
Decreased markers of atopy in children with presumed early exposure to allergens, unhygienic conditions, and infections

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Background: Several risk factors for the development of asthma and atopic disease in children have been described. Furthermore, there is consistent evidence that the prevalence of atopy increases with higher socioeconomic status. The knowledge about risk factors and preventive factors for atopy needs to be improved.

Objective: To compare 2 child populations (foster care and reference children) with different risk and protective factors for the development of atopy.

Methods: The study group consisted of 415 children, living in all 10 community foster homes in Lodz, a large industrial city in Poland. The study was performed from April 2, 2004, to April 30, 2006. The reference group consisted of 500 children, living with their parents at home, recruited from primary care centers. The primary outcome measures were skin prick test results and specific IgE in serum. Secondary outcomes included symptoms of allergic diseases and family history, including life conditions in early childhood.

Results: The full analysis set included 408 study children and 402 reference children. Significant differences were observed in the prevalence of atopy between the study and reference groups (11.3% vs 25.9%). We observed more positive skin prick test results in children from the reference group than in study children. To explain this phenomenon, we selected 16 variables that differ in both groups in early life and relate these to atopy. We found that the more cumulative features characteristic of the foster home population (poor living conditions), the lower the risk of atopy.

Conclusion: Extremely unfavorable environmental circumstances, which are characteristic of the foster home population during early childhood, might prevent from atopy.

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INTRODUCTION

Within the past century, there has been a reduction of members of families, improvement of life conditions, and an increase in personal hygiene, which have led to a decrease in the frequency of cross-infections in families and could be a reason for the higher expression of atopic diseases.¹ Less exposure to microbes can lead to disturbance in the optimal balance between T_H1 and T_H2 lymphocytes and the prevalence of T_H2 cytokines and to excessively high production of IgE. Many studies confirm the protective role of some viral,^{2,3} bacterial,^{4,5} or parasitic⁶ infections against atopy develop-

ment. On the other hand, antibiotic exposure in early infancy increased the risk for childhood atopy and asthma in some studies.⁷ A mechanism and a role of every microbe are being described in the development of atopic illnesses.⁸ Several risk factors for the development of asthma and atopic disease in children, such as passive smoke exposure during pregnancy and infancy, low birth weight, and high body mass index later in life, have been described. Furthermore, there is consistent evidence that the prevalence of atopy increases with higher socioeconomic status. For the improvement of knowledge about risk factors and preventive factors for atopy, the Protection Against Allergy: Study in Rural Environments project in Europe has been designed.⁹

The aim of this study was to compare 2 distinct populations of children with different life experiences and with different risk and protective factors for the development of atopy.

We studied 2 groups of children, male and female, aged 5 to 18 years: (1) children living in foster homes (study children) and (2) children living at home with their parents (reference children). We focused on fetal and infant development, housing conditions, size of the families, childhood vaccination scheme, and antibiotic courses as risk and preventive factors for atopic disorders in childhood and speculate about possible mechanisms underlying the relationships observed.

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METHODS

Study Population

To avoid the influence of external environment, all children were living in Lodz, a large industrial city in Poland. The study group consisted of all 415 children living in all 10 community foster homes in the city. The reference group consisted of children, living with their birth parents at home, recruited from the insurance agency (all children in Poland are insured); 50 addresses of children were randomly selected from each of 10 public or nonpublic health centers. In Poland, all insured children must belong to the chosen primary care center (public or nonpublic); therefore, children recruited from health centers are representative of the Polish population of children.

