

Early life environmental exposure in relation to new onset and remission of allergic diseases in school children: Polish Mother and Child Cohort Study

M. Bobrowska-Korzeniowska, M.D., Ph.D.,¹ K. Kapszewicz, M.D.,¹ J. Jerzynska, M.D., Ph.D.,¹ W. Stelmach, M.D., Ph.D.,² K. Polanska, M.D., Ph.D.,³ J. Gromadzinska, M.D., Ph.D.,⁴ K. Mikolajewska, M.Sc.,⁴ W. Hanke, M.D., Ph.D.,³ and I. Stelmach, M.D., Ph.D.¹

ABSTRACT

Background: This study was based on data from the Polish Mother and Child Cohort Study.

Objective: The aim was to study associations between home environment factors and allergic diseases at 1 year of life and new onset and remission of children's allergy diagnosis at ages 7–9 years.

Methods: Children's health status was assessed at ~12 months of age and then at ages between 7–9 years by using a questionnaire administered to the mothers. Children were assessed by pediatrician/allergists. The patients, who were 7–9 years old, underwent skin-prick tests. Exposure to tobacco smoke was evaluated with a questionnaire addressed to parents and/or caregivers and cotinine measurements were taken of mother's saliva during pregnancy and in children's urine at ages 7–9 years. Incidence and remission were calculated by comparing symptoms in the first year of life with symptoms at 7–9 years. We studied the associations among demographic data, home environment, and new onset and remission of food allergy, atopic dermatitis, and asthma and allergic rhinitis in logistic regression analysis. All associations were adjusted for independent risk factors of dependent variables.

Results: Data from 211 participants were included in the analysis. During the first year of life, food allergy was the most common symptom (39%), followed by atopic dermatitis (35%) and asthma (12%). When comparing diagnoses at ages 7–9 years with the first year of life, food allergy had decreased by as much as 18.6%, atopic dermatitis decreased by as much as 23.8%, and asthma decreased by as much as 8%, whereas asthma and allergic rhinitis had increased from 6% to 14.8%. More frequent house cleaning negatively correlated with the new onset of atopic dermatitis and of asthma and allergic rhinitis. Hypersensitivity to seasonal allergens and mites and to any other allergen positively correlated with new onset of food allergy, atopic dermatitis, and asthma and allergic rhinitis. Parental atopy positively correlated with the new onset of asthma and negatively correlated with asthma remission.

Conclusion: Analysis of our findings indicated that new onset and/or remission of allergic diseases was linked with hypersensitivity to house-dust mites in children who were polysensitized and with parental atopy. In addition, children who had food allergy, allergic rhinitis, or atopic dermatitis at the age of 1 year had more of a chance developing other atopic disease (except asthma) at ages 7–9 years and less of a chance of having a remission of the disease.

(Allergy Asthma Proc 40:329–337, 2019; doi: 10.2500/aap.2019.40.4237)

The home environment can influence childhood allergies and respiratory health, but there is little information on the allergy-promoting effects of various factors, such as pets in the home, parents' education,

modality of childbirth, and housing conditions (e.g., the presence of cockroach, indoor molds, home dampness) in an urban population of children.^{1–4} The influence of various environmental factors on allergy and/or asthma development has been shown to be age dependent^{5,6} Early life exposure plays an important role in the development of allergic diseases,⁷ but the etiologic pathway is complex and dynamic, and involves genetic factors and environmental exposures.

The influence of second-hand tobacco smoke on the child is currently under specific research and detailed analysis. The results of a pooled analysis based on eight European birth cohorts showed that maternal smoking during pregnancy was related to asthma in preschool age among children whose mothers did not smoke after birth.⁸ Children's exposure to environmental tobacco smoke can be measured by urine cotinine,

From the ¹Department of Pediatrics and Allergy, Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland, ²Department of Social and Preventive Medicine, Medical University of Lodz, Lodz, Poland, ³Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland, and ⁴Department of Biological and Environmental Monitoring, Nofer Institute of Occupational Medicine, Lodz, Poland

The authors have no conflicts of interest to declare pertaining to this article

The study was performed under the project supported by the grant from the National Science Center 2017/25/B/NZ5/02338 and 2014/15/B/NZ7/00998

Address correspondence to Iwona Stelmach, M.D., Department of Pediatrics and Allergy, Medical University of Lodz, N. Copernicus Memorial Hospital, 71 Al. Pilsudskiego, 90–329, Lodz, Poland

E-mail address: alergol@kopernik.lodz.pl

Copyright © 2019, OceanSide Publications, Inc., U.S.A.

which is a sensitive and specific biomarker for discriminating the source of tobacco smoke exposure, especially when the biomarker is measured while a person is receiving ongoing exposure to tobacco smoke.⁹ Finnish investigators observed that moisture damage and mold at an early age in the child's main living areas were associated with the risk of developing physician-diagnosed asthma ever, persistent asthma, and respiratory symptoms during the first 6 years.¹⁰ Exposure to animal allergens constitutes a relevant risk factor for the development of allergic sensitization and respiratory allergic diseases (e.g., asthma and rhinoconjunctivitis) in individuals who are susceptible.¹¹

In a previous report on our Polish Mother and Child Cohort (REPRO_PL) study, the associations between different environmental factors that affect pregnant women and young children and children's health status were found.^{12–15} Our hypothesis of this study is that early exposure to some environmental factors might influence the new onset and remission of atopic diseases in early school-aged children. The aim was to study associations between home environment factors and allergic diseases at 1 year of life and new onset and remission of children's allergic diagnosis at ages 7–9 years. The incidence and remission were calculated by comparing diagnoses in the first year of life with diagnoses at ages 7–9 years.

