

Perinatal risk factors for asthma in children with allergic rhinitis and grass pollen sensitization

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ABSTRACT

Background: Results of epidemiologic studies have determined several risk factors for asthma in school-age children.

Objective: To examine whether parental and perinatal risk factors, along with infantile feeding patterns, were associated with asthma in children with grass pollen allergy and allergic rhinitis.

Methods: We retrospectively analyzed the data of our cohort, which consisted of children with allergic rhinitis. Only children with grass pollen sensitization were enrolled. A detailed questionnaire regarding demographic features and perinatal events was given to the parents.

Results: A total of 293 children (200 boys [68.3%]; with median age, 10.2 years [interquartile range {IQR}, 7.4–13.0 years]) were included. A total of 109 children (37.2%) had accompanying asthma. The median age of onset of rhinitis symptoms was earlier (5.3 years [IQR, 4.0–8.0 years] versus 7.0 years [IQR, 5.0–10.0 years]; $p = 0.001$), histories of prematurity (16.7 versus 6.5%; $p = 0.006$), preeclampsia (5.5 versus 0%; $p = 0.001$), neonatal intensive care unit admission (15.1 versus 6.0%; $p = 0.01$), phototherapy (17.9 versus 7.1%; $p = 0.004$), early formula feeding (58.7 versus 41.2%; $p = 0.006$), and parental asthma (25.0 versus 11.4%; $p = 0.002$) were more frequent in children with asthma. Multivariate logistic regression analysis revealed prematurity (odds ratio [OR] 2.78 [95% confidence interval [CI], 1.24–6.24]; $p = 0.013$), history of formula feeding (OR 1.81 [95% CI, 1.09–3.01]; $p = 0.022$), and parental asthma (OR 2.37 [95% CI, 1.22–4.63]; $p = 0.011$) were associated with asthma in school-age children with grass pollen-induced allergic rhinitis.

Conclusion: Close monitoring of patients with these risk factors may help with an earlier diagnosis of asthma and prompt initiation of therapeutic interventions in children with allergic rhinitis and who were sensitized to grass pollen.

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Allergic rhinitis is one of the most common chronic diseases of childhood.¹ It is well established that asthma develops more commonly in patients with allergic rhinitis when compared with children without rhinitis.^{2,3} Aeroallergen sensitization, particularly house-dust mite and *Aspergillus* mold sensitizations, have emerged as independent risk factors for asthma in children.⁴ However, different patterns of aeroallergen sensitization are found to be related to varying degrees of asthma risk,⁵ and every child with aeroallergen sensitization does not present with asthma symptoms.

In contrast to other inhalant allergies, pollen sensitization was not always associated with asthma,

and pulmonary symptoms were not found to be more frequent in patients with pollen-induced rhinitis when compared with patients without rhinitis.⁶ Nevertheless, ~40% of children with seasonal allergic rhinitis have asthma.⁷ Moreover, severe asthma exacerbations have been reported during dry and sunny days in some patients naturally exposed to pollens.⁸

Results of several studies determined several genetic and environmental risk factors for asthma in children with allergic rhinitis, with varying degrees of heterogeneity across studies.^{9–11} Furthermore, infantile feeding patterns are reported to be related to asthma risk.^{12,13} However, a vast majority of these results are provided from general population-based studies. Although the children with grass pollen sensitization and allergic rhinitis constitute a reasonable number of patients who are under regular follow-up in pediatric allergy departments, there is a lack of data that demonstrate the early life risk factors associated with asthma risk in these groups of children. The aim of our study was to examine whether parental and perinatal risk factors, along with infantile feeding patterns, were associated with asthma in school-age children with grass pollen sensitization and allergic rhinitis.

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METHODS

Design and Cohort

The study was performed in a tertiary pediatric allergy and asthma unit in Ankara, Turkey. Data of 293 children with grass pollen-induced allergic rhinitis who had regular follow-ups between 2011 and 2015 in our outpatient department were retrospectively analyzed. The patients were consecutively recruited and needed to fulfill the following inclusion criteria: (1) patients ages > 6 years, (2) patients regularly attended outpatient clinic visits during the follow-up period, and (3) patients only sensitized to grass pollen. All the children had a history of allergic rhinitis symptoms and had been followed up, and had the diagnosis of allergic rhinitis by pediatric allergy specialists.

The patients were regularly followed up with 3-month intervals. During the clinic visits, along with the symptom questionnaire and physical examination, pulmonary function tests were performed. However, the patients had the opportunity to go to the emergency department with respiratory symptoms (*e.g.*, asthma exacerbations or uncontrolled asthma symptoms) in the context of an unscheduled visit. Patients with multiple sensitizations, additional or coexisting chronic upper airway and/or lung diseases (*e.g.*, bronchiectasis), and/or other chronic diseases were excluded. Children were also excluded from the study if the information on their perinatal period was missing. All the patients and parents provided written informed consent for the study procedures, and the institutional review board of Gulhane Military School of Medicine approved the study.