Our study children live in foster care, which is a group home for all, even young, children; they were taken from their, often large, pathologic families. These families have a low economic status, where parents' unemployment and alcoholism are the main problem. These children grow up in small, overflowing flats, mainly in old housing among numerous siblings, and are particularly subjected to contact with various infection factors, in bad sanitary conditions, often without access to running water. In our study, neglect was the most frequent placement reason (80.1%), followed by parental incapacity (14.5%), abandonment (8.2%), no available caretaker (orphans) (1.9%), and more than 1 reason (53.3%). Family characteristics included alcoholism and unemployment (80.3%), living in a single-parent family (20.8%) and no parent family (1.9%) before placement, coming from a high-risk family (92.6%), and having a family with multiple problems (23.4%). Parents' alcoholism and unemployment were the most frequent family problems. Children living in foster homes entered them at various ages, only a few of them just after birth, most after the second year of life, and stay until they are aged 18 years. Each study foster home had 24 to 74 children living in rooms with 2- to 9-person occupancy per room; children shared the canteen, learning room, and bathrooms.

Study Design

The study was performed from April 2, 2004, to April 30, 2006. The study was approved by the Medical Ethical Committee of the Medical University of Lodz, and all children, all foster home authorities, and all patients' parents or guardians gave their written consent for participation in the study. All children had a chance to refuse to undergo testing. A study physician (K.S.) with a nurse visited all foster homes and selected health services. Procedures described later were conducted on all children.

Outcome Measurement: Atopy and Atopic Disease Indicators

The primary outcome measures were skin prick test (SPT) results and specific IgE in serum (markers of atopy). At the visit, the clinical evaluation included a medical history and a physical examination, the attainment of a blood sample, and

SPT with the following inhalant and food allergens: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria*, *Cladosporium*, cat dander, dog dander, mixed grass pollen, rye, birch, hazel, ribwort, alder, motherwort, feather, cocoa, milk, egg, and peanut. Positive (histamine chloride, 10 mg/mL) and negative (glycerol) controls (extracts from Nexter-Allergopharma, Reinbek, Germany) were also used. A positive SPT reaction was defined as a mean wheal diameter of greater than 3 mm in excess of the negative control. Atopy was defined as a positive skin test response to any of the 18 allergens tested. To confirm the sensitization, blood samples were measured for concentration of allergen-specific IgE antibodies for the allergens with the positive skin reaction.

Secondary outcomes included symptoms of asthma and other allergic diseases; lung function; parental allergy only for children from the reference group; family history, including life conditions in early childhood; and markers of allergy, such as total IgE serum concentration and eosinophil blood cell count.

The following symptom reports were studied: wheezing (at night and apart from cold), rhinitis symptoms (apart from cold and including sneezing, runny nose, or congestion), itching eczema, number of colds (all whenever and for the past 12 months), and physician-diagnosed asthma, rhinitis, and atopic dermatitis. Questions about allergic symptoms, addressed to guardians or parents, were the same as used in the International Study of Asthma and Allergies in Childhood questionnaire.¹⁰ The data from the questionnaire consisted of symptoms from the respiratory system, the number of respiratory infections in the first 5 years of life, antibiotic courses, the duration of stay in the foster homes, characteristics of the family, number of older siblings, pet ownership, and, in children living with their parents, attendance in day care centers or nurseries. The diagnosis of asthma was established by symptoms of asthma and by improvement in the prebronchodilator forced expiratory volume in 1 second of 12% or greater after the administration of salbutamol, 200 µg. The forced expiratory volume in 1 second was measured by a microspirometer (Spirodoc; MIR, Rome, Italy); the highest of 3 successive measurements was taken. Reference values were taken according to the recommendations of the American Thoracic Society Standards of Acceptability and Reproducibility.

Medical documentation has been analyzed in foster homes and primary care clinics from birth until the time of the visit. Data about background factors, such as socioeconomic factors, sanitary conditions, and hygienic habits of the family, were obtained from social workers for children living in foster care centers and for the reference group. Total IgE serum concentration was measured in all children by using a kit (CAP kit; Pharmacia, Uppsala, Sweden). The number of eosinophils was measured in all children by an automated hematology analyzer (model K-4500; Sysmex, Kobe, Japan) and expressed as the number of cells per microliter. In nonatopic children with a serum IgE level above the reference

