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Parental History of Atopic Diseases and Presence of Allergic Rhinitis and Asthma in Children with Atopic Dermatitis

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Abstract

Objective – To assess the prevalence of allergic rhinitis and asthma in children with and without parental history of atopic dermatitis (AD) as well as to explore the association between parental history of atopic diseases and presence of allergic rhinitis or asthma in children diagnosed with AD. **Methods** – From January to June 2014, we recruited a total of 98 children with AD and their parents who presented at the Clinic of Dermatovenereology, Clinical Center of Serbia, Belgrade, Serbia. The parents filled in a questionnaire. The severity of AD was assessed using the SCORing Atopic Dermatitis (SCORAD) Index. **Results** – Of 98 parents, 33 (33.7%) reported having history of AD. In children with parental history of AD, the prevalence of allergic rhinitis and asthma was 18.2% and 24.2%, respectively. In children without parental history of AD, the prevalence of allergic rhinitis and asthma was 12.3% and 23.1%, respectively. Adjusted logistic regression analyses showed that: neither mothers' nor fathers' history AD were associated with presence of allergic rhinitis or asthma; fathers' history of asthma was associated with presence of asthma and mothers' history of asthma was associated with presence of allergic rhinitis. Fathers' history of allergic rhinitis was associated with presence of allergic rhinitis and mothers' history of allergic rhinitis was associated with presence of asthma. **Conclusion** – Our findings suggest that, compared to parental history of AD, parental history of asthma and allergic rhinitis were stronger contributors to the presence of atopic comorbid disorders in children with AD.

Key Words: Atopic Dermatitis ▪ Children ▪ Comorbidity ▪ Parents ▪ Atopy.

Introduction

Atopic dermatitis (AD) is a chronic skin disease that usually appears during childhood. The estimated worldwide prevalence of AD in children altogether is approximately 7% (1). In infants, however, the prevalence is often up to 20% (2). Children with AD may have physical, psychological and psychosocial difficulties due to AD (3). Specifically, the physical impact of AD refers to itching, scratching and visible changes of the skin (3). Mood swings, irritability, disrupted sleep or lack of sleep account for the psychological impact of AD on child's life (3, 4). The psychosocial impact of AD comprises restriction in social contact, teasing and embarrassment (3, 5). Because of these features, AD often has unfavorable effect on family functioning as a whole (6).

It is estimated that more than half of children with AD are at risk of developing concomitant atopic diseases such as allergic rhinitis or asthma (7). Presence of comorbidity might predispose progression and persistence of AD (8). A prospective cohort study of more than 1,000 children from 5 Western European countries found that phenotype plays an important role in timing and clinical course of AD (9). This study also found that chil-

dren whose parents previously had allergies were 5 times more likely to develop AD, allergic rhinitis or asthma (9). Similar findings on the association of family AD history with the development of respiratory allergies among children with AD were observed in a cohort of children from Bosnia and Herzegovina (10). While origins of AD are not entirely clear, compelling evidence suggests that parental history of AD can be a risk factor for AD or other atopic diseases, such as allergic rhinitis or asthma in their children (7-10). We hypothesized that parental history of AD, asthma and allergic rhinitis is associated with presence of allergic rhinitis and asthma comorbidity in children with AD.

The aim of this study was to 1) assess the prevalence of allergic rhinitis and asthma in children with and without parental history of AD and 2) to explore the association of parental history of atopic diseases with presence of allergic rhinitis and asthma in children with AD.

Methods

Participants

This study is part of a comprehensive study on AD-related quality of life among children with AD and their parents (11). While the previous study included a prospective cohort design (11), this analysis is performed using a cross-sectional study methodology. From January to June 2014, we recruited 98 children with AD and their parents who presented at the Clinic of Dermatovenereology, Clinical Center of Serbia, Belgrade, Serbia. The sample size was calculated using Raosoft sample size calculator (12) based on margin of error of 5%, confidence interval od 95%, population size of children aged 0-18 years residing in Belgrade of 300,000, and worldwide prevalence of AD (response distribution) of 7% (1). The calculated sample size was 100.

The diagnosis of AD in children was made according to Hanifin and Rajka diagnostic criteria (13). All children were treated with emollient creams, topical mid-potency corticosteroids (mometasone furoate, fluocinolone acetonide or betamethasone dipropionate), and oral second-generation non-sedating antihistamines (desloratadin or levocetirizin) according to the clinical presentation. The inclusion criteria were: confirmed diagnosis of AD in children, absence of other skin diseases and the ability of parents to speak and understand Serbian language.

