

Maria FOTOPOULOU¹
Maria IORDANIDOU¹
Eleni VASILEIOU¹
Grigorios TRYPSIANIS²
Athanasios CHATZIMICHAEL¹
Emmanouil PARASKAKIS¹

¹ Department of Paediatrics,
University Hospital of Alexandroupolis,
Democritus University of Thrace,
Alexandroupolis, Greece

² Department of Medical Statistics,
Democritus University of Thrace,
Alexandroupolis, Greece

Reprints: E. Paraskakis
<eparaska@med.duth.gr>

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

Background: Atopic dermatitis (AD) is one of the most common, chronic or chronically relapsing inflammatory skin diseases that affect children. Multiple genetic and environmental factors appear to regulate the pathogenesis of AD. **Objectives:** Our aim was to investigate the possible association between family, social, dieting, atopic and environmental factors and the severity of AD evaluated by SCORAD scores in children. **Materials & methods:** The study group included 100 children with AD who attended a paediatric dermatology outpatient clinic with a median age of 18.5 months. The diagnosis of AD was established on the basis of the clinical criteria according to the American Dermatology Society, while the SCORAD score was used to evaluate disease severity. **Results:** Multivariate linear regression analysis disclosed that excessive cleanliness ($p < 0.001$), RAST level greater than 0.7 KU/l ($p < 0.001$), breastfeeding for less than two months ($p = 0.001$), and the absence of an older sibling ($p = 0.049$) were statistically significant independent determinants for high SCORAD scores. Multivariate logistic regression analysis showed that excessive cleanliness ($p < 0.001$) was the strongest independent risk factor for severe AD (SCORAD > 36) (aOR: 59.4; 95% CI: 10.9-322.6). RAST level greater than 0.7 KU/l (aOR: 7.9; 95% CI: 1.5-41.0; $p = 0.014$) and severe passive smoking (aOR: 4.6; 95% CI: 1.0-22.1; $p = 0.050$) also showed a significant independent, but clearly weaker, association with severe AD. **Conclusions:** A short duration of breastfeeding, absence of older siblings, parental passive smoking, food allergens along with aeroallergens, and excessive cleanliness should be considered as negative prognostic factors, leading to a higher SCORAD score in children with AD.

Key words: atopic dermatitis, breastfeeding, cleanliness, hygiene hypothesis, passive smoking

Article accepted on 21/05/2017

Atopic dermatitis (AD) is one of the most common, chronic or chronically relapsing inflammatory skin diseases that affect approximately 5-25% of children worldwide [1]. In contrast to the typical and distinct clinical picture, the pathophysiology of AD appears to be rather complex and obscure. A multitude of genetic and environmental factors seem to be involved, regulating the pathogenesis of AD. Although the involvement of genetic factors in the pathogenesis and clinical manifestations of AD has been demonstrated in recent studies, its increasing incidence in developed countries, as well as the wide range of disease severity on an individual basis, imply that there might be environmental factors determining the clinical expression and severity of the disease [2-4]. In response to an increasing recognition of the role of the environment in atopic diseases, the so called “hygiene hypothesis” was formulated in the late 1980s, based on the observation that AD and other atopic diseases were noted

to be more common in children growing up in urban areas with a western lifestyle (smaller families, excessive cleanliness, day-care attendance, and a higher socioeconomic status) [5, 6]. The hygiene hypothesis postulates that the overprotective environment of western lifestyle leads the immune system to be less exposed to environmental allergens and infections during early life and thus to be more susceptible to allergies. Moreover, a number of previous studies have shown that several environmental factors, such as breastfeeding [7], passive smoking [8], and sensitization to food or aeroallergens [9, 10], affect AD. However, there are studies with contradictory results regarding the association between the above-mentioned factors and the development or the severity of AD in children [11-13]. In this study, our aim was to investigate the possible association between multiple family, social, dieting, atopic and environmental factors and the severity of AD evaluated by the SCORAD score in children.

doi: 10.1684/ejd.2017.3165

Methods

This was a single-centre study addressing the possible association between several factors and AD severity in children. After approval by the local ethics committee and institutional scientific review, along with the parental consent, 100 children were evaluated on an outpatient basis by the Dermatology Department of Pentelis General Hospital of Pediatrics, in Athens, Greece.