S. Bagci and S.T. Yavuz had primary responsibilities for protocol development and the analytic framework of the study, review of the files, patient screening, enrollment, data entry, outcome assessment, and manuscript preparation. S. Siebert participated in the development of the protocol and analytic framework for the study, contributed to outcome assessment and data analysis, and prepared the manuscript with S. Bagci and S.T. Yavuz. O. Akın and M. Arslan contributed to data generation, patient screening, and data analysis, and prepared the manuscript with S. Bagci and S.T. Yavuz. E. Civelek contributed to protocol development, data analysis and preparation, and revision of the manuscript.

Diagnosis of Allergic Rhinitis

Allergic rhinitis was diagnosed by the presence of rhinitis symptoms (rhinorrhea, nasal obstruction, nasal itching and sneezing), which are reversible spontaneously or with treatment in children with grass pollen sensitization in a skin-prick test.⁹

Diagnosis of Asthma

Asthma was diagnosed by demonstrating the reversible airway obstruction as defined by at least a 12% improvement in forced expiratory volume during the first second (FEV₁) after bronchodilator administration in children with asthma symptoms or by improvement in the symptoms after oral and/or inhaled steroid therapy at any time during the follow-up period.¹⁴

Diagnosis of Conjunctivitis

Allergic conjunctivitis was diagnosed by the presence of conjunctivitis symptoms (tearing, burning, itching, and redness in the eyes), which are reversible spontaneously or with treatment in children with grass pollen sensitization in a skin-prick test.⁹

Diagnosis of Atopic Dermatitis

Atopic dermatitis is clinically defined by the presence of pruritus and a relapsing eczematous rash typically found over flexor surfaces.¹⁵

Covariates

As possible confounders for the association between asthma and allergic rhinitis with grass pollen sensitization, we included pregnancy disorders, parental features, and postnatal exposures. Medical records, linked birth certificates, and physician registries during the infancy provided information on perinatal characteristics and perinatal medical problems. Information on maternal and parental characteristics and on the data regarding early diet patterns was obtained from a questionnaire completed by the mother. Candidate risk factors were selected based on previous literature.

Definitions

"Parental asthma" was determined by asking the parent on the enrollment questionnaire if the mother or father of the child ever had physician-diagnosed asthma.

"Gestational age at birth" was estimated from the first day of the last menstrual period. The variables "oligohydramnios" and "preeclampsia" included recorded oligohydramnios and preeclampsia during the pregnancy.

"Breast-feeding" was defined as positive if the child was breast-fed for at least 12 weeks. "Exclusive breast-feeding" was defined as positive if the child was only breast-fed for at least 12 weeks without any additive formula feeding. The introduction of cow's milk-based formula for at least 8 weeks before 6 months of age is defined as a positive history of "early formula feeding."

Study Measurements

Skin-Prick Tests. All the children in our cohort underwent skin-prick testing with common aeroallergens for our region,¹⁶ including house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, and *Avena eliator*) weed pollen mix, tree pollen mix, molds (*Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*), animal dander (cat, dog, and horse), and histamine (10 mg/mL of histamine phosphate) as positive controls, and 0.9% sterile saline solution as the negative control. The volar surfaces of both forearms were used for application. The test results were recorded after 15 minutes and considered as positive if the mean wheal diameter was ≥ 3 mm compared with the negative control. Grass pollen sensitization was defined as a positive skin-prick test response to grass pollen mix allergen.

Blood Eosinophil Counts and Serum Total Immunoglobulin E Levels. Blood eosinophil counts were determined from Coulter Counter (Beckman Coulter, Fullerton, CA) leukocyte measurements. Serum total immunoglobulin E (IgE) levels were measured with the ImmunoCAP system (Phadia AB, Uppsala, Sweden).

Pulmonary Function Tests. Pulmonary function tests were performed by a physician with the patient in the sitting position by using a spirometer (Zan 100; Nspire Health, Oberthulba, Germany) according to recommendations of the European Respiratory Society.¹⁷ Lung function measures, such as forced vital capacity (FVC), FEV₁, FEV₁:FVC ratio, peak expiratory volume, and forced expiratory flow between 25% and 75%, were measured, and the predicted values were calculated. During the measurement, volume and flow curves were closely monitored to detect artifacts and to confirm that the participants rendered enough effort. Overall, three appropriate measurements were recorded, and the highest value was considered the basal value. All values were represented as percentages according to age, sex, weight, and height.

Statistical Analysis

The SPSS Statistics Version 21.0 (IBM, Chicago, IL) was used for all the calculations. Descriptive data for categorical variables were expressed as frequencies. The distributions of all numerical variables, including age, total IgE levels, blood eosinophil counts, and anthropometric measures, were skewed; thus, the results were summarized as medians and interquartile ranges. Group comparisons were established by using Mann-Whitney tests for medians (interquartile ranges) and the χ^2 test for categorical variables.

Table 1 Demographic data of the study group (N = 293)

Age, median (IQR), y	10.2 (7.4–13.0)
Boys, no. (%)	200 (68.3)
Asthma, no. (%)	109 (37.2)
Rhinitis age at diagnosis, median (IQR), y	8.0 (6.1–10.5)
Conjunctivitis, no. (%)	225 (76.7)
Age at AR symptoms start, median (IQR), y	6.6 (4.7–9.2)
Rhinitis duration, median (IQR), y	3.1 (1.8–5.1)
Duration of follow-up, median (IQR), y	3.3 (2.0–3.8)

IQR = Interquartile range; AR = allergic rhinitis.