Table 1. Current Characteristics of the Study Population^a

Characteristic	Children living in foster homes (n = 408)	Children living with their parents (n = 402)	P value
Demographic and anthropometric data			
Age, y ^b	10.9 ± 2.2	11.4 ± 5.6	.09
Female sex ^c	50.7	48.3	.49
Body mass index ^{b,d}	18.2 ± 3.7	18.5 ± 2.7	.18
Starting age of placement in foster center, y	3.8 (2.1–7.2)	NA	NA
Length of placement in foster center, y	6.7 (3.3–9.2)	NA	NA
Starting age of day care or nursery attendance, y	NA	4.5 (2.2–8.2)	NA
Atopic status			
Atopy in the family ^e	NA	120 (29.9)	NA
Children with a positive SPT result ^e	46 (11.3)	104 (25.9)	<.001
Specific IgE, IU/mL			
<i>Dermatophagoides pteronyssinus</i>	2.2 (1.0–4.9)	10.9 (1.8–63.2)	.007
<i>Dermatophagoides farinae</i>	2.1 (1.0–8.3)	11.1 (1.3–55.8)	.007
Cocksfoot	3.7 (1.5–100.0)	8.8 (1.8–93.3)	.86
Timothy	0.8 (0.2–25.5)	13.2 (2.3–88.0)	.02
Rye	1.8 (0.5–79.1)	13.2 (1.9–100)	.06
Mugwort	1.0 (0.7–2.4)	4.2 (1.8–10.9)	.04
Birch	2.1 (0.1–90.2)	5.4 (1.1–100.0)	.40
Alder	5.5 (2.0–6.0)	2.9 (1.4–14.8)	.59
Hazel	3.2 (1.3–3.3)	2.9 (1.3–24.3)	.77
Mold ^f	0.8 (0.1–0.9)	1.3 (0.7–3.5)	.16
Cat	1.3 (0.6–19.0)	14.6 (3.1–100)	.16
Dog	0.3 (0.2–0.4)	1.3 (0.5–2.1)	.14
Egg	0.9 (0.5–1.6)	0	NA
Allergic disease ^e			
Asthma	10 (2.5)	34 (8.5)	<.001
Allergic rhinitis	22 (5.4)	38 (9.5)	<.001
Atopic dermatitis	13 (3.2)	41 (10.2)	<.001
Laboratory measurements			
FEV ₁ , % predicted ^b	98.4 ± 10.4	97.5 ± 10.9	.23
Eosinophil blood cell count above the reference range ^{e,g}			
Atopic children	12 (26.1)	28 (26.9)	.74
Nonatopic children	92 (25.4)	35 (11.7)	<.001
Total IgE above the reference range ^{e,g}			
Atopic children	46 (100)	103 (99.0)	.87
Nonatopic children	14 (3.9)	16 (5.4)	.07

Abbreviations: FEV₁, forced expiratory volume in 1 second; NA, data not applicable; SPT, skin prick test.

^a Data are given as median (interquartile range) unless otherwise indicated.

^b Data are given as mean ± SD.

^c Data are given as percentage of each group.

^d Calculated as weight in kilograms divided by height in meters squared.

^e Data are given as number (percentage) of each group.

^f Mold mixtures included *Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Candida albicans*, and *Alternaria tenuis*.

^g For children living in foster homes, the denominator for atopic children was 46; and for nonatopic children, 362. For children living with their parents, the denominator for atopic children was 104; and for nonatopic children, 298.

range and/or an eosinophil blood cell count of 350/μL or greater, 3 stool samples from each child were collected and qualitatively analyzed for parasite eggs and *Giardia lamblia* cysts.