Complete physical examination and routine laboratory parameter tests were carried out for each child participating in the study. In addition, disease-specific parameter tests were performed, including serum IgE, specific prick tests for food allergens, and specific IgE measurement (RAST test) for aeroallergens. The diagnosis of AD was established on the basis of the clinical criteria according to the American Dermatology Society, while the SCORAD score was used to evaluate disease severity. A questionnaire was completed for each child by the examining physician. The questionnaire included the following sections:

- (1) Personal history: this section examines children's history relevant to atopic dermatitis (time at onset, symptoms, severity, and exacerbations) or other atopic diseases, such as asthma, hay fever or disorders of the digestive system.
- (2) Family history of AD, asthma or hay fever.
- (3) Food allergy, including time at onset of allergy to solid food or any kind of reaction related to food, and duration of breastfeeding.
- (4) Socioeconomic status, early-life exposure to infections, and kindergarten or school attendance.

The specific IgE (RAST) for the following allergens were tested: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, egg white, egg yolk, cow milk, alpha-lactalbumin, beef, orange, banana, tomato, gluten, soya, cereal mix, nut mix, fish, pellitory, fungi, and olive tree. In addition, each child with AD was classified according to the maximum RAST level, as assessed for at least one of the studied allergens (Class O, I, II, III). Assessment of overall cleanliness was based not only on house hygiene, but also on personal hygiene. House hygiene included the general appearance of the house, kitchen hygiene, as well as frequency of house cleaning, and personal hygiene included frequency of hand and face washing and frequency of bathing. House cleaning was defined mainly according to times per week that the family cleans the house. We classified house cleaning as normal (1-2 times/week), frequent (3-4 times/week), and very frequent (daily, including daily cleanliness of the bathroom using antiseptics and bleach). Passive smoking was also evaluated. Questions about smoking in the house (whether the mother or father smokes) and the number of cigarettes smoked daily inside the house were included in the questionnaire.

Statistical analysis

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences (SPSS), version 19.0 (SPSS, Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test for normality was performed. SCORAD, which was normally distributed, was expressed as the mean $\pm$ standard deviation (SD), while non-normally distributed variables

were expressed as the median and interquartile range (IQR). The median split was used to convert several continuous variables into dichotomous variables. Categorical variables were expressed as frequencies (and percentage). The Student's *t* test and one-way analysis of variance were used to determine differences of SCORAD between two or more groups of patients, respectively; post hoc analyses were performed using the Tukey's test. The chi-square test was used to evaluate any potential association between the presence of severe AD (SCORAD > 36; median value) and the patients' characteristics; odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated by means of simple logistic regression analysis, as the measure of the above associations. To assess the independent effect of patients' characteristics on SCORAD and the presence of severe AD, multivariate stepwise linear and logistic regression models were respectively constructed. All tests were two-tailed and statistical significance was considered for *p* values less than 0.05.

Results

The study group consisted of 100 children with AD who attended a paediatric dermatology outpatient clinic with a median age of 18.5 months (range: 1-105; mean age of 23.39 ± 20.96 months). Of these, 53 (53.0%) were girls, with a median age of 17 months (IQR: 5.50-35.5 months) and 47 (47.0%) were boys, with a median age of 22 months (IQR: 7-36 months). Data included information about demographical characteristics, family status, medical and family history of allergic diseases, breastfeeding, hygiene status, and kindergarten attendance, and is presented in tables 1, 2. The social class of the family was recorded with respect to the father's occupation: (A) Upper class: professionals, directors, business managers; (B) Middle class: "White collar" workers; and (C) Lower class: "Blue collar" workers, farmers, and labourers.