Data Collection

The parents of children with AD were asked to fill in a questionnaire. The questionnaire was divided in two segments: one referred to child's characteristics and the other referred to parental characteristics. The questionnaire examined the following child's characteristics: gender, age, duration of AD, whether or not the child has had allergic rhinitis or asthma. Parents provided information about their age, education level, number of children in the household and birth order of the child with whom they presented at the Clinic as well as about family history of AD, asthma and allergic rhinitis (Appendix).

The majority of children with AD (more than 80%) presented with both parents. On that occasion, the parents were invited to participate in this study. However, both parents filled in one single questionnaire together. Because of this, we were not able to specify parental gender within their demographic characteristic.

The severity of AD in children was examined by a treating dermatologist, using the SCORing Atopic Dermatitis (SCORAD) Index (14). The SCORAD consists of three different aspects: 1) extent, 2) severity and 3) subjective feelings. First, the extent of the affected skin is calculated using the "rule of nine" (head and neck account for 9%, upper limbs account for 9%+9% = 18%, each lower limb accounts for 18%, anterior trunk and back each account for 18% and genitals account for 1%). The percentages for each body area affected by AD is added up, which means that the extent of AD can be numerically expressed from 0 (minimum) to 100 (maximum) depending on the skin surface affected by AD. This part makes 20% of the SCORAD score. This means that the raw score for the extent of AD is divided by 5. The range of score is 0-20.

Second, grading of severity of AD is based on six elements: erythema, edema/papulation, oozing/crusts, excoriations, lichenification and dryness. Each of these elements is graded on a 4-point scale, from 0 to 3 where 0 refers to absence, l refers to mild change, 2 refers to moderate change and 3 refers severe change. Grading is performed on a part of skin with neither the most intense nor the least intense changes. In this way, the average change of all the affected areas is representative of AD intensity. Scores for each element are added in a summary score which ranges from 0 to 18. This part makes 60% of the SCORAD score. This means that the score needs to be mathematically adjusted according to the formula 7 x severity score / 2. The range of severity score is from 0 to 63.

Third, subjective feeling of pruritus and sleeplessness is added to the previous two scores. The two subjective feelings are rated on a visual scale from 0 (no itch, no sleeplessness) to 10 (severe itch, severe sleeplessness). Because SCORAD measures two subjective feelings, this score ranges from 0 to 20. This part also makes 20% to the SCORAD score. The SCORAD score is obtained by summing scores for each of the three examined parts. The SCORAD score ranges from 0 to 103 (20+63+20). Higher scores denote higher degree of AD extend and severity (15).

Ethics Statement

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade (Approval no. 29/XII-21). All the parents provided signed informed consent for participation in the study.

Data Analysis

The Statistical Package for Social Sciences (SPSS), version 20 (SPSS Inc, Chicago, IL, USA) was used to analyze the data. Normality of distribution for parental and children's characteristics was examined using the Kolmogorov Smirnov test. Children's age, number of children in the family and AD duration were not normally distributed. These variables were described using median and corresponding interquartile range (IR). Characteristics that were normally distributed were presented as mean with corresponding standard deviation (SD). Differences in characteristics of parents and children according to parental history of AD were evaluated using the following tests: 1) t-test for 2 independent samples (for normally distributed continuous variables – parental age, SCORAD), 2) Mann Whitney U test (for not normally distributed continuous variables – children's age, AD duration and number of children in the family), 3) Chi square test and Chi square linear-by-linear association (for categorical variables with two and three categories, respectively, as well as when number of observations per cell was 5 and above) and 4) Fisher's exact test (for categorical variables when number of observations per cell was below 5).

Parental history of AD was analyzed separately for mothers and for fathers as well as a combined variable labelled 'parental history' (where history of AD for mothers and fathers was observed as a single variable). To examine the association of parental history of AD, asthma and allergic rhinitis with presence of allergic rhinitis or asthma comorbidity in children with AD, we used the logistic regression models. The models were divided according to the exposures: 1) history of AD, 2) asthma and 3) allergic rhinitis. The exposure was divided in two independent variables: mothers' and fathers' history of AD, asthma and allergic rhinitis, respectively. Other independent variables (covariates) in the models were child's and parental demographic characteristics (child's age and gender, parental age and education level and child's birth order) and child's AD characteristics (AD duration and SCORAD score). The dependent variables in all three models were presence of allergic rhinitis and asthma in children with AD (yes/no). Probability level of $P<0.05$ was considered as the limit of statistical significance.