Statistical Analyses

In the first step, we compared the 2 populations and defined the distinctive feature of foster home children. In the next step, we used a univariate and multivariate model of logistic

regression analysis to test relationships between these features and atopy in children from the reference group. Regression analyses were conducted in 2 stages. First, separate analyses were conducted for each of the independent variables (univariate model). Statistically significant predictors of atopy together with family history of atopy were then included in the second stage to determine the best combination of predictors (multivariate model). In the final model, only significant statistical predictors of atopy were presented. Cu-

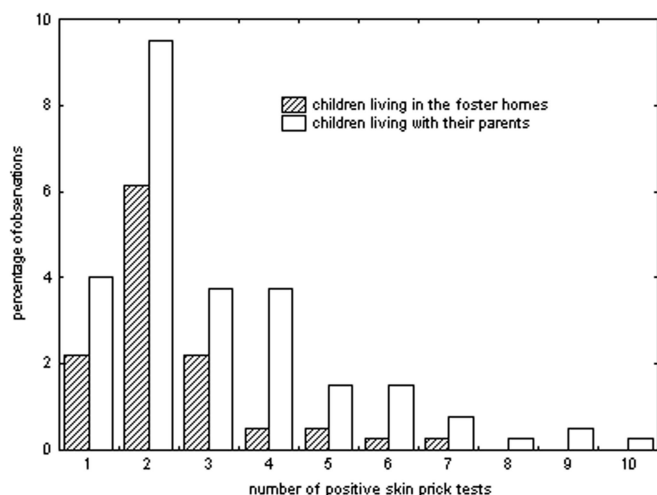


Figure 1. Differences in the number of positive skin prick test results between study and reference children.

mulative features characteristic of the foster home population, named in our article as cumulative poor living conditions, were included at all stages of analysis as continuous variables. All statistical analyses were performed using commercially available software programs (SPSS for Windows [SPSS Inc, Chicago, Illinois] and STATISTICA for Windows, release 6.0 [StatSoft, Inc, Tulsa, Oklahoma]). $P < .05$ was used as the definition of statistical significance.

RESULTS

Of the 415 children living in foster homes and the 500 children living with their parents, the full analysis set included 408 study children and 402 reference children. Seven children from foster homes were excluded from the study because of lack of cooperation with the medical staff. Ninety-eight children from the reference group did not respond. The characteristics of the children during the study are described in Table 1. Significant differences were observed in the prevalence of atopy and allergic diseases between study

Table 2. Characteristics of the Study Population in the First Year of Life^a

Characteristic ^b	Children living in foster homes	Children living with their parents	P value
Early medical history			
Birth weight (385/402)			
Mean (SEM), g	2,691.3 (48.5)	3,257.3 (26.0)	<.001
Less than the mean for foster home children	44.1	11.7	<.001
Apgar score (271/402)			
Median (interquartile range)	8 (7–9)	9 (8–9)	.01
Less than the median for foster home children	41.7	26.1	<.001
Premature delivery (320/402)	36.5	9.2	<.001
Breastfeeding (215/402)	17.2	73.1	<.001
BCG vaccine scar (257/400)			
Mean (SEM), mm	4.25 (0.06)	4.06 (0.11)	.045
Greater than the mean for foster home children	43.6	33.7	.01
Antibiotic courses (299/399)			
Median (interquartile range)	6 (4–8)	4 (2–5)	<.001
Less than the median for foster home children	40.5	13.3	<.001
Family status (408/402)			
Large family (>2 children)	40.2	3.2	<.001
Older siblings	76.2	39.5	<.001
Serious family problem			
Single-parent family (408/402)	20.8	2.0	<.001
No parent family (408/402)	1.9	0	<.001
Alcoholism (395/402)	80.5	7.5	<.001
Unemployment (355/402)	82.2	11.4	<.001
Housing conditions			
Old homes (385/402) ^c	88.2	13.4	<.001
No. of placements <3 (375/402)	81.5	5.7	<.001
No central heating (351/402)	91.8	38.2	<.001
ETS exposure (391/402)	91.1	41.6	<.001

Abbreviation: ETS, environmental tobacco smoke.

^a Data are given as percentage of each group unless otherwise indicated.

^b Data in parentheses indicate the number of observation in the analysis: children living in foster homes/children living with their parents.

^c Built before 1940.

