5.0%)	0.9 (0.6–1.3)
Itchy rash					
Ever	241/962 (25.1%)	290/905 (32.0%)	1.4 (1.2–1.7)	382/1189 (32.1%)	1.4 (1.2–1.7)
12-month prevalence	196/962 (20.4%)	224/909 (24.6%)	1.3 (1.0–1.6)	316/1190 (26.6%)	1.4 (1.2–1.7)
Positive skin prick test					
Any allergen	95/643 (14.8%)	173/859 (20.1%)	1.5 (1.1–1.9)	266/992 (26.8%)	2.1 (1.6–2.8)
Pollen	41/643 (6.4%)	143/859 (16.6%)	2.9 (2.0–4.3)	187/992 (18.9%)	3.4 (2.4–4.9)
Animal dander	60/643 (9.3%)	96/859 (11.2%)	1.2 (0.9–1.7)	186/992 (18.8%)	2.2 (1.6–3.1)

*Tallinn as reference; CI: confidence interval.

Table 3. Sociodemographic characteristics and wheezing status among Estonian (Tallinn) and Swedish (Linköping and Östersund) children

	Tallinn			Linköping			Östersund		
	Wheezing	Non-wheezing	P-value	Wheezing	Non-wheezing	P-value	Wheezing	Non-wheezing	P-value
Older sibling (≥ 1)	29/64 (45%)	115/213 (54%)	ns	40/62 (65%)	98/143 (69%)	ns	63/109 (58%)	110/170 (64%)	ns
Younger sibling (≥ 1)	33/63 (52%)	99/216 (46%)	ns	25/62 (40%)	70/143 (49%)	ns	61/109 (56%)	89/170 (52%)	ns
One-family house	20/65 (31%)	62/223 (28%)	ns	46/62 (74%)	97/142 (68%)	ns	82/108 (76%)	116/169 (69%)	ns
> 3 rooms	22/67 (33%)	77/227 (34%)	ns	55/60 (92%)	136/142 (96%)	ns	96/109 (88%)	151/170 (89%)	ns
≥ 1 person per room	54/66 (82%)	190/223 (85%)	ns	18/59 (31%)	58/140 (41%)	ns	35/105 (33%)	84/170 (49%)	< 0.01
Condensation on the windows (sleeping room)	31/67 (46%)	82/227 (36%)	ns	18/61 (30%)	31/142 (22%)	ns	25/108 (23%)	33/169 (20%)	ns
Any kind of damp damage in the home	29/67 (43%)	105/227 (46%)	ns	21/62 (34%)	49/142 (35%)	ns	34/109 (31%)	54/170 (32%)	ns
Mother smoking during pregnancy	2/66 (3%)	10/221 (5%)	ns	20/61 (33%)	28/141 (20%)	< 0.05	20/105 (19%)	33/165 (20%)	ns
Mother current smoker	19/65 (29%)	83/219 (38%)	ns	14/60 (23%)	28/141 (20%)	ns	25/108 (23%)	33/167 (20%)	ns
Ever had whooping cough	11/65 (17%)	21/219 (10%)	ns	26/59 (44%)	59/140 (42%)	ns	60/106 (57%)	74/167 (44%)	< 0.05

(Table 4). A positive bronchial challenge in children with current wheezing was closely related to SPT positivity. The proportion with positive bronchial challenge was 52% in Swedish children with current wheezing and positive SPT and only 26% in Swedish children with current wheezing and negative SPT (OR 3.1, 95% CI 1.5–6.5). Corresponding proportions among wheezing children in Estonia were 30% and 6%, respectively (OR 6.4, 95% CI 0.9–46.1). The mean inhalation time, necessary to provoke BHR was significantly shorter for wheezers than for non-wheezers and for Swedish, as compared to Estonian children (data not shown). The percentage of children not completing the challenge test due to subjective complaints or lack of motivation was smaller in Estonia than in Sweden, i.e. 0, 2% and 13% for wheezers and 2%, 7% and 16% for non-wheezers in Tallinn, Linköping and Östersund, respectively. The mean output from the nebuliser was slightly higher in Estonia than in Sweden, i.e. 1.85 mL/min (standard deviation, SD 0.48) in Tallinn, 1.41 mL/min (SD 0.86) in Linköping, and 1.45 mL/min (SD 0.86) in Östersund.