Results

A total of 98 parent-child pairs were included in the study. Thirty-three parents reported having history of AD (33.7%). Of those, 20 (60.6%) were fathers and 13 (39.4%) were mothers. Socio-demographic

and AD-related characteristics according to family AD history are presented in Table 1. Of all the examined variables, only parental education level and birth order of children with AD differed between the parents with and without history of AD. In our sample, there were more highly educated parents with history of AD. Also, parents with history of AD had more children with AD who were born later (Table 1).

In children with AD, asthma was more often reported compared to allergic rhinitis. The prevalence of allergic rhinitis and asthma did not differ between children with and without parental history of AD. In children who had parental history of AD, the prevalence of allergic rhinitis was 18.2% and of asthma 24.2%. In children without parental history of AD, the prevalence of allergic rhinitis was 12.3% and of asthma 23.1%.

Table 1. Socio-Demographic Characteristics of Parents and Children with Atopic Dermatitis

Variable	Positive parental history of AD N=33	Negative parental history of AD N=65	P
Parental characteristics			
Age in years (mean±SD)	38.7±4.2	36.8±6.0	0.101
Highest education attainment			
Primary school	0 (0)	2 (3.1)	
Secondary school	7 (21.2)	31 (47.7)	
Higher education	26 (78.8)	32 (49.0)	0.004
Having asthma			
Yes	10 (30.3)	17 (26.2)	
No	23 (69.7)	48 (73.8)	0.664
Having allergic rhinitis			
Yes	12 (36.2)	17 (26.2)	
No	21 (63.8)	48 (73.8)	0.295
Children's characteristics			
Gender			
Male	21 (63.6)	33 (50.8)	
Female	12 (36.4)	32 (49.2)	0.226
Median age in years (IR)	4.5 (7.7)	7.0 (9.4)	0.293
Birth order of the child with AD			
First	19 (57.6)	52 (80.0)	
Second	12 (36.4)	13 (20.0)	0.008
Third	2 (6.1)	0 (0)	
Median duration of disease (IR)	3.0 (7.0)	4.5 (7.7)	0.576
Having allergic rhinitis			
Yes	6 (18.2)	8 (12.3)	
No	27 (81.8)	57 (87.7)	0.432
Having asthma			
Yes	8 (24.2)	15 (23.1)	
No	25 (75.8)	50 (76.9)	0.898
SCORAD (mean±SD)	36.9±15.2	33.4±15.0	0.279

AD=Atopic dermatitis; SD=Standard deviation; IR=Interquartile range; SCORAD=Scoring Atopic Dermatitis Index; Values in brackets represent corresponding percentages; Difference in continuous variables presented as mean±SD was examined using t-test for 2 independent samples; Differences in continuous variables presented as median (IR) were examined using Mann-Whitney U test; Differences in categorical variables were examined using Chi square linear-by-linear association (parental education level, birth order) and Chi square test (child's gender, having asthma and having rhinitis).

Table 2. Prevalence of Atopic Comorbidity in Children with Atopic Dermatitis According to Disease Severity Based on the Median Scoring Atopic Dermatitis Index Score and Parental History of Atopic Dermatitis

Variable	SCORAD					
	SCORAD ≤32.6 (N=49)			SCORAD >32.6 (N=49)		
	Parental history of AD					
	Yes (N=12)	No (N=37)	P	Yes (N=21)	No (N=28)	P
Having AR (N; %)	1 (8.3)	4 (10.3)	0.644	5 (23.8)	4 (14.3)	0.314
Having A (N; %)	1 (8.3)	10 (27.0)	0.252	7 (33.3)	5 (14.3)	0.213

AD=Atopic dermatitis; AR=Allergic rhinitis; A=Asthma; SCORAD=Scoring Atopic Dermatitis Index. Differences for variables where cells had count of less than 5 were tested using Fisher's exact test. Variables with count of 5 and above were tested using Chi square test.