METHODS

Study Design and Population

The present study was based on data from the REPRO_PL study, a multicenter prospective cohort study established in 2007.^{12–15} The recruitment of mothers and the follow-up procedures and complete description of the methodological assumptions have been published elsewhere.^{16,17} Briefly, the women were recruited during the first trimester of pregnancy at maternity units or clinics in two regions of Poland (Lodz and Legnica) if they fulfilled the following inclusion criteria: single pregnancy up to 12 weeks of gestation, no assisted conception, no pregnancy complications, and no chronic diseases as specified in the study protocol.¹⁶ Women were interviewed during their pregnancy and gave biologic samples for assessment of the level of exposure to a variety of environmental factors. One year after the child's birth, an invitation letter was sent to the mothers to participate in the REPRO_PL study that proposed having the child's health status examined. Within the next 2 weeks, a telephone call was made to schedule a mother and child visit at the medical center for an examination by a pediatrician/allergist (JJ, MBK, KK).¹⁷

At 7 and 9 years after the child's birth, an invitation letter was again sent to the mothers with an offer to participate in follow-up examinations that

covered exposure (including questionnaire data and cotinine measurements in the child's urine) and the child's health status assessment.¹⁸ The current analysis was restricted to 214 children by the age of 7–9 years. All the mothers of the patients gave their written consent before the study. The study was approved by the ethics committee of the Nofer Institute of Occupational Medicine, Łódź, Poland (decision 7/2007, 3/2008, and 22/2014), for the mothers and children up to 7 years of age, and by the medical ethics committee of the Medical University of Lodz (decision RNN/388/17/KE) for the older children.

Assessment of Children's Prenatal and Postnatal Exposure to Environmental Factors

The relevant exposure data were assessed based on the questionnaire during interviews. The questionnaire covered demographic and socioeconomic information, medical and reproductive history, and home environment. Prenatal exposure to tobacco constituents was assessed based on the questionnaire data and cotinine levels in saliva collected from the mothers during the third trimester of pregnancy (range, 30–34 weeks).¹⁹ The child's exposure to environmental tobacco smoke was assessed based on cotinine levels in urine collected from children at ages 7–9 years (as described by Stragierowicz *et al.*²⁰ and Lupsa *et al.*²¹). The cotinine levels in saliva and in urine were analyzed by using high-performance liquid chromatography coupled with tandem mass spectrometry–positive electrospray ionization and by using the isotope dilution method. A description of the methodological assumptions has been published elsewhere.^{18–20}

Children's Health Assessment

Children's health status was assessed at ~12 months of age (range, 11–14 months) and then at an age between 7 and 9 years. For the appropriate recognition of children's health status, a questionnaire was administered to the mothers and supplemented with information from the medical chart of each child. The clinical examination was performed by a pediatrician/allergist (JJ, MBK, KK) in the presence of the mother or a relative. This part of the questionnaire was developed by an allergist based on recommendations from the International Study of Asthma and Allergies in Childhood and has been applied previously.^{22,23} In addition, the occurrence of allergy among family members was noted. The patients were defined as having food allergy, asthma, allergic rhinitis, or atopic dermatitis if they had ever been diagnosed by an allergist; asthma at 12 months of age was diagnosed based on modified API (Asthma Predictive Index)²⁴ criteria, which requires four or more wheezing episodes in the past year in addition to one of three major criteria: physician-

diagnosed parental asthma, physician-diagnosed child eczema, sensitization to one or more aeroallergens, or to two of three minor criteria (wheezing apart from colds, blood eosinophil values $\geq 4\%$, or sensitization to one or more food allergens).²⁵ Asthma at ages 7–9 years was defined according to Global Initiative for Asthma (GINA) guidelines.²⁶

The 7–9-year-old patients underwent skin-prick tests. Detailed information on the methods used is available in our previous article.²⁷ Skin-prick testing to standard allergen extracts was done by using Allergopharma, Reinbek, Germany. Reactions > 3 mm in diameter above the negative control recorded at 15 minutes were considered a positive result. Clinical remission of allergic diseases in our patients at ages 7–9 years was defined as the absence of symptoms without the use of medications for at least 12 months before the visit.²⁸ New onset of allergic diseases was defined according to the GINA guidelines.²⁶

Statistical Analysis

The discrete traits were described by using their absolute values and percentages. The numerical traits were depicted by using their mean $32 \pm$ standard deviation values. The measurements of concentrations of cotinine were transformed logarithmically, hence, natural logs were used in consecutive analyses. The associations of a range of potential predictors, such as study participants’ demographic characteristics, environmental and/or housing conditions, environmental tobacco smoke exposure with the prevalence, inclusive of new onsets, and remissions of food allergy, allergic rhinitis, atopic dermatitis, and asthma were assessed by logistic regression. Initially, univariate logistic regression models were applied to assess the relationships between dependent variables and each of the independent variables. Then, a stepwise forward regression was used to select potentially significant co-factors. The independent variables with a *p* value of at least 0.1, estimated in the univariate model, were included in multivariate regression analyses. For non-normally distributed variables, robust standard errors (sandwich estimators) were used. Multivariate regression model estimates for each dependent variable are displayed in the Results section. Missing data were casewise deleted. All the statistical computations were carried out by using Stata special edition release 14.2 (StataCorp LP, College Station, TX). A level of *p* < 0.05 was deemed statistically significant.