The classification of contributing factors according to patients' age revealed that a short period of breastfeeding was more frequent in younger ages (82% in subjects ≤ 18.8 months vs 36% in subjects > 18.8 months; $p < 0.001$). Excessive house cleaning was more frequent in younger ages (14%, 16%, and 70% of subjects ≤ 18.8 months vs 36%, 34% and 30% of subjects > 18.8 months were classed with normal, frequent and very frequent cleanliness, respectively; $p < 0.001$). Similarly, passive smoking was more frequent in younger ages (48% in subjects ≤ 18.8 months vs 22% in subjects > 18.8 months; $p = 0.006$). On the other hand, absence of an older sibling was similar in the two age groups (56% in subjects ≤ 18.8 months vs 66% in subjects > 18.8 months; $p = 0.305$).

Among the entire cohort, SCORAD ranged from 8 to 72 with a mean value of 38.55 ± 18.67 (median value: 36). A higher SCORAD was associated with younger age ($p = 0.013$), absence of an older sibling ($p = 0.050$), breastfeeding for less than two months ($p < 0.001$), non-attendance at kindergarten ($p = 0.028$), excessive house cleaning ($p < 0.001$), paternal/maternal smoking of more than one pack per day ($p < 0.001$), severe passive smoking ($p < 0.001$), reported food allergy to more than three allergens ($p < 0.001$), specific IgE to more than one allergen ($p = 0.004$), and a RAST level of more than 0.7 kU/l (Class I)

Table 1. Epidemiological data of patients.

	Patients <i>n</i> = 100
Kindergarten	
No	84
1-12 months	2
13-24 months	10
>24 months	4
Older sibling	
No	61
Yes	39
Social status	
Low	4
Medium	75
High	21
Cleanliness	
Normal	25
Frequent	25
Very frequent	50
Breastfeeding	
No	3
Intermittent up to 2 months	0
Intermittent for 3-5 months	34
Regularly up to 2 months	56
Regularly for 3-5 months	7
Personal history	
Other atopic disease	90
Allergic rhinitis	10
Asthma	0
Family history	
Other atopic disease	51
Allergic rhinitis	0
Asthma	49
Gender	
Male	47
Female	53
Parental smoking (cigarettes/day)	
0	35
1-10	13
11-20	17
>20	35
Passive smoking	
Median IQR	4 (0-6)
Range	0-6
Age (months)	
Median IQR	18.5 (6-36)
Range	1-105

($p < 0.001$). In contrast, SCORAD was not associated with gender ($p = 0.948$), social status ($p = 0.132$), medical history of atopic diseases ($p = 0.716$), family history of atopic diseases ($p = 0.848$), reported aeroallergens ($p = 0.826$), or total serum IgE levels ($p = 0.083$). Multivariate linear regression analysis disclosed that excessive house cleaning ($p < 0.001$), RAST level greater than 0.7 kU/l ($p < 0.001$), breastfeeding for less than two months ($p = 0.001$), and the absence of an older sibling ($p = 0.049$) remained statistically significant

Table 2. Clinical characteristics of patients.

	Patients
Food allergy	
No	46
1-3	29
>3	25
(Median IQR)	1 (0-3)
Aeroallergens	
Sensitized to 0-4	83
Sensitized to >4	17
IQR RAST (Number)	3 (2-4)
Median IQR	1 (0-2)
Range	0-4
RAST (Level)	
<0.35 kU/l (Class 0)	42
0.35-0.7 kU/l (Class I)	14
0.7-3.5 kU/l (Class II)	37
>3.5 kU/l (Class III)	7
Total serum IgE (IU/ml)	
Median IQR	28.50 (13.98-64.75)
Range	1.00-800.00

independent determinants for high SCORAD scores, which account for the 60.3%, 7.1%, 3.5%, and 1.2% variation of variables, respectively (*table 3, 4*).