Median SCORAD index was 32.6. A total of 24.5% (12/49) children whose AD severity scored below median SCORAD had parental history of AD. On the other hand, 42.8% (21/49) of children whose AD severity scored above median SCORAD had parental history of AD. The difference was not deemed statistically significant (χ^2=3.700; P=0.054). Although not reaching statistical significance level, there was a tendency among children with higher SCORAD scores to have parental history of AD.

The prevalence of allergic rhinitis and asthma among children who were classified as having more severe AD (SCORAD above median value) were 18.4% (9/49) and 24.5% (12/49), respectively. The prevalence of allergic rhinitis and asthma among children who were classified as having less severe AD (SCORAD below median value) were 10.2% (5/49) and 22.4% (11/49), respectively. The observed difference was not statistically significant (χ^2=0.949; P=0.323). When children with AD were stratified according to mean SCORAD value and parental history of AD, no difference in the prevalence of allergic rhinitis and asthma was observed (Table 2).

Correlation coefficients between the examined variables and their probability values are presented in Table 3. Having parental history of AD correlated with higher education level of the parents. Having parental history of asthma correlated with presence of asthma and allergic rhinitis in children with AD. Having parental history of allergic rhinitis correlated only with child's allergic rhinitis. In children, having asthma correlated with having allergic rhinitis, male gender, older age of the parents, later birth order and longer AD duration. Having allergic rhinitis in children correlated with older age of both children and parents and longer AD duration (Table 3).

The association of parental AD with child's allergic rhinitis and asthma is presented in Table 4. Neither mothers' nor fathers' history of AD were associated with presence of allergic rhinitis or asthma in children with AD. Older age of the parents was associated with presence of allergic rhinitis. Older age of children with AD and later birth order were associated with presence of asthma (Table 4).

Table 3. Correlations Between Socio-Demographic and Clinical Characteristics of Children with Atopic Dermatitis

Variables	Correlation coefficients	Parents AD	Parents asthma	Parents rhinitis	Child asthma	Child rhinitis	Child age	Child gender	Parents age	Parents education	Birth order	AD duration
Parents AD	rho	-	-	-	-	-	-	-	-	-	-	-
	P	-	-	-	-	-	-	-	-	-	-	-
Parents asthma	rho	0.044	-	-	-	-	-	-	-	-	-	-
	P	0.668	-	-	-	-	-	-	-	-	-	-
Parents rhinitis	rho	0.106	0.251	-	-	-	-	-	-	-	-	-
	P	0.300	0.013	-	-	-	-	-	-	-	-	-
Child asthma	rho	0.013	0.305	-0.148	-	-	-	-	-	-	-	-
	P	0.899	0.002	0.146	-	-	-	-	-	-	-	-
Child rhinitis	rho	0.079	0.270	0.246	0.256	-	-	-	-	-	-	-
	P	0.437	0.007	0.014	0.011	-	-	-	-	-	-	-
Child age	rho	-0.122	-0.004	-0.102	0.033	0.229	-	-	-	-	-	-
	P	0.230	0.968	0.316	0.750	0.023	-	-	-	-	-	-
Child gender	rho	-0.107	-0.189	-0.136	0.389	-0.075	0.217	-	-	-	-	-
	P	0.295	0.063	0.183	0.001	0.461	0.032	-	-	-	-	-
Parents age	rho	0.162	0.092	0.036	0.328	0.355	0.577	0.143	-	-	-	-
	P	0.112	0.369	0.722	0.001	0.001	0.001	0.161	-	-	-	-
Parents education	rho	0.289	0.102	0.181	-0.040	-0.010	-0.020	-0.003	0.121	-	-	-
	P	0.004	0.319	0.075	0.698	0.925	0.847	0.974	0.236	-	-	-
Birth order	rho	-0.010	-0.065	-0.154	0.253	0.004	0.105	0.041	0.181	-0.060	-	-
	P	0.922	0.522	0.130	0.012	0.969	0.303	0.691	0.074	0.560	-	-
AD duration	rho	-0.057	-0.028	-0.114	0.260	0.252	0.840	0.133	0.471	-0.065	0.153	-
	P	0.578	0.786	0.265	0.010	0.013	0.001	0.192	0.001	0.527	0.133	-
SCORAD	rho	0.111	0.157	0.057	0.085	0.073	0.015	-0.011	0.062	-0.015	0.046	0.018
	P	0.278	0.126	0.581	0.407	0.477	0.881	0.915	0.547	0.882	0.650	0.859

Legend: AD=Atopic dermatitis; SCORAD=Scoring Atopic Dermatitis Index.