RESULTS

Description of the Study Population

Data from 211 participants were included in the analysis (due to loss of follow-up, three participants were excluded). A description of the study cohort, including

Table 1 Description of the study cohort (N = 211)	
Investigated Trait	Statistics
Male patients, <i>n</i> (%)	94 (44.55)
Mother’s age at the child’s birth, mean $\pm$ SD, y	29.18 $\pm$ 4.57
Father’s age at the child’s birth, mean $\pm$ SD, y	31.13 $\pm$ 5.89
Mother’s education, <i>n</i> (%)	
Primary school	7 (3.32)
High school	70 (33.17)
University	134 (63.51)
Father’s education, <i>n</i> (%)	
Primary school	13 (6.22)
High school	107 (51.20)
University	89 (42.58)
Modality of childbirth, <i>n</i> (%)	
Natural spontaneous birth	94 (47.24)
Natural induced childbirth	27 (13.56)
Forceps birth or vacuum extraction	4 (2.01)
Cesarean section	74 (37.19)
Birth weight, mean $\pm$ SD, g	3343.21 $\pm$ 469.23
Male patients	3434.79 $\pm$ 477.19
Female patients	3268.35 $\pm$ 450.99
Breast-feeding, <i>n</i> (%)	188 (95.43)
Breast-feeding, (“How long, in months, have you exclusively breast-fed your child?”), median (interquartile range), mo	6 (3–12)
Parental atopy (“Have you or your spouse or any of your children had allergies?”): “yes” answers, <i>n</i> (%)	63 (29.86)

SD = Standard deviation.

the sex of the child, parental age, education, atopy, type of childbirth, feeding, and birth weight, is given in Table 1. The lifetime prevalence of the selected outcomes is given. Approximately 30% of children had a positive parental history of atopy. Pets were kept in 51% of homes. The level of parental education was high (63.5% of mothers and 42.6% of fathers had a university-level education).

Health Outcomes and Environmental Factors in the First Year of Life and at Ages 7–9 Years

During the first year of life, food allergy was the most common symptom (39%), followed by atopic dermatitis (35%), and asthma (12%). When comparing symptoms at 7–9 years of age with the first year of life, food allergy had decreased by as much as 18.6%, atopic dermatitis had decreased by as much as 23.8%, and

Table 2 Descriptive statistics for the studied patients' home environment and allergic conditions (N =211)

Investigated Trait	Age 1 y	Ages 7–9 y	<i>p</i> *
Parents smoking ("Does anybody in the domicile smoke?"), <i>n</i> (%)	81 (38.57)	60 (28.87)	0.002
Pets at home ("Do you keep cats or dogs in your house—a minimum period of 6 months"), <i>n</i> (%)	102 (51.43)	108 (48.57)	0.503
Age of building, mean $\pm$ SD, y		32.15 $\pm$ 21.86	
Method of heating the flat, <i>n</i> (%)			0.450
Central, oil, or gas heating	69 (75.00)	152 (72.38)	
Coal-fired, coke-fired, or tiled stove	33 (25.00)	58 (27.62)	
There is moisture and/or mold in the house, <i>n</i> (%)	22 (11.34)	31 (14.83)	0.170
There are cockroaches in the house, <i>n</i> (%)	1 (1.05)	3 (1.43)	0.625
There is visible condensation on the windowpanes, <i>n</i> (%)	37 (38.14)	80 (38.10)	0.874
There are carpeted surfaces in the house, <i>n</i> (%)	45 (46.39)	84 (41.18)	0.884
The frequency of house cleaning, <i>n</i> (%)			<0.001
Less than once a wk	57 (59.38)	4 (1.90)	
Once a wk	22 (22.91)	57 (27.15)	
2 times a wk	17 (17.71)	65 (30.95)	
>2 times a wk	0 (0.00)	84 (40.00)	
Concentration of cotinine in mother's saliva, mean $\pm$ SD, pg/mL**	3.66 $\pm$ 1.19		
Concentration of cotinine in children's urine, mean $\pm$ SD, pg/mL**	1.94 $\pm$ 1.58	1.76 $\pm$ 0.99	0.456
Food allergy ("Was your child ever diagnosed with a food allergy by a physician?"), <i>n</i> (%)	70 (39.33)	39 (18.57)	<0.001
Allergic rhinitis ("Was your child ever diagnosed with allergic rhinitis by a physician?"), <i>n</i> (%)	10 (6.02)	31 (14.76)	0.014
Atopic dermatitis ("Was your child ever diagnosed with atopic dermatitis by a physician?"), <i>n</i> (%)	73 (35.44)	50 (23.81)	0.003
Asthma ("Was your child ever diagnosed with asthma by a physician?"), <i>n</i> (%)	20 (12.05)	17 (8.10)	0.296
Skin test panel, <i>n</i> (%)			
Negative		121 (60.50)	
Single allergen		7 (3.5)	
House-dust mites only		13 (6.50)	
Animal dander only		2 (1.00)	
Seasonal allergens only		23 (11.50)	
Mites and other allergens only		34 (17.00)	

SD = Standard deviation.

The data in bold, in every time, represent statistically significant relationships.

*Compared variables at ages 1 y and 7–9 y.

asthma had also decreased by as much as 8%, whereas allergic rhinitis had increased from 6% to 14.8%. At the age of 1 year, in 38.6% of the homes, at least one parent was a smoker, and, at ages 7–9 years, this number had decreased by as much as 28.6%. When comparing reports on the home environment of the children ages 7–9 years, there was a significant increase of reports on house cleaning; the frequency of house cleaning (twice a week) went up from 17.7% to 30.9%. All other home environmental values were similar at both points of measurement. Data about the health outcomes and home environmental factors are given in Table 2.