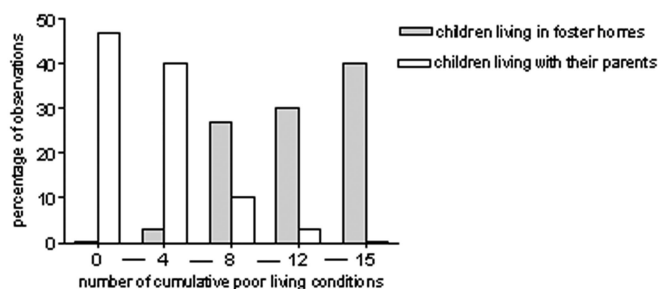


Figure 2. Differences in the number of cumulative features between study and reference children.

groups. Among the 408 children living in foster homes, 46 had atopy, 10 had diagnosed asthma, 22 had allergic rhinitis, and 13 had atopic dermatitis. Among the 402 reference children, the prevalences of atopy, diagnosed asthma, allergic rhinitis, and atopic dermatitis were as follows: 104, 34, 38, and 41 children, respectively. We observed more positive SPT results in children from the reference group than in study children (Fig 1). Children from the reference group also had higher specific IgE levels in serum than those in the study group (Table 1). We showed total IgE above the reference range in all atopic children from foster homes and in 99.0% of children from the reference group. Among nonatopic children, 3.9% from foster homes and 5.4% from the reference group had total IgE levels above the reference range (Table 1). We observed significant differences in the percentage of nonatopic children with a high eosinophil blood cell count

between groups; 25.4% of nonatopic children from foster homes vs 11.7% of reference children had an eosinophil blood cell count of 350/ μ L or greater. In nonatopic children with a high serum IgE concentration and/or a high eosinophil blood cell count (Table 2), we found no parasite eggs in any samples, and only 2 samples from children living with their parents contained *G lamblia* cysts.

Characteristics of the Study Population During the First Year of Life

Medical history and family and home environment information from the first year of life of the study population is presented in Table 2. Most population characteristics were different among the 2 groups of children, except for an incomplete vaccination scheme. Children living in the foster homes compared with reference children had a lower birth weight, a lower Apgar score, and a larger BCG vaccine scar; breastfeeding and antibiotic courses were less often recorded and premature delivery was more often recorded in these children. Also, children from foster homes had more older siblings than children living with their parents. Most of the children living in foster homes came from a large family with serious problems. More than 80% of these children came from old homes, with the number of placements ranging from 1 to 2. In more than 90% of the children from foster homes, environmental tobacco smoke exposure was recorded. The mentioned data were aggregated and presented as cumulative features characteristic of the foster home population. Figure 2 shows the differences in cumulative poor living conditions between the 2 groups of children.

Table 3. Unadjusted Associations of Study Variables With Atopy in Children Living With Their Parents

Variable	OR (95% CI)	P value
Early medical history		
Birth weight (<mean for foster home children)	0.65 (0.11–5.19)	.91
Apgar score (<mean for foster home children)	0.47 (0.28–0.77)	.003
Premature delivery	0.51 (0.21–1.23)	.13
Breastfeeding	0.87 (0.53–1.44)	.60
BCG vaccine scar (>mean for foster home children)	0.40 (0.11–0.48)	<.001
Antibiotic courses (<mean for foster home children)	0.69 (0.29–0.89)	<.001
Family status		
Large family (>2 children)	0.46 (0.28–0.77)	.003
Older siblings	0.48 (0.34–0.69)	<.001
Serious family problem		
Single-parent family	0.78 (0.45–0.98)	.01
Alcoholism	0.67 (0.34–0.84)	.002
Unemployment	0.88 (0.74–1.11)	.10
Housing conditions		
Old home ^a	1.00 (0.52–1.93)	.99
No. of placements <3	1.27 (0.51–3.18)	.61
No central heating	1.20 (1.10–1.31)	.49
ETS exposure	1.31 (0.84–2.06)	.24
Cumulative features characteristic for foster homes ^b	0.79 (0.58–0.92)	<.001
Atopy in the family	2.54 (1.59–4.06)	<.001

Abbreviations: CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio.