Six children in Sweden (five with current wheezing) and none in Estonia had a baseline FEV₁ of less than 75% of the predicted value. The FEV₁ mean value was similar in

wheezers (2.8 L, SD 0.5) as well as non-wheezers in Estonia (2.8 L, SD 0.5). In contrast, wheezing children in Sweden had lower baseline FEV₁ mean value than non-wheezing children, i.e. 2.6 L (SD 0.5) in wheezers and 2.8 L (SD 0.5) in non-wheezers in Linköping and 2.4 L (SD 0.4) and 2.6 L (SD 0.5) in Östersund. In Linköping, however, wheezing children were challenged at a younger age than non-wheezing children. The lower baseline FEV₁ in wheezing children in Sweden persisted only among children in Östersund after analysis of variance with adjustment for height, weight, gender and age (mean difference between wheezing and non-wheezing children 0.1 L, 95% CI, 0.03–0.2). The mean baseline FEV₁ was higher in Estonia than in Sweden both in wheezing and non-wheezing children also after adjustment for gender, height, weight and age. The mean difference between Tallinn and Linköping after adjustment was 0.2 L (95% CI 0.09–0.4) in wheezers and 0.2 L (95% CI 0.1–0.3) in non-wheezers. The mean difference between Tallinn and Östersund after adjustment was 0.3 L (95% CI 0.2–0.4) in wheezers and 0.3 L (95% CI 0.2–0.4) in non-wheezers. Ninety-five per cent confidence intervals for corresponding differences between Linköping and Östersund included zero after adjustment.

Table 4. Atopic symptoms, positive skin prick tests and lung function by wheezing status among Estonian (Tallinn) and Swedish (Linköping and Östersund) children

	Tallinn			Linköping			Östersund		
	Wheezing	Non-wheezing	Crude OR (95% CI)	Wheezing	Non-wheezing	Crude OR (95% CI)	Wheezing	Non-wheezing	Crude OR (95% CI)
Allergic rhino-conjunctivitis (12-month prevalence)*	13/81 (16%)	4/256 (2%)	12.0 (3.8–38.0)	35/72 (49%)	21/198 (11%)	8.0 (4.2–15.2)	48/119 (40%)	27/243 (11%)	5.4 (3.1–9.3)
Itchy rash (12-month prevalence)*	29/81 (36%)	41/255 (16%)	2.9 (1.7–5.1)	35/71 (49%)	51/207 (25%)	3.0 (1.7–5.2)	56/120 (47%)	48/242 (20%)	3.5 (2.1–5.7)
Eczema at any localization (objectively verified)‡	2/54 (4%)	6/171 (4%)	1.1 (0.2–5.4)	11/59 (19%)	9/124 (7%)	2.9 (1.1–7.5)	30/109 (28%)	25/171 (15%)	2.2 (1.2–4.0)
≥ 1 positive SPT†	14/54 (26%)	16/171 (9%)	3.4 (1.5–7.5)	30/60 (49%)	31/188 (16%)	5.1 (2.7–9.6)	58/100 (58%)	43/200 (22%)	5.0 (3.0–8.5)
Positive bronchial challenge‡	7/56 (13%)	5/184 (3%)	5.1 (1.6–16.8)	27/56 (48%)	18/117 (15%)	5.1 (2.5–10.6)	37/77 (48%)	40/135 (30%)	2.2 (1.2–3.9)
Positive bronchial challenge or reversibility test‡	8/56 (14%)	8/188 (4%)	3.8 (1.3–10.5)	29/58 (50%)	19/118 (16%)	5.2 (2.6–10.6)	48/94 (51%)	43/139 (31%)	2.3 (1.3–3.9)

OR: odds ratio; CI: confidence interval; FEV₁: forced expiratory volume in 1 s; SPT: skin prick test.

*Based on data from the prevalence study in 1997 and includes all children who were invited to participate in the case-control study.

†The skin prick tests were conducted in 1997.

‡Includes only children participating in the case-control study in 1998.

Discussion

Atopic symptoms and positive SPT were more common in Swedish than in Estonian children. This was particularly true for allergic rhinoconjunctivitis and sensitization to pollen. On the other hand, respiratory symptoms related to colds were more common in Estonia. These findings show that the previously repeated differences in the prevalence of atopic manifestations between western industrialized and east-European post socialist countries still exist [13–15]. Furthermore, diagnosed asthma and antiasthmatic medication was four times more common in Sweden than in Estonia.

It has been suggested that wheezing in childhood may

represent different phenotypes, which differ in relation to atopy. In the Tucson Children's Respiratory Study, three wheezing phenotypes were distinguished, i.e. transient early wheezing, non-atopic wheezing in toddlers and during early school years, and persistent IgE-associated wheeze/asthma appearing at any age [6]. In a Norwegian study positive SPT were twice as common in children with asthma than in either wheezers with no asthma or non-wheezers [16]. The lung function and BHR in wheezers were also more similar to non-wheezers than asthmatic children.