New Onset and Remission of Asthma Symptoms

In univariate analysis, maternal education (university degree) decreased the risk of new onset of asthma and increased the risk of asthma remission; however, this relationship was absent in multivariate analysis. In both uni- and multivariate analyses, parental atopy increased the risk of new onset of asthma and decreased the risk of asthma remission. The odds ratio (OR) for the variables in multivariate logistic regression analysis was OR 4.00 (95% confidence interval [CI], 2.11–7.58; $p < 0.001$) and OR 0.25 (95% CI, 0.13–0.47; $p < 0.001$), respectively.

New Onset and Remission of Food Allergy

In univariate analysis, the father's age decreased the risk of new onset of food allergy and increased the risk of food allergy remission; however, this relationship was absent in multivariate analysis. In both uni- and multivariate analyses, hypersensitivity to seasonal allergens (OR 4.28 [95% CI, 2.07–8.85], $p < 0.001$) and to mites and any other allergen (OR 2.89 [95% CI, 1.46–5.71], $p = 0.002$) increased the risk of new onset of food allergy and decreased the risk of food allergy remission (OR 0.23 [95% CI, 0.11–0.48], $p < 0.001$; and OR 0.35 [95% CI, 0.17–0.68], $p = 0.002$, respectively). ORs for the variables are given for multivariate logistic regression analysis.

New Onset and Remission of Allergic Rhinitis

In both, uni- and multivariate analyses, more frequent house cleaning decreased the risk of new onset of allergic rhinitis (OR 0.21 [95% CI, 0.06–0.71], $p = 0.012$) and increased the risk of allergic rhinitis remission (OR 4.74 [95% CI, 1.41–15.95], $p = 0.012$). In both, uni- and multivariate analyses, hypersensitivity to mites and other allergens increased the risk of new onset of allergic rhinitis (OR 5.06 [95% CI, 2.06–12.42], $p < 0.001$) and decreased the risk of allergic rhinitis remission (OR 0.20 [95% CI, 0.08–0.49], $p < 0.001$). The ORs for the variables are given for multivariate logistic regression analysis.

New Onset and Remission of Atopic Dermatitis

In both, uni- and multivariate analyses, more frequent house cleaning decreased the risk of new onset of atopic dermatitis (OR 0.05 [95% CI, 0.01–0.28], $p = 0.001$) and increased the risk of atopic dermatitis remission (OR 19.17 [95% CI, 3.59–10.24], $p = 0.001$). In both uni- and multivariate analyses, hypersensitivity to mites and any other allergen increased the risk of new onset of atopic dermatitis (OR 3.27 [95% CI, 1.32–8.05], $p = 0.010$) and decreased the risk of atopic dermatitis remission (OR 0.31 [95% CI, 0.12–0.63], $p = 0.010$). ORs for the variables are given for multivariate logistic regression analysis. In univariate analysis, the cotinine concentration in mother's saliva at pregnancy decreased the risk of the new onset of atopic dermatitis and increased the risk of atopic dermatitis remission; however, this relationship was absent in multivariate analysis.

New Onset and Remission of Allergic Diseases at the Ages 7–9 Years

Ten children (5.6%) developed food allergy until age 7–9 years, 24 (14.5%) developed allergic rhinitis, 19 (9.3%) developed atopic dermatitis, and 13 (7.9%) developed asthma. The remission of symptoms was observed in 41 children (23%) for food allergy, 9 (5.5%)

for allergic rhinitis, 42 (20.5%) for atopic dermatitis, and 20 (12%) for asthma.

Associations Between the New Onset and Remission of Symptoms at Ages 7–9 Years and Allergic Diseases at 1 Year of Life

With regard to new onset allergic diseases at ages 7–9 years, food allergy, allergic rhinitis, and atopic dermatitis, there was a positive correlation with the presence of another allergic disease (except asthma) at the first year of life; the correlation with the remission was negative. Children who had food allergy, allergic rhinitis, or atopic dermatitis at the age of 1 year had more of a chance of developing other atopic diseases (except asthma) at the age of 7–9 years and less chance of having remission of symptoms. The above associations were not observed with regard to asthma. Data are presented in Table 3.

DISCUSSION

We conducted the study to establish a possible association among demographic data, atopy, and environmental factors present in the first year of life and new onset and remission of atopic diseases in early school-aged children. In the present study, the common risk factor for new onset/remission of atopic dermatitis, food allergy, and allergy rhinitis was hyperreactivity to mites and any other allergen. For new onset/remission of allergic rhinitis and atopic dermatitis, frequent house cleaning was associated with less new onset of the disease at ages 7–9 years. Parental atopy was the only factor associated with new onset/remission of asthma. Many studies found that early life home environment can influence the development of childhood asthma and allergic diseases later in life.^{1,6,8} Lin *et al.*¹ found that home environment factors, such as mold contamination, stuffy odor, air dryness, and environmental tobacco smoke exposure in the first 2 years of life were positively associated with new onset of asthmatic and allergic symptoms among preschool children and negatively associated with the remission of symptoms.

The BAMSE (Swedish abbreviation for Children, Allergy, Milieu, Stockholm, Epidemiology) study²⁹ and subsequent follow-ups revealed that exposure to mold or dampness during infancy increased the risk of asthma and rhinitis up to 16 years of age, particularly for nonallergic disease. Early exposure to mold or dampness seemed particularly associated with persistent asthma through adolescence.³⁰ Tischer *et al.*³¹ showed that exposure to visible mold and/or dampness during the first 2 years of life was associated with an increased risk of allergic rhinitis later in childhood.