^a Built before 1940.

^b The minimum was 1 feature; and the maximum, 15 features.

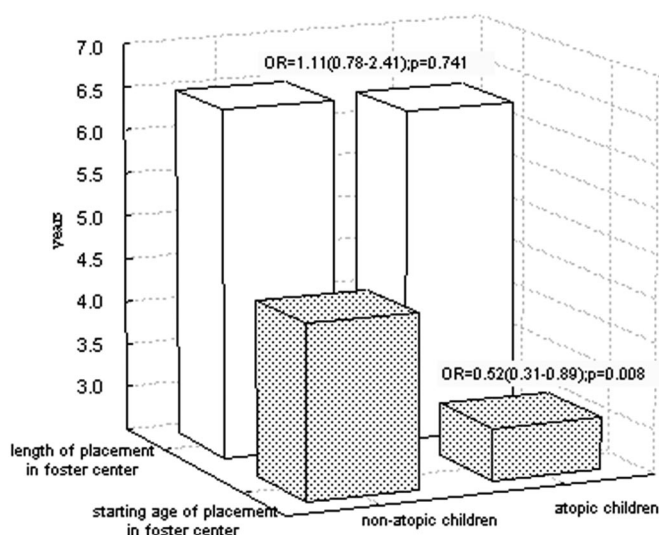


Figure 3. Relationships among starting age of placement (filled boxes), length of placement (opened boxes), and atopy. Unadjusted odds ratios (ORs) are shown.

Influence of Early Medical History and Home Environment on Atopy

In our study, greater atopy was observed in children living with their parents. To explain this phenomenon, we tried to define variables that differ in both groups in early life. To confirm the association of these variables with atopy, we built the model of regression analysis in a random sample of general population children living with their parents. Because the population of children living in foster homes was “exposed” to most of the study variables, the analysis of the association with atopy is unjustified in such a population. Based on the data from the first year of life in both groups (Table 2), we selected variables, significantly different in both groups, for further analysis. Individual regression data for the previously mentioned variables for logistic regression are given in Table 3. Adjusted data for factors independently affecting atopy in children living with their parents are as follows. For cumulative features characteristic of foster homes, the odds ratio (OR) was 0.80 (95% confidence interval [CI], 0.68–0.90); and for atopy in the family, the OR was 1.94 (95% CI, 1.45–3.01) ($P < .001$ for both). The more cumulative features characteristic of the foster home population (cumulative poor living conditions), the lower the risk of atopy (Fig 2). In addition, we showed a significant relationship between starting age of placement and atopy (a higher starting age of placement decreased the risk of atopy; OR, 0.52; 95% CI, 0.31–0.89) ($P = .008$). There was no relationship between length of placement in a foster center and atopy (OR, 1.11; 95% CI, 0.78–2.41; $P = .74$) (Fig 3).

DISCUSSION

Surprisingly, we observed a significantly lower prevalence of atopy and atopic diseases in children living in foster care

centers (11.3%) than in a population of children living with their parents (approximately 26%); all children came from the same area. We observed more positive SPT results in children from the reference group than in children from foster homes, and reference children had higher specific serum IgE levels than the study group, which indicates “more expressed” atopy in children living with their parents.

The prevalence of atopy in the general population of children living in the city center in Lodz, observed in a large epidemiologic study,¹¹ was close to 25%. Also, the lower prevalence of atopic diseases observed in the foster home population in our study is statistically significant compared with the general population of children in Lodz.¹¹ Although the reasons for this phenomenon remain unclear, we discuss possible mechanisms underlying the relationships observed.