Table 4. Adjusted Regression Model Examining the Association of Parental History of Atopic Dermatitis with Allergic Rhinitis and Asthma in Children with Atopic Dermatitis

Variables	Allergic rhinitis OR (95% CI)	Asthma OR (95% CI)
Mother's history of AD	0.87 (0.07-10.35)	0.16 (0.01-2.08)
Father's history of AD	1.66 (0.31-8.92)	1.32 (0.27-6.40)
Child's age	0.93 (0.73-1.20)	1.34 (1.08-1.66)†
Child's gender	0.51 (0.13-1.91)	0.77 (0.24-2.42)
Parental age	1.26 (1.07-1.49)†	1.06 (0.92-1.23)
Parental education level	0.76 (0.21-2.70)	0.72 (0.25-2.06)
Birth order	0.71 (0.20-2.55)	3.41 (1.16-10.03)*
AD duration	1.13 (0.88-1.46)	0.90 (0.74-1.09)
SCORAD	1.02 (0.98-1.06)	1.01 (0.98-1.05)

AD=Atopic dermatitis; SCORAD=Scoring Atopic Dermatitis Index; OR=Odds ratio; CI=Confidence interval; *P<0.05; †P<0.01.

Table 5 illustrates the associations between having parental history of asthma with presence of allergic rhinitis and asthma among children with AD. In this model, we observed that fathers' history of asthma was associated with presence of asthma in children with AD. Mothers' history of asthma was associated with presence of allergic rhinitis in children with AD. Older age of the parents was associated with presence of allergic rhinitis. Older age of children with AD and later birth order were associated with presence of asthma (Table 5).

The results of the last logistic regression model are shown in Table 6. Father's history of allergic rhinitis was associated with presence of allergic rhinitis in children with AD. Mothers' history of allergic rhinitis was associated with presence of asthma in children with AD. Older age of the parents was associated with presence of allergic rhinitis. Older age of children with AD was associated with presence of asthma (Table 6).

Table 5. Adjusted Regression Model Examining the Association of Parental History of Asthma with Allergic Rhinitis and Asthma in Children with Atopic Dermatitis

Variables	Allergic rhinitis OR (95% CI)	Asthma OR (95% CI)
Mother's history of asthma	5.52 (1.02-29.93)*	2.31 (0.41-12.92)
Father's history of asthma	2.72 (0.49-15.11)	68.34 (6.77-689.73)†
Child's age	0.94 (0.73-1.22)	1.55 (1.14-2.11)†
Child's gender	0.71 (0.17-2.85)	0.93 (0.24-3.62)
Parental age	1.29 (1.08-1.54)†	0.97 (0.81-1.17)
Parental education level	0.77 (0.21-2.96)	0.41 (0.12-1.39)
Birth order	0.72 (0.20-2.57)	4.81 (1.31-17.67)*
AD duration	1.12 (0.86-1.46)	0.90 (0.70-1.15)
SCORAD	1.01 (0.97-1.06)	0.99 (0.96-1.04)

AD=Atopic dermatitis; SCORAD=Scoring Atopic Dermatitis Index; OR=Odds ratio; CI=Confidence interval. *P<0.05; †P<0.01.

Table 6. Adjusted Regression Model Examining the Association of Parental History of Allergic Rhinitis with Allergic Rhinitis and Asthma in Children with Atopic Dermatitis

Variables	Allergic rhinitis OR (95% CI)	Asthma OR (95% CI)
Mother's history of allergic rhinitis	2.23 (0.47-10.60)	1.08 (1.01-1.89)*
Father's history of allergic rhinitis	6.38 (1.01-40.63)*	2.42 (0.35-16.62)
Child's age	0.91 (0.68-1.21)	1.29 (1.05-1.59)*
Child's gender	0.64 (0.16-2.58)	0.60 (0.18-1.99)
Parental age	1.26 (1.06-1.51)†	1.11 (0.95-1.30)
Parental education level	0.67 (0.19-2.45)	0.61 (0.20-1.85)
Birth order	0.75 (0.20-2.75)	2.48 (0.85-7.21)
AD duration	1.19 (0.89-1.59)	0.93 (0.76-1.12)
SCORAD	1.02 (0.98-1.07)	1.02 (0.98-1.05)

AD=Atopic dermatitis; SCORAD=Scoring Atopic Dermatitis Index; OR=Odds ratio; CI=Confidence interval; *P<0.05; †P<0.01.