In contrast, the Boston birth cohort identified a protective effect of yeasts measured in bedroom dust sam-

Table 3 Analysis of the association between new onsets and remission of food allergy, allergic rhinitis, atopic dermatitis, and asthma at the ages 7–9 years compared with age 1 year, with reference to the remaining conditions in question (multivariate regression models) (N = 211)

Health Condition	New Onset		Remission	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Food allergy				
Allergic rhinitis	2.62 (1.04–6.62)	0.041	0.38 (0.15–0.96)	0.041
Atopic dermatitis	11.32 (6.35–20.16)	<0.001	0.09 (0.05–0.16)	<0.001
Asthma	2.06 (0.82–5.16)	0.121	0.48 (0.19–1.21)	0.121
Allergic rhinitis RGIC rhinitis				
Food allergy	3.06 (1.16–8.06)	0.023	0.33 (0.12–0.86)	0.023
Atopic dermatitis	3.31 (1.37–7.97)	0.008	0.30(0.13–0.73)	0.008
Asthma	1.01 (0.30–3.41)	0.989	0.99 (0.29–3.35)	0.989
Atopic dermatitis [C dermatitis]				
Food allergy	11.23 (6.28–20.09)	<0.001	0.09 (0.05–0.16)	<0.001
Allergic rhinitis	3.52 (1.50–8.24)	0.004	0.28 (0.12–0.67)	0.004
Asthma	1.78 (0.72–4.36)	0.211	0.56 (0.23–1.38)	0.211
Asthma				
Food allergy	1.89 (0.66–5.40)	0.234	0.53 (0.18–1.51)	0.234
Allergic rhinitis	1.26 (0.40–3.94)	0.688	0.79 (0.25–2.47)	0.688
Atopic dermatitis	2.00 (0.74–5.44)	0.173	0.50 (0.18–1.35)	0.173

OR = Odds ratio; CI = confidence interval.

The data in bold, in every time, represent statistically significant relationships.

*Compared variables at ages 1 y and 7–9 y.

ples taken at the age 3 months, on wheezing at 1 year, and on the development of asthma at age 13 years.^{32,33}

In the LISA (Influence of Life-style factors on Development of the Immune System and Allergies in East and West Germany) German birth cohort study,³⁴ exposure to higher fungal diversity in the living room during infancy, assessed by using molecular techniques, was associated with a reduced risk of developing sensitization at 6 years and ever-wheezing until the age of 10 years. However, these associations were no more significant in the longitudinal analyses when considering the impact of several follow-ups. We did not find any statistically significant correlation between levels of dampness and/or mold present at home at both study points (as reported by parents or caregivers) and new onset or remission of any allergic diseases.

An increased risk of allergic diseases among individuals exposed to tobacco smoke is biologically plausible because smoking is known to facilitate sensitization to perennial indoor allergens, such as those caused by furry animals as well as to some outdoor allergens, *e.g.*, pollen.³⁵ Based on the Pregnancy-related Assessment Monitoring Survey,³⁶ the most recent results show that even > 12% of pregnant women in Poland smoke.³⁷

Our analysis found evidence for associations between the concentration of cotinine in mother's saliva collected during the third trimester of pregnancy and new onset and remission of atopic dermatitis in chil-

dren ages 7–9 years (only in univariate analysis). These findings were in accordance with the study by Taylor-Robinson *et al.*³⁸ in which smoking during pregnancy was associated with reduced odds of eczema. Data collected in Sweden by Hjern *et al.*³⁹ found that children of mothers who smoked at least 15 cigarettes a day tended to have lower odds for having atopic eczema.

A large Danish study also showed a tendency toward a protective effect of smoking on hay fever and eczema.⁴⁰ A population-based birth cohort study in Japan, which included 3296 mother-child pairs, revealed that maternal serum cotinine during pregnancy was associated with an increased risk of wheezing in the children at ages 1, 2, and 4 years but disappeared at age 7 years. In contrast, maternal cotinine levels were inversely associated with the prevalence of eczema in children at age 7 years.⁴¹ Several studies found no association, and others found the opposite.⁴ This relationship may be modified by some confounding factors related to their socioeconomic position³⁸ or genetic polymorphism in Glutathione S-transferase Mu 1, tumor necrosis factor α TLR4/Toll-like receptor 4/GSTP1 - Glutathione S-Transferase Pi 1.^{42,43} In our study, this relationship was observed only in univariate analysis.

In the present study, the children who had food allergy, allergic rhinitis, or atopic dermatitis at the age 1 year had more of a chance of developing other aller-

gic disease (except of asthma) at ages 7–9 years and less of a chance of having a remission of symptoms; the above associations were not observed with regard to asthma. These results were consistent with other studies. Several prospective birth cohorts showed associations between early onset of atopic dermatitis and the development of asthma and allergic rhinitis in school-aged children.^{44,45} The risks seem to be even greater in children with the early onset persistent atopic dermatitis phenotype.⁴⁶ The combined study by the high-risk Melbourne Atopy Cohort Study⁴⁷ and the population-based Influences of Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood plus Air Pollution and Genetics cohort⁴⁸ found that food sensitization in the first 2 years of life was associated with increased risks of asthma and allergic rhinitis by age 10 years.⁴⁹

The majority of studies of food allergy are based only on self-reported food reactions than on objective measures, and oral food challenges do not have consistent or standardized criteria in defining outcomes.⁵⁰ For the purpose of the present study, we decided to base the diagnosis of food allergy on the allergist's report to minimize the risk of data overestimation. Food allergy was observed in almost 40% of our patients at the age of 1 year, which was high compared with data from Western countries where the prevalence of challenge-proven food allergy has been reported to be 4% in the United Kingdom, 6.8% in Norway, and >10% at age 12 months in Australia.⁵¹ There is evidence of ethnic-dependent variability and a strong environmental influence on food allergy risk.