Some studies^{12,13} showed that multiple airway infections and day care attendance were independently associated with asthma and allergic symptoms. Our children living in foster homes, coming from a “high-risk” family (mostly large, with older siblings, living in poverty and poor sanitary conditions before placement), were particularly subjected to contact with various infection factors. Surprisingly, these children had lower antibiotic exposure in the first year of life than children living with their parents, probably because of neglect.⁷ The natural course of infections in those children may decrease atopic immune responses.¹⁴ The average starting age in public day care in our children was 4 years, and after entering the day care center, these children had nearly the same number of airway infections as children living in foster homes. Regarding the previous observation, multiple infections only during infancy and early childhood may lead to less sensitization later in life.

Almost 90% of foster home children, before placement, lived in old houses. Home dampness, indoor microbial growth, and indoor mold growth, well-known risk factors for respiratory illness and impaired lung function in children, were common in children from foster homes. One of the best-described and most robust environmental variables associated with decreased risk of atopy and asthma is the “farm effect.”^{15,16} This protective effect was attributed to the exposure with bacterial endotoxin (lipopolysaccharides [LPSs]), which were found at increased doses in farming environments and were inversely correlated with the risk of allergic sensitization and disease.¹⁷ The Prevention and Incidence of Asthma and Mite Allergy study¹⁸ showed that in older houses, the LPS concentration in dust from smooth floors was twice as high compared with that in new houses. Also, early exposure to an extracellular polysaccharide concentration, a marker of indoor mold growth that might inhibit the development of atopy and asthma,^{19,20} was 2 times higher when a home had reports of home dampness.¹⁸ Because almost 90% of our children, before placement in foster homes, lived in older houses, built before at least 1940, we can expect that they were exposed to high levels of LPSs and extracellular polysaccharides in early childhood. We can suspect that our children’s immune system was exposed to microbial stimu-

lation as early as during gestation. In animal models, immunomodulation with bacterial compounds during this time might be an effective mode for first-step primary prevention against allergic diseases.¹⁶

Parasitic infections are popular in poor socioeconomic and hygienic conditions (characteristic for early childhood in our foster home population); some studies^{21,22} suggest that high degrees of parasite infection might prevent atopy and asthma.

Although during our study, we observed high eosinophil blood cell counts and high total IgE concentrations, mainly in foster home nonatopic children, we found no parasite eggs in any stool samples, which can be related to intestinal helminth infection. We cannot explain current high eosinophil blood cell counts other than by current parasitic infection in many children residing together in a foster home. However, we did not evaluate this problem by all available methods (ie, IgE specific against each parasite), and it is documented that the sensitivity of a stool examination is relatively low.

Our findings also showed that all children from foster homes were more likely to be formula fed from the beginning and to have smoking parents (vs the reference group). These are both well-known risk factors for asthma and allergic diseases.

Taking into account that most of the children in foster homes have been maltreated and have multiple ongoing stressors, they might have higher levels of stress hormones, which might account for their lower rate of atopy.^{23,24}

All previous observations clearly showed the extreme differences between the 2 studied populations, mainly in the first year of life. We could suspect that all observed characteristic features of the foster home population (poor living conditions) can explain such a low prevalence of atopy and atopic diseases in these children.

Following this idea, in the next step of our analysis, we tested relationships between these features with atopy in children from the reference group. More cumulative poor living conditions decreased the risk of atopy, independently from family history of atopy, in a population of children living in this large industrial city.

The main limitation of our study is the retrospective design. Another problem in this study was the dropout rate; almost all children in foster care centers completed the study, but only 80% did so in the reference group, which could somewhat influence our study results.

In conclusion, our findings suggest that extremely unfavorable environmental factors, appearing during infancy and early childhood, may be protective against atopy. These data may suggest that many of our recommendations to parents (ie, clean the house, reduce mold, and prevent infections) are not protective against the development of atopy. The finding of a low atopy rate in a population of children from foster homes provides the opportunity to explore the basis of the apparent "resistance" to atopy and allergic diseases in this population. The genotyping and cytometric study will be performed by our study group within the next year. There is a need for prospective investigations, especially coming from

eastern European countries, where poverty and pathological features in families are still the main reasons for placement in a foster home; these investigations will potentially shed more light on the cause of atopic diseases.

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