The median SCORAD score (36) was selected as a cut-off point to subdivide patients into the following two groups: mild AD (SCORAD ≤ 36) and severe AD (SCORAD > 36). Severe AD was significantly more frequent among younger ages ($p = 0.005$), families with medium or high social class ($p = 0.040$), children who were breastfed for less than two months ($p < 0.001$), children who did not attend kindergarten ($p = 0.045$), children of families with excessive house cleaning ($p < 0.001$), paternal/maternal smoking of more than one pack per day ($p < 0.001$), severe passive smoking ($p < 0.001$), reported food allergy to more than three allergens ($p < 0.001$), and a RAST level greater than 0.7 kU/l ($p < 0.001$) (*table 5*). Multivariate logistic regression analysis showed that excessive house cleaning was the strongest independent risk factor for severe AD ($p < 0.001$), with an adjusted odds ratio of almost 60 (aOR: 59.4; 95% CI: 10.9-322.6). A RAST level greater than 0.7 kU/l (aOR: 7.9; 95% CI: 1.5-41.0; $p = 0.014$) and severe passive smoking (aOR: 4.6; 95% CI: 1.0-22.1; $p = 0.050$) also showed a significant independent, but clearly weaker, association with severe atopic dermatitis.

Discussion

To the best of our knowledge, this study is the first to attempt to investigate an association between SCORAD scores, the scoring system for AD severity [14-16], and multiple family, social, dieting, atopic, and environmental factors. In particular, the short period of breastfeeding in infancy, excessive house cleaning, absence of an older sibling in the family, elevated RAST levels, along with an exposure to parental smoking have been shown to be related to more

Table 3. SCORAD values according to the different variables investigated in children with AD.

	SCORAD	<i>p</i> value	Tukey's test
Kindergarten			
No	40.33 ± 18.66	0.028	
Yes	29.19 ± 16.17		
Older sibling			
No	41.38 ± 19.08	0.050	
Yes	34.13 ± 17.02		
Social status			
Low	24.50 ± 10.91	0.132	
Medium	37.83 ± 18.81		
High	43.81 ± 18.11		
Cleanliness			
Normal (I)	22.64 ± 11.02	<0.001	0.651, I vs II
Frequent (II)	25.60 ± 8.28		<0.001, I vs III
Very frequent (III)	52.92 ± 13.56		<0.001, II vs III
Breastfeeding			
Up to 2 months	47.59 ± 15.81	<0.001	
3-5 months	25.54 ± 14.35		
Personal history			
Other atopic disease	38.32 ± 18.57	0.716	
Allergic rhinitis	40.60 ± 20.46		
Family history			
Other atopic disease	38.20 ± 19.34	0.848	
Asthma	38.92 ± 18.13		
Gender			
Male	38.68 ± 19.55	0.948	
Female	38.43 ± 18.04		
Food allergens			
None (I)	35.63 ± 17.32	<0.001	0.572, I vs II
1-3 (II)	31.55 ± 18.91		0.001, I vs III
>3 (III)	52.04 ± 13.89		<0.001, II vs III
Spearman's ρ correlation coefficient	0.360	0.004	
Aeroallergens			
≤2	39.08 ± 19.36	0.826	
>2	38.23 ± 18.39	0.434	
Spearman's ρ correlation coefficient	-0.079		

severe clinical features of AD and higher SCORAD scores in children. In contrast, we found that SCORAD scores were not influenced by gender, age, social status, family or personal history of atopy, or kindergarten attendance.

Our results support the significance of microbial exposure in infancy regarding the prevention of atopic dermatitis, the so-called “hygiene hypothesis”. In favour of this hypothesis, our study showed that children with no siblings and those who experienced excessive cleanliness exhibited a more severe form of AD, as indicated by SCORAD scores, suggesting that these factors should be considered as independent aggravating factors affecting severity [5].

Until now, epidemiological studies have shown that environmental exposure during early age has a significant role in the maturation of the immune system and the susceptibility to allergic diseases throughout childhood [17]. The “hygiene hypothesis” was derived from evidence for an association between atopy, family size, and birth order [18]. Thus, we hypothesized that all variables associated with microbial exposure could be associated with lower risks

of severe AD. Younger children spend most of their time at home, therefore environmental factors have more influence on the development of their immune system than in adults [19]. Family size and the presence of older siblings were inversely associated with incidence of atopic diseases, probably because infections are transmitted by older siblings to younger children in a family [20], strengthening the evidence for a “parity effect” originating *in utero* [21], as has been suggested by studies reporting altered immune function as a consequence of birth order [22]. The presence of older siblings has been associated not only with the transmission of infections but also with atopy [23-25]. The decrease in family size coincides with the increase in incidence of atopy in industrialized countries since the early 20th century [18]. In the same period, new products and equipment were developed for house cleanliness and there was increasing emphasis, not only on house, but also on personal, cleanliness [18]. In our study, we report that parental social status, that depicts the parental education level, is positively associated with AD, although this is not a strong

Table 4. SCORAD values according to the different variables investigated in children with AD.