A meta-analysis of 13 cohorts that studied the atopic march also demonstrated that early food sensitization was associated with increased risks of wheeze and/or asthma and allergic rhinitis at 4 to 8 years of age.⁵² A review by Tham and Leung⁵³ explored the evidence that supports the concept that an impaired epithelial barrier in atopic dermatitis initiates progression to epicutaneous sensitization, food allergy, and allergic airway disease in later life. Inherent genetic susceptibility influence one's risk of progression from atopic dermatitis to allergic airway disease, which was confirmed in the Genome-wide association study.⁵⁴

Data collected in 399 school-aged participants of the urban Perinatale Asthma Umwelt Langzeit Allergie Studie indicated that home cleanliness effectively reduced the dust amount. These quantifiable dust exposures protected from asthma and allergies in this prospective study.⁵⁵ In the present study, more frequent house cleaning negatively correlated with new onset of allergic rhinitis and atopic dermatitis, and positively correlated with allergic rhinitis and atopic dermatitis remission in both uni- and multivariate analyses. In contrast, Fotopoulou *et al.*⁵⁶ observed that excessive cleanliness should be considered as a negative prog-

nostic factor, which leads to a higher Scoring Atopic Dermatitis score in children with atopic dermatitis, which is consistent with our previous research.¹³

Limitations of our study were the self-reported parental data with regard to the home environment. Another limitation was that the assessment of allergic diseases at age 1 year was based on a physician's diagnosis without allergy testing. However, there are data that skin testing for aeroallergens may not be a routine procedure in small children due to low rates of aeroallergens sensitization and lack of predictors of sensitization in children with asthma during the first 2 years of life.⁵⁷

Recent investigations implicate parental atopic history among the risk factors for development of multiple atopic comorbidities in young children with atopic dermatitis.⁵⁸ A family history of asthma and atopy is one of the strongest risk factors for childhood asthma,⁵⁹ and for rhinoconjunctivitis in 9-to-11-year-old children,⁶⁰ which is in accordance with our observations. Atopic dermatitis and mother's and siblings' atopy were risk factors for the development of atopy. Moreover, asthma was positively associated with a mother's history of atopy in Italian children.⁶¹ Data collected from a prospective, longitudinal cohort study of children born in western Sweden showed that parental allergic rhinitis is the independent risk factor for allergic rhinitis,⁶² and the most common trigger factors for it were pollen (85%), furry animals (34%), and house-dust mites (17%). In the present study, sensitization to house-dust mites and other allergens was associated with new onset of allergic rhinitis, atopic dermatitis, and food allergy.

According to the current understanding, it may be argued that maternal education is the most important social determinant of early child health and a risk factor for early childhood asthma across Europe. Across many cohorts, children born to mothers in the lowest tertile of education were 46% more likely to develop asthma than children born to mothers in the highest tertile.⁶³ However, in our article, this association was not observed in multivariate analysis.

CONCLUSION

Our findings indicated that new onset or remission of allergic diseases were linked with hypersensitivity to house-dust mites in children who were polysensitized and with parental atopy. In addition, children who had food allergy, allergic rhinitis, or atopic dermatitis at the age of 1 year had more of a chance of developing other diseases (except asthma) at the age of 7–9 years and a lesser chance of remission of symptoms.

REFERENCES

1. Lin Z, Norback D, Wang T, et al. The first 2-year home environment in relation to the new onset and remission of asthmatic