In our study, wheezing was significantly associated with atopic symptoms and atopic sensitization in both countries. The proportion of wheezing children with positive SPT was

Table 5. Use of medication in wheezing and non-wheezing children in Estonia and Sweden

	Tallinn		Linköping		Östersund	
	Wheezing <i>n</i> = 67	Non-wheezing <i>n</i> = 227	Wheezing <i>n</i> = 62	Non-wheezing <i>n</i> = 143	Wheezing <i>n</i> = 109	Non-wheezing <i>n</i> = 170
Any asthma medication	12 (17%)	0	39 (63%)	4 (3%)	81 (73%)	15 (9%)
β ₂ -agonist	11 (16%)	0	37 (60%)	2 (1%)	81 (73%)	13 (7%)
Inhaled steroid or cromoglycate	8 (12%)	0	25 (40%)	4 (3%)	48 (44%)	6 (4%)
Asthma ever	14 (21%)	0	39 (63%)	7 (5%)	74 (69%)	10 (6%)

much higher in Sweden, however, suggesting that wheezing is less related to atopy in Estonia than in Sweden, i.e. 26% and 55%, respectively.

In both countries, wheezing was closely related to BHR, although very few Estonian children had a positive bronchial challenge. Numerous studies have demonstrated a close relationship between SPT reactivity, BHR and the frequency of wheezing symptoms [17]. The mechanisms underlying bronchial responsiveness are probably different in atopic and non-atopic individuals. Hyper-responsiveness to adenosine 5'-monophosphate (AMP) is likely to be a marker of allergic inflammation in the airways [18]. Our study may indicate that this is also true for BHR to hypertonic saline. This would at least partly explain the low number of positive challenges among wheezing children in Estonia.

An increased awareness of asthma and allergies may in theory explain the high proportion of wheezing children in Sweden with diagnosed asthma and current treatment. However, the high rate of BHR and frequent wheezing in Sweden despite anti-asthmatic medication would rather suggest differences in the severity of wheezing between Swedish and Estonian children. A major part of the wheezers in Sweden used β_2 -agonists. Concerns have been raised that long-term treatment with β_2 -agonists could contribute to increased BHR and worsening of asthmatic symptoms [19].

None of the environmental risk factors, although significantly different between Estonia and Sweden, were strongly associated with wheezing in either country. Domestic crowding was the only exception, being inversely related to wheezing in Östersund, where crowding was much less common than in Tallinn. This observation could be consistent with a previous Estonian-Swedish study, which demonstrated an inverse association between overcrowding and atopic sensitization [10]. The finding should be interpreted with caution, however. A protective effect of domestic crowding (and older siblings) probably acts predominantly during a rather short period early in life [20]. Many families have moved since the child was born and the reported data on home conditions referred to the current situation.

The high prevalence of respiratory symptoms in Tallinn cannot be explained by a poor indoor climate. Thus, even if dampness at home was more commonly reported in Tallinn, an analysis of the indoor climate in typical flats in Tallinn during the winter and spring 1998 showed the air to be relatively dry during the winter and the air exchange rate to be higher than in Scandinavian countries [21]. We have previously observed a poor relationship between damage due to dampness in the apartments and ventilation [22]. Due to the poor quality of most apartment buildings that were built in Soviet time, damp spots usually indicate

leakage, from the roof and outer walls, rather than being a marker of poor ventilation.

There is always a risk for methodological differences in comparative studies between different centres, even if the protocols are identical. In this study, the response rate to the questionnaires was similar in all the three centres, while less children in Tallinn participated in the SPT. The prevalence of respiratory and atopic symptoms was similar in children who were and were not skin prick tested, however, [22]. Although the field workers were trained together and adhered to the same protocol, the degree of effort by them could influence the results, as indicated by the different dropout rates in Estonia and Sweden. Still, because of the better basic lung function, higher output of the nebuliser, and the smaller number of dropouts in Estonia, poor technique would not explain the lower prevalence of BHR.

We could not exclude that the higher baseline FEV₁ values in Tallinn (in wheezing as well as non-wheezing children) were caused by some kind of systematic error. If this would be the case, however, the impact was negligible on the outcome of the bronchial challenge based on a relative change in FEV₁. Moreover, a higher baseline FEV₁ in Estonian children would be in agreement with the lower prevalence of atopy and BHR in this population.

In conclusion, our study suggested that wheezing symptoms were less severe in Estonia. More frequent symptoms and a high rate of atopy and BHR characterized wheezing children in Sweden. They were also likely to take asthma drugs, particularly β_2 -agonists. In contrast, BHR, atopy and treatment for asthma were uncommon among wheezing children in Estonia.

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