	SCORAD	p value	Tukey's test
RAST (number)			
≤1 (= median)	34.76 ± 18.44		
>1	45.91 ± 17.06	0.004	
Spearman's ρ correlation coefficient	0.292	0.003	
RAST (Level)			
<0.35 or 0.35-0.7 kU/l (Class 0, I)	30.73 ± 16.56	<0.001	
>0.7 kU/l (Class II, III)	48.50 ± 16.46		
RAST (Level)			
<0.35 kU/l (Class 0)	31.48 ± 17.43	<0.001	
0.35-0.7 kU/l (Class I)	28.50 ± 13.95		
0.7-3.5 kU/l (Class II)	48.70 ± 16.78		
>3.5 kU/l (Class III)	47.43 ± 15.83		
Cigarettes/day			
0 (I)	34.77 ± 18.22		0.830, I vs II
1-20 (II)	27.10 ± 15.02	<0.001	<0.001, I vs III
>20 (III)	52.14 ± 13.04		<0.001, II vs III
Passive smoking			
≤4 (= median)	30.38 ± 16.30		
>4	53.08 ± 12.97	<0.001	
Spearman's ρ correlation coefficient	0.476	<0.001	
Age			
≤18.5 months (= median)	42.86 ± 18.10		
>18.5 months	34.24 ± 18.40	0.020	
Spearman's ρ correlation coefficient	-0.248	0.013	
Total serum IgE			
≤28.5 (= median)	35.08 ± 18.27	0.063	
>28.5	42.02 ± 18.60		
Spearman's ρ correlation coefficient	0.174	0.083	

influencing factor. In other studies, family socioeconomic status [26] and parental education level [27] were also positively associated with AD. However, Bisgaard *et al.* did not verify that social status is associated with AD [28].

The results of previous studies regarding the exact role of food allergy in AD are contradictory [25, 26, 28, 29]. In our study, we found that a higher RAST level and sensitization to food allergens are associated not only with a higher risk of AD in children but also with a more severe form of AD, as defined by SCORAD scores. The allergic nature of the disease might be a good explanation for the finding that children with elevated RAST levels experience more severe clinical features. Personal or family history of atopy was neither associated with the development of AD nor its severity. Similar to our results, Schafer *et al.* reported that the prevalence of AD increased significantly with increasing RAST class and the prevalence of sensitization increased with the severity of AD [30]. Regarding sensitization to aeroallergens and SCORAD scores, only three studies have been carried out, showing that there is a significant association between higher SCORAD scores and higher serum IgE levels or more frequent sensitization to aeroallergens [9, 31]. However, studies on family history of atopy and the severity of AD are contradictory [9, 12, 26, 28, 32]. Also, a recent study revealed that the degree of sensitization to house dust mite in children, as examined by the skin prick test, was associated with a higher total SCORAD score [32].

Another significant contributing factor in the development of AD is breastfeeding. In our study, we found that a short period of breastfeeding, less than two months, is associated with higher SCORAD scores in children. In particular, the short duration of breastfeeding (1-2 months) leads to a more intense clinical picture and a higher SCORAD score, compared with a duration of 3-5 months. This means that an additional month of breastfeeding during the initial six months of life could be highly significant in protecting from a severe clinical phenotype. The protective role of breastfeeding against atopic diseases appears to be based on the transmission of maternal antibodies. However, short periods of breastfeeding, of less than three months, have little or no protective effect against atopy [33]. Moreover, the data concerning the contribution of breastfeeding on the development of AD are conflicting [11, 12]. There are many studies suggesting that breastfeeding is positively associated with the development of atopic diseases, including AD, with a protective role against these conditions [7, 26, 34]. Studies revealing that breastfeeding may be associated with a higher risk of AD give the impression that it is a causative factor for AD. This association, however, is due to the fact that the vast majority of AD initially appears within the first month of life and, in any case, breastfeeding for a month is not adequate to protect against atopic diseases [29]. Also, hyperallergenic food intake by the mother or the transmission of environmental contaminants through the breast milk are other possible factors

Table 5. High SCORAD values (>36) according to patient characteristics.