- and allergic symptoms in 4246 preschool children. *Sci Total Environ.* 2016; 553:204–210.
2. Caillaud D, Leynaert B, Keirsbulck M, Nadif R; mould ANSES working group. Indoor mould exposure, asthma and rhinitis: findings from systematic reviews and recent longitudinal studies. *Eur Respir Rev.* 2018; 15:27. pii: 170137.
 3. Weinmayr G, Gehring U, Genuneit J, et al. Dampness and moulds in relation to respiratory and allergic symptoms in children: results from phase two of the International Study of Asthma and Allergies in Childhood (ISAAC Phase Two). *Clin Exp Allergy.* 2013; 43:762–774.
 4. Saulyte J, Regueira C, Montes-Martínez A, Khudyakov P, Takouche B. Active or passive exposure to tobacco smoking and allergic rhinitis, allergic dermatitis, and food allergy in adults and children: a systematic review and meta-analysis. *PLoS Med.* 2014; 11:e1001611.
 5. Manthei DM, Jackson DJ, Evans MD, et al. Protection from asthma in high-risk birth cohort by attenuated P2X(7) function. *J Allergy Clin Immunol.* 2012; 130:496–502.
 6. Chan-Yeung M, Hegele RC, Dimich-Ward H, et al. Early environmental determinants of asthma risk in high-risk birth cohort. *Pediatr Allergy Immunol.* 2008; 19:482–489.
 7. Kozyrskyj AL, Bahreinian S, Azad MB. Early life exposures: impact on asthma and allergic disease. *Curr Opin Allergy Clin Immunol.* 2011; 11:400–406.
 8. Neuman Å, Hohmann C, Orsini N, et al. Maternal smoking in pregnancy and asthma in preschool children: a pooled analysis of eight birth cohorts. *Am J Respir Crit Care Med.* 2012; 186:1037–1043.
 9. Maatta AM, Huovinen AE, Kotaniemi-Syrjänen A, et al. Urine cotinine as a marker of environmental tobacco smoke exposure in recurrent respiratory symptoms of early childhood. *Am J Respir Crit Care Med.* 2017; 195:A1304.
 10. Karvonen AM, Hyvärinen A, Korppi M, et al. Moisture damage and asthma: a birth cohort study. *Pediatrics.* 2015; 135:e598–e606.
 11. Konradsen JR, Fujisawa T, van Hage M, et al. Allergy to furry animals: new insights, diagnostic approaches, and challenges. *J Allergy Clin Immunol.* 2015; 135:616–625.
 12. Stelmach I, Grzelewski T, Bobrowska-Korzeniowska M, et al. The role of zinc, copper, plasma glutathione peroxidase enzyme, and vitamins in the development of allergic diseases in early childhood: the Polish Mother and Child Cohort study. *Allergy Asthma Proc.* 2014; 35:227–232.
 13. Stelmach I, Bobrowska-Korzeniowska M, Smejda K, et al. Risk factors for the development of atopic dermatitis and early wheeze. *Allergy Asthma Proc.* 2014; 35:382–389.
 14. Stelmach I, Majak P, Jerzynska J, et al. Cord serum 25-hydroxyvitamin D correlates with early childhood viral-induced wheezing. *Respir Med.* 2015; 109:38–43.
 15. Stelmach I, Majak P, Jerzynska J, et al. The effect of prenatal exposure to phthalates on food allergy and early eczema in inner-city children. *Allergy Asthma Proc.* 2015; 36:72–78.
 16. Polańska K, Hanke W, Gromadzińska J, et al. Polish Mother and Child Cohort study—defining the problem, the aim of the study and methodological assumptions. *Int J Occup Med Environ Health.* 2009; 22:383–391.
 17. Polańska K, Hanke W, Jurewicz J, et al. Polish Mother and Child Cohort Study (REPRO_PL)—methodology of follow-up of the children. *Int J Occup Med Environ Health.* 2011; 24:391–398.
 18. Polańska K, Hanke W, Król A, et al. Mother and Child Cohort Study (REPRO_PL)—Methodology of the follow-up of the children at the age of 7. *Int J Occup Med Environ Health.* 2016; 29:883–893.
 19. Polanska K, Krol A, Kaluzny P, et al. Estimation of saliva cotinine cut-off points for active and passive smoking during pregnancy-Polish Mother and Child Cohort (REPRO_PL). *Int J Environ Res Public Health.* 2016; 13. pii: 1216.
 20. Stragierowicz J, Mikołajewska K, Zawadzka-Stolarz M, Polańska K, and Ligocka D. Estimation of cutoff values of cotinine in urine and saliva for pregnant women in Poland. *Biomed Res Int.* 2013; 2013:386784.
 21. Lupsa IR, Nunes B, Ligocka D, et al. Urinary cotinine levels and environmental tobacco smoke in mothers and children of Romania. Portugal and Poland within the European human biomonitoring pilot study. *Environ Res.* 2015; 141:106–117.
 22. Gromadzinska J, Polanska K, Kozłowska L, et al. Vitamins A and E during pregnancy and allergy symptoms in an early childhood-lack of association with tobacco smoke exposure. *Int J Environ Res Public Health.* 2018; 15. pii: E1245.
 23. Strachan D, Sibbald B, Weiland S, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol.* 1997; 8:161–176.
 24. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med.* 2000; 162(4 Pt 1):1403–1406.
 25. Chang TS, Lemanske RF Jr, Guilbert TW, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract.* 2013; 1:152–156.
 26. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2014 [cited]. Available from: <http://www.ginasthma.org/>. Accessed on 20 May 2018.
 27. Stelmach I, Smejda K, Jerzynska J, et al. Decreased markers of atopy in children with presumed early exposure to allergens, unhygienic conditions, and infections. *Ann Allergy Asthma Immunol.* 2007; 99:170–177.
 28. Assar S, Idani E, Monajemzadeh M, Ganai M, Rahim F. Remission of childhood asthma after entering the second decade of life: a hospital based cohort. *Iran J Allergy Asthma Immunol.* 2013; 12:124–128.
 29. Schultz ES, Hallberg J, Andersson N, et al. Early life determinants of lung function change from childhood to adolescence. *Respir Med.* 2018; 139:48–54.
 30. Thacher JD, Gruzdeva O, Pershagen G, et al. Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. *Allergy.* 2017; 72:967–974.
 31. Tischer CG, Hohmann C, Thiering E, et al. Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy.* 2011; 66:1570–1579.
 32. Behbod B, Sordillo JE, Hoffman EB, et al. Wheeze in infancy: protection associated with yeasts in house dust contrasts with increased risk associated with yeasts in indoor air and other fungal taxa. *Allergy.* 2013; 68:1410–1418.
 33. Behbod B, Sordillo JE, Hoffman EB, et al. Asthma and allergy development: contrasting influences of yeasts and other fungal exposures. *Clin Exp Allergy.* 2015; 45:154–163.
 34. Tischer C, Weikl F, Probst AJ, Standl M, Heinrich J, Pritsch K. Urban dust microbiome: impact on later atopy and wheezing. *Environ Health Perspect.* 2016; 124:1919–1923.
 35. Lannerö E, Wickman M, van Hage M, Bergström A, Pershagen G, Nordvall L. Exposure to environmental tobacco smoke and sensitisation in children. *Thorax.* 2008; 63:172–176.
 36. Shulman HB, D'Angelo DV, Harrison L, Smith RA, Warner L. The Pregnancy Risk Assessment Monitoring System (PRAMS): Overview of Design and Methodology. *Am J Public Health.* 2018;108(10):1305–1313.
 37. Wojtyła A, Goździewska M, Paprzycki P, Biliński P. Tobacco-related foetal origin of adult diseases hypothesis—population studies in Poland. *Ann Agric Environ Med.* 2012; 19:117–128.