Discussion

In our sample of children with AD asthma was more prevalent compared to allergic rhinitis. There was no difference in the prevalence of allergic rhinitis or asthma between children with and without parental history of AD. Similar results were observed when the children were additionally stratified according to AD severity. This study also found that presence of parental atopic diseases were not consistently associated with atopic comorbidity in children with AD, because having parental history of AD was not associated with either allergic rhinitis or asthma among children with AD. Concordance between atopic entities was seen between fathers and children with AD. Specifically, fathers' history of asthma was associated with presence of asthma and mothers' history of asthma was associated with presence of allergic rhinitis in children with AD. Fathers' history of allergic rhinitis was associated with presence of allergic rhinitis and mothers' history of allergic rhinitis was associated with presence of asthma in children with AD.

Studies on children who have atopic comorbidities reported inconsistent findings. For example, in South Africa, the prevalence of allergic rhinitis in children with AD was 53% and that of asthma 39% (16). In this cohort of children (16), atopic disorders such as allergic rhinitis and asthma, as well as sensitivity to aeroallergens had an increasing tendency with advancing age. Studies in Asian population, such as in South Korea (17), reported that the prevalence of AD and allergic rhinitis were the highest at the age of 4-6 years (10.2%). Although some decline in the prevalence is seen in later age, no appreciable decrease was observed. Thus, the prevalence of AD and allergic rhinitis at age 10-13 years was 7.7%. The pattern of prevalence of asthma in children with AD was somewhat different. The prevalence was the highest at age 0-3 years (4.7%), after which a steady decline was reported. The lowest prevalence was observed among children aged 10-13 years (1.8%). In consideration of literature data (16, 17) and the prevalence of allergic rhinitis and asthma in children with AD observed in our study, it can be assumed that ethnic differences in atopic comorbidities exist, and they can be explained by different phenotypes (18).

A previous study showed that parental atopy, especially that of the mothers, was associated with presence of asthma in children (19). Similar findings were observed when the association between parental history of allergic rhinitis and presence of childhood allergic rhinitis was examined (20). A long term perspective study that followed close to 1,000 children with atopic diseases found that parental history of atopy was a strong predictor of atopic comorbidities in their children (21). Also, a recent study suggested that several clusters of AD severity and comorbidity can be identified in children with AD (22). Parental history of asthma and AD was observed along with the cluster of children who had moderate-severe AD and high prevalence of comorbidity (22).

In this study, we observed that parental history of atopic diseases was not consistently associated with allergic rhinitis and asthma in children with AD. While previous studies highlight that maternal atopy plays a more important role in the development of atopic disorders in children (19, 20), in our sample of parents and children with AD we observed that both mothers' and fathers' history of asthma and allergic rhinitis contribute to the presence of atopic comorbidities in children with AD. In fact, a concordance between atopic entities was observed between fathers and children with AD. Our results are in line with the previous evidence where fathers' history of asthma has been observed to increase the risk of having asthma in their children (23). Similarly, fathers' allergic rhinitis has been identified as a risk factor for the development of AD (24). Our findings suggest that parental history of asthma and allergic rhinitis are stronger factors associated with the presence of atopic comorbid disorders in children with AD compared to parental history of allergic rhinitis and AD, probably though genetic pathways transmitted across generations.

The exact etiopathogenesis of AD and atopic comorbidities in AD is not fully understood. While longer duration of AD was not associated

with the presence of allergic rhinitis or asthma in the regression models, we did find a significant correlation between them. Most authors agree that the underlying mechanisms might be multifactorial, because the evidence suggests that genetics and environmental exposures contribute to the onset of atopic diseases (25). Mutations in the gene coding the protein filaggrin are responsible for the changes in keratinocytes, their differentiation and function. In this way, the affected skin does not represent an adequate barrier (26). The genetic risk score has also been associated with higher risk of persistent AD (27). Of the intrinsic risk factors, dysfunction of the innate and adaptive immunity with strong T-helper type 2 lymphocyte response has also been observed in persons with AD (26). Because of the involvement of the immune system in AD, persons with AD are more likely to have autoimmune illnesses compared to general population (28).