	High SCORAD >36	<i>p</i> value	OR (95% CI)
Kindergarten			
No	44 (52.4)	0.045	3.3 (1.0-11.1)
Yes	4 (25.0)		
Older sibling			
No	32 (52.5)	0.264	1.6 (0.7-3.6)
Yes	16 (41.0)		
Social status			
Low	0 (0.0)	0.040	-
Medium	35 (46.7)		-
High	13 (61.9)		-
Cleanliness			
Normal - frequent	4(8.0)	<0.001	84.3 (22.3-319.2)
Very frequent	44 (88.0)		
Breastfeeding			
Up to 2 months	41 (69.5)	<0.001	11.1 (4.1-29.6)
3-5 months	7 (17.1)		
Personal history			
Other atopic disease	44 (48.9)	0.594	0.7 (0.2-2.6)
Allergic rhinitis	4 (40.0)		
Family history			
Other atopic disease	23 (45.1)	0.553	1.3 (0.6-2.8)
Asthma	25 (51.0)		
Gender			
Male	21 (44.7)	0.532	1.3 (0.6-2.8)
Female	27 (50.9)		
Food allergens			
0-3	28 (37.3)	<0.001	6.7 (2.3-19.9)
>3	20 (80.0)		
Aeroallergens			
≤2	19 (50.0)	0.754	1.1 (0.5-2.6)
>2	29 (46.8)		
RAST (number)			
≤1	28 (42.4)	0.120	1.9 (0.8-4.5)
>1	20 (58.8)		
RAST (Level)			
(Class 0, I)	17 (30.4)	<0.001	5.5 (2.3-13.0)
(Class II, III)	31 (70.5)		
Cigarettes/day			
0-20	18 (27.7)	<0.001	15.7 (5.3-46.7)
>20	30 (85.7)		
Passive smoking			
≤4	16 (25.0)	<0.001	24.0 (7.3-78.4)
>4	32 (88.9)		
Age			
≤18.5 months	31 (62.0)	0.005	3.2 (1.4-7.2)
>18.5 months	17 (34.0)		
Total serum IgE			
≤28.5	21 (42.0)	0.230	1.6 (0.7-3.6)
>28.5	27 (54.0)		

[26, 29]. However, many studies suggest that the positive association between breastfeeding and atopic diseases may be attributed to inverse causality. Indeed, the development of AD or the presence of a higher risk of atopic diseases tend to prolong the duration of breastfeeding in the hope

that breastfeeding will have a protective effect [35]. Consequently, this inverse causality can be misinterpreted to suggest that a longer duration of breastfeeding leads to AD, whereas the symptoms of AD result in a longer duration of breastfeeding [36].

Regarding passive smoking, to our knowledge, no study has been published regarding an association with SCORAD scores in childhood AD. However, our results do not suggest an association between passive smoking and the development or the severity of AD, in accordance with most of the studies that have been carried out to date [12, 29, 37, 38]. On the contrary, an association was found between parental smoking and a higher risk of AD in children [8, 39, 40]. Importantly, our study differs from others based on the fact that our data indicate that environmental factors, previously suggested as risk factors, appear to play a major role as independent factors in the severity of AD according to SCORAD scoring. However, we note that there are some limitations in our study that affect the interpretation of our results. First of all, due to the limited number of children who participated in the study, definitive conclusions cannot be drawn. It should also be mentioned that the number of children in our study who attended kindergarten was limited, thus the results regarding kindergarten attendance should be considered with caution. Secondly, our results may not be applicable to the general population due to the urban origin of all the participating children. Certain factors might predominantly affect children who live in rural regions; factors that are either absent in urban areas or more overwhelming in rural areas. However, the diagnosis of AD was based on specific and strict criteria through medical examination using an adequate definition of AD. Also, we used SCORAD scores for the evaluation of AD severity, which is the most highly recommended scoring system for AD.