38. Taylor-Robinson DC, Williams H, Pearce A, Law C, Hope S. Do early-life exposures explain why more advantaged children get eczema? Findings from the U.K. Millennium Cohort Study. *Br J Dermatol*. 2016; 174:569–578.
39. Hjern A, Hedberg A, Haglund B, Rosén M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. *Clin Exp Allergy*. 2001; 31:908–914.
40. Magnusson LL, Olesen AB, Wennborg H, Olsen J. Wheezing, asthma, hayfever, and atopic eczema in relation to maternal occupations in pregnancy. *Occup Environ Med*. 2006 Sep;63(9): 640–6.
41. Goudarzi H, Konno S, Kimura H, et al. Contrasting associations of maternal smoking and pre-pregnancy BMI with wheeze and eczema in children. *Sci Total Environ*. 2018; 639:1601–1609.
42. Choi KY, Yang SI, Lee E, et al. Prenatal second-hand smoke increases atopic dermatitis in children with TNF- α /TLR4/GSTP1 polymorphisms. *Pediatr Allergy Immunol Pulmonol*. 2017; 30:18–25.
43. Wang IJ, Guo YL, Lin TJ, Chen PC, Wu YN. GSTM1, GSTP1, prenatal smoke exposure, and atopic dermatitis. *Ann Allergy Asthma Immunol*. 2010; 105:124–129.
44. Saunes M, Øien T, Dotterud CK, et al. Early eczema and the risk of childhood asthma: a prospective, population-based study. *BMC Pediatr*. 2012; 12:168.
45. von Kobyletzki LB, Bornehag CG, Hasselgren M, Larsson M, Lindström CB, Svensson Å. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. *BMC Dermatol*. 2012; 12:11.
46. Carlsten C, Dimich-Ward H, Ferguson A, et al. Atopic dermatitis in a high-risk cohort: natural history, associated allergic outcomes, and risk factors. *Ann Allergy Asthma Immunol*. 2013; 110:24–28.
47. Lowe AJ, Lodge CJ, Allen KJ, et al. Cohort profile: Melbourne Atopy Cohort study (MACS). *Int J Epidemiol* 2017; 46: 25–26.
48. Heinrich J, Brüske I, Cramer C, et al. GINIplus und LISApplus - Design und ausgewählte Ergebnisse zweier deutscher Geburtskohorten zum natürlichen Verlauf atopischer Erkrankungen sowie deren Determinanten. [GINIplus and LISApplus - Design and selected results of two German birth cohorts about natural course of atopic diseases and its determinants]. *Allergologie*. 2012;35(1):20–31.
49. Alduraywish SA, Standl M, Lodge CJ, et al. Is there a march from early food sensitization to later childhood allergic airway disease? Results from two prospective birth cohort studies. *Pediatr Allergy Immunol*. 2017; 28:30–37.
50. Rona RJ, Keil T, Summers C, et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007; 120:638–646.
51. Loh W, Tang MLK. The epidemiology of food allergy in the global context. *Int J Environ Res Public Health*. 2018; 15. pii: E2043.
52. Alduraywish SA, Lodge CJ, Campbell B, et al. The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies. *Allergy*. 2016; 71:77–89.
53. Tham EH, Leung DY. Mechanisms by which atopic dermatitis predisposes to food allergy and the atopic march. *Allergy Asthma Immunol Res*. 2019; 11:4–15.
54. Ferreira MA, Vonk JM, Baurecht H, et al. Shared genetic origin of asthma, hay fever and eczema elucidates allergic disease biology. *Nat Genet*. 2017; 49:1752–1757.
55. Weber J, Illi S, Nowak D, et al. Asthma and the hygiene hypothesis. Does cleanliness matter?, *Am J Respir Crit Care Med*. 2015; 191:522–529.
56. Fotopoulou M, Iordanidou M, Vasileiou E, Trypsianis G, Chatzimichael A, Paraskakis E. A short period of breastfeeding in infancy, excessive house cleaning, absence of older sibling, and passive smoking are related to more severe atopic dermatitis in children. *Eur J Dermatol*. 2018; 28:56–63.
57. Sahiner UM, Buyuktiryaki AB, Yavuz ST, et al. The spectrum of aeroallergen sensitization in children diagnosed with asthma during first 2 years of life. *Allergy Asthma Proc*. 2013; 34:356–361.
58. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. *J Allergy Clin Immunol*. 2019; 143:46–55.
59. Strina A, Barreto ML, Cooper PJ, Rodrigues LC. Risk factors for non-atopic asthma/wheeze in children and adolescents: a systematic review. *Emerg Themes Epidemiol*. 2014; 11:5.
60. Civelek E, Yavuz ST, Boz AB, et al. Epidemiology and burden of rhinitis and rhinoconjunctivitis in 9- to 11-year-old children. *Am J Rhinol Allergy*. 2010; 24:364–370.
61. Indinnimeo L, Porta D, Forastiere F, et al. Prevalence and risk factors for atopic disease in a population of preschool children in Rome: challenges to early intervention. *Int J Immunopathol Pharmacol*. 2016; 29:308–319.
62. Vasileiadou S, Wennergeren G, Strömberg C, et al. Eating fish and farm life reduce allergic rhinitis at the age of twelve. *Pediatr Allergy Immunol*. 2018; 29:283–289.
63. Lewis KM, Ruiz M, Goldblatt P, et al. Mother's education and offspring asthma risk in 10 European cohort studies. *Eur J Epidemiol*. 2017; 32:797–805. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.