Of the extrinsic factors, skin changes in AD have been linked to the changes of the skin microbiome, predominantly with regards to *S. epidermidis* (28). The severity of AD has been associated with reduced levels of serum nutrients, such as omega-3 and -6 fatty acids, calcium, folate and vitamin D (29, 30) as well as a higher body mass index (31); while supplementation with a concoction of prebiotics and probiotics showed a significant improvement of AD, particularly among children with more severe AD forms (32). Furthermore, immune response to biological agents, such as *S. aureus*, has recently been indicated to influence the severity of AD (33), while higher levels of house dust mites have been reported to correlate with more severe AD in children (34). Thus, severe and persistent childhood AD, that represents a risk factor for the development of atopic comorbidities, such as allergic rhinitis or asthma, seems to be the result of complex interplay of genetic and environmental factors. Difficulties in elucidating triggers and causes of severe AD forms represent a challenge in management and long-term outcomes of AD.

In our study, being born later was associated with higher likelihood of presence of asthma in children with AD. A recent longitudinal study of more than 47,000 children in Japan reported that increased birth order was associated with lower risk of food allergies, but higher risk of developing AD (35). Our findings contrast some evidence in literature, where having more siblings was suggested to be protective against development of AD (36-39). Several authors reported that children with more siblings (particularly older siblings) were less likely to develop AD, compared to children with less or no siblings (36-39). While this association is not fully understood, one potential explanation is related to the "hygiene theory" (38). This theory suggests that atopic diseases are less frequent in families with more children due to more exposure to various antigens (most commonly originating from infectious agents) that mobilize immune response, which, in turn, protects from allergic sensitization (40).

There are several limitations of this study. The sample size was relatively small. The inclusion of more parent-child pairs could have increased the statistical power of the study. The sample was selected from the largest urban area of the country. Inclusion of parents and children from semi-urban or rural areas could have yielded different results. Therefore, we cannot generalize our results to the entire population of Serbia. The parents' history of atopic diseases was self-reported. Some studies indicate that self-reporting of atopic diseases among the parents is open to bias (41). We have not explicitly analyzed the number of medications or type of therapy for AD. Other factors, such as secondhand smoke exposure, pet keeping, duration of exclusive breastfeeding or use of daycare were not analyzed. Cross-sectional study design, where exposure and outcomes were measured at the same time, cannot provide definite inference on causality.

Conclusion

To conclude, the prevalence of asthma is higher than prevalence of allergic rhinitis in children with AD. The prevalence of these atopic comorbidities in children with AD did not differ according to parental history of AD. Parental history of atopic diseases was not consistently associated with pres-

ence of atopic comorbidities in children with AD. The association between fathers' history of asthma and allergic rhinitis was concordant with the presence of asthma and allergic rhinitis in children with AD. The association between mothers' history of asthma and allergic rhinitis was discordant. Namely, mothers' history of asthma and allergic rhinitis were associated with presence of allergic rhinitis and asthma, respectively.

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Appendix

General questionnaire about children with atopic dermatitis

I General data about the child with atopic dermatitis

1. Age (years): _____
2. Sex 1) Male 2) Female

II Information about atopic dermatitis

3. Age of diagnosis of atopic dermatitis _____
4. Has anybody from the nuclear family ever had atopic dermatitis (mother, father, sister, brother)?
   0) No 1) Yes (please specify who _____ _____)

III Information about comorbidities

5. Has the child ever had had allergic rhinitis (hay fever)? 0) No 1) Yes
6. Has anybody from the child's nuclear ever had allergic rhinitis (hay fever)? 0) No 1) Yes
   If you answered 'yes', please specify who it was (mother, father, sister, brother) _____
7. Has the child ever had had asthma? 0) No 1) Yes
8. Has anybody from the child's nuclear ever had asthma? 0) No 1) Yes
   If you answered 'yes', please specify who it was (mother, father, sister, brother) _____

IV General data about the accompanying parent

9. Age (years) _____
10. Sex 1) Male 2) Female
11. Level of education: 1) Elementary school 2) Secondary school 3) College and University
12. Employment status: 1) Employed 2) Unemployed 3) Retired
13. What is the total number of children living in your household? _____
14. What is the birth order of the child with atopic dermatitis? _____