To conclude, this is a study that clearly highlights the correlation between certain environmental factors and AD severity in children. The short duration of breastfeeding, the absence of older siblings, parental passive smoking, food allergens along with aeroallergens, and excessive cleanliness should be considered as negative prognostic factors, leading to higher SCORAD scores in children with AD. Our results are useful in understanding AD and, therefore, could be utilized for effective management of the disease. However, the extent to which each of the above factors contributes to the severity of the disease and the possible use of some of them as a disease biomarker remains to be clarified, stressing the need for larger, multicentre studies in the future, to explore, in addition, gene-environmental interactions. ■

Disclosure. Financial support: none. Conflict of interest: none.

References

1. Novak N. New insights into the mechanism and management of allergic diseases: atopic dermatitis. *Allergy* 2009; 64: 265-75.
2. Thomsen SF, Ulrik CS, Kyvik KO, et al. Importance of genetic factors in the etiology of atopic dermatitis: a twin study. *Allergy Asthma Proc* 2007; 28: 535-9.
3. Weidinger S, Illig T, Baurecht H, et al. Loss-of-function variations within the filaggrin gene predispose for atopic dermatitis with allergic sensitizations. *J Allergy Clin Immunol* 2006; 118: 214-9.
4. Schultz Larsen F. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1993; 28: 719-23.
5. Purvis DJ, Thompson JM, Clark PM, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol* 2005; 152: 742-9.
6. Schram ME, Tedja AM, Spijker R, Bos JD, Williams HC, Spuls PI. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol* 2010; 162: 964-73.
7. Ito J, Fujiwara T. Breastfeeding and risk of atopic dermatitis up to the age 42 months: a birth cohort study in Japan. *Ann Epidemiol* 2014; 24: 267-72.
8. Morales Suarez-Varela M, García-Marcos L, Kogan MD, et al. Parents' smoking habit and prevalence of atopic eczema in 6-7 and 13-14 year-old schoolchildren in Spain. ISAAC phase III. *Allergol Immunopathol (Madr)* 2008; 36: 336-42.
9. Laske N, Niggemann B. Does the severity of atopic dermatitis correlate with serum IgE levels? *Pediatr Allergy Immunol* 2004; 15: 86-8.
10. Wang U, Lin YT, Yang YH, et al. Correlation between age and allergens in pediatric atopic dermatitis. *Ann Allergy Asthma Immunol* 2004; 93: 334-8.
11. Miyake Y, Tanaka K, Sasaki S, et al. Breastfeeding and atopic eczema in Japanese infants: The Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2009; 20: 234-41.
12. Parazzini F, Cipriani S, Zinetti C, et al. Perinatal factors and the risk of atopic dermatitis: a cohort study. *Pediatr Allergy Immunol* 2014; 25: 43-50.
13. Zutavern A, Hirsch T, Leupold W, Weiland S, Keil U, von Mutius E. Atopic dermatitis, extrinsic atopic dermatitis and the hygiene hypothesis: results from a cross-sectional study. *Clin Exp Allergy* 2005; 35: 1301-8.
14. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology* 1993; 186: 23-31.
15. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; 195: 10-9.
16. Gartner LM, Morton J, Lawrence RA, et al. Breastfeeding and the use of human milk. *Pediatrics* 2005; 115: 496-506.
17. Horner AA. Toll-like receptor ligands and atopy: a coin with at least two sides. *J Allergy Clin Immunol* 2006; 117: 1133-40.
18. Bloomfield SF, Stanwell-Smith R, Crevel RW, Pickup J. Too clean, or not too clean: the hygiene hypothesis and home hygiene. *Clin Exp Allergy* 2006; 36: 402-25.
19. Tse K, Horner AA. Allergen tolerance versus the allergic march: the hygiene hypothesis revisited. *Curr Allergy Asthma Rep* 2008; 8: 475-83.
18. Carson CG. Risk factors for developing atopic dermatitis. *Dan Med J* 2013; 60: B4687.
20. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989; 299: 1259-60.
21. Benn CS, Melbye M, Wohlfahrt J, Björkstén B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *BMJ* 2004; 328: 1223.
22. Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002; 32: 43-50.
23. Taylor B, Wadsworth J, Golding J, Butler N. Breast feeding, eczema, asthma, and hayfever. *J Epidemiol Community Health* 1983; 37: 95-9.
24. Dom S, Droste JH, Sariachvili MA, et al. The influence of parental educational level on the development of atopic sensitization, wheezing and eczema during the first year of life. *Pediatr Allergy Immunol* 2009; 20: 438-47.
25. Bisgaard H, Halkjaer LB, Hinge R, et al. Risk analysis of early childhood eczema. *J Allergy Clin Immunol* 2009; 123: 1355-60.
26. Karmaus W, Arshad SH, Sadeghnejad A, Twiselton R. Does maternal immunoglobulin E decrease with increasing order of live offspring? Investigation into maternal immune tolerance. *Clin Exp Allergy* 2004; 34: 853-9.

- 27.** Wadonda-Kabondo N, Sterne JA, Golding J, *et al.* A prospective study of the prevalence and incidence of atopic dermatitis in children aged 0-42 months. *Br J Dermatol* 2003; 149: 1023-8.
- 28.** Strobel S. Dietary manipulation and induction of tolerance. *J Pediatr* 1992; 121: 74-9.
- 29.** Munasir Z, Sastroasmoro S, Djauzi S, *et al.* The role of allergic risk and other factors that affect the occurrence of atopic dermatitis in the first 6 months of life. *Asia Pac Allergy* 2011; 1: 73-9.
- 30.** Schafer T, Heinrich J, Wjst M, Adam H, Ring J, Wichmann HE. Association between severity of atopic eczema and degree of sensitization to aeroallergens in schoolchildren. *J Allergy Clin Immunol* 1999; 104: 1280-4.
- 31.** Cosickic A, Skokić F, Colić-Hadžić B, Suljendić S, Hasanović E. Hypersensitivity to aeroallergens in children with atopic dermatitis. *Acta Clin Croat* 2012; 51: 591-600.
- 32.** Kutlu A, Karabacak E, Aydin E, *et al.* Relationship between skin prick and atopic patch test reactivity to aeroallergens and disease severity in children with atopic dermatitis. *Allergol Immunopathol (Madr)* 2013; 41: 369-73.
- 33.** Oddy WH, Holt PG, Sly PD, *et al.* Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. *BMJ* 1999; 319: 815-9.
- 34.** Bergmann RL, Diepgen TL, Kuss O, *et al.* Breastfeeding duration is a risk factor for atopic eczema. *Clin Exp Allergy* 2002; 32: 205-9.
- 35.** Lowe AJ, Carlin JB, Bennett CM, *et al.* Atopic disease and breast-feeding-cause or consequence? *J Allergy Clin Immunol* 2006; 117: 682-7.
- 36.** Carson CG. Risk factors for developing atopic dermatitis. *Dan Med J* 2013; 60: B4687.
- 37.** Yang CY, Cheng MF, Hsieh YL. Effects of indoor environmental factors on risk for atopic eczema in a subtropical area. *J Toxicol Environ Health A* 2000; 61: 245-53.
- 38.** Tanaka K, Miyake Y, Sasaki S, Ohya Y, Hirota Y, & Osaka Maternal and Child Health Study Group. Maternal smoking and environmental tobacco smoke exposure and the risk of allergic diseases in Japanese infants: the Osaka Maternal and Child Health Study. *J Asthma* 2008; 45: 833-8.
- 39.** Song N, Mohammed S, Zhang J, *et al.* Prevalence, severity and risk factors of asthma, rhinitis and eczema in a large group of Chinese schoolchildren. *J Asthma* 2014; 51: 232-42.
- 40.** Solis-Soto MT, Patiño A, Nowak D, Radon K. Association between environmental factors and current asthma, rhinoconjunctivitis and eczema symptoms in school-aged children from Oropeza Province - Bolivia: a cross-sectional study. *Environ Health* 2013; 12: 95.