The association between the prenatal risk factors and asthma was analyzed by using logistic regression modeling. Variables with $p < 0.1$ in univariate analysis were used for multivariate analysis. Sex, atopic dermatitis, prematurity, birth weight < 2000 g, preeclampsia, neonatal intensive care unit admission, phototherapy, early formula feeding, parental asthma, and breastfeeding for at least 4 months were used for multivariable analysis. The strength of association between the severity of asthma and risk factors was measured by using odds ratios (OR) and 95% confidence intervals (CI). A p level of < 0.05 was considered significant. Among the significant variables in the logistic regression analysis, prematurity had the lowest prevalence in the study groups. Therefore, we performed a power analysis by using the variable “prematurity” by using OpenEpi version 3.0 (OpenEpi, Atlanta, GA) open source calculator, and the power of the study was calculated as 80.3%.

RESULTS

A total of 293 children (200 boys [68.3%]; age range between 5.7 and 17.1 years; median age, 10.2 years [IQR, 7.4–13.0 years]) were included. The median follow-up duration of the study group was 3.3 years (IQR, 2.0–3.8 years) (Table 1). The allergic rhinitis symptoms were exclusively limited to the pollen season in the majority of patients (87%), whereas 13% of the patients had also reported symptoms out of the pollen season. A total of 109 children (37.2%) had accompanying asthma. In 44% of the children with asthma, the symptoms had started before the rhinitis symptoms. Eighty-one children (74.3%) already had a diagnosis of asthma during the recruitment period. In 28 children, the diagnosis of asthma was made during the clinical follow-up period. In 59.7% of the patients with asthma, the symptoms were limited to the pollen season.

There were no statistically significant differences between children with or without asthma in terms of sex and the duration of rhinitis. However, the current me-

dian age (8.8 years [IQR, 6.9–11.6 years] versus 11.3 years [IQR, 8.0–13.3 years]); $p = 0.001$) and the age of onset of rhinitis symptoms were younger (5.3 years [4.0–8.0 years] versus 7.0 years [5.0–10.0 years]; $p = 0.001$) in children with asthma. Accompanying conjunctivitis was more frequent in children without asthma (69.7 versus 81.0%; $p = 0.027$). The histories of prematurity (16.7 versus 6.5%; $p = 0.006$), preeclampsia (5.5 versus 0%; $p = 0.001$), neonatal intensive care unit admission (15.1 versus 6.0%; $p = 0.01$), phototherapy (17.9 versus 7.1%; $p = 0.004$), early formula feeding (58.7 versus 41.2%; $p = 0.006$), maternal asthma (15.7 versus 7.6%; $p = 0.03$), and parental asthma (asthma of any parent) (25.0 versus 11.4%; $p = 0.002$) were also more frequent in children with asthma. The median durations of breast-feeding and exclusive breast-feeding were shorter, and the history of early formula feeding was more frequent in children with asthma. However, the differences between the groups were slightly insignificant (Table 2).

Eosinophil counts, eosinophil percentages, and total IgE levels were not different between the groups. However, the lung function values were significantly lower in children with asthma (Table 3). Results of multivariate logistic regression analysis revealed that prematurity (OR 2.78 [95% CI, 1.24–6.24]; $p = 0.013$), history of early formula feeding (OR 1.81 [95% CI, 1.09–3.01]; $p = 0.022$), and parental asthma (OR 2.37 [95% CI, 1.22–4.63]; $p = 0.011$) were associated with asthma in school-age children with grass pollen-induced allergic rhinitis (Table 4).

DISCUSSION

In this cross-sectional study, we found that prematurity, early formula feeding, and parental asthma were independently associated with asthma in school-age children with grass pollen sensitization and allergic rhinitis. Prematurity (or preterm delivery) is one of the most reported variables associated with asthma in general population studies, including children. Jaakkola *et al.*¹⁸ concluded that prematurity (a gestational age of <37 weeks) is a risk factor for asthma. Been *et al.*¹⁹ analyzed the data of ~1.5 million children derived from worldwide observational studies and preterm birth is found to be associated with an increased risk of childhood disorders when adjusted for potential confounders. Recently, Matheson *et al.*²⁰ found that the negative effects of prematurity on the airways continue into middle age. In line with the previous major meta-analyses and studies, we replicated the same finding in our cohort, which consisted of children with grass pollen sensitization and allergic rhinitis.

Several researchers investigated the role of parental asthma in offspring asthma. Lim *et al.*²¹ report that maternal asthma had ~3-fold greater odds of offspring

asthma when compared with those without maternal asthma and concluded that maternal asthma is a greater risk factor for offspring asthma than paternal asthma. However, no significant differences were observed between maternal and paternal effects when the analysis was restricted to studies in which the asthma diagnosis was made by a physician or when the analysis was restricted to children ≥ 5 years. In our study, in parallel with the findings of the previous meta-analysis, maternal asthma was significantly associated with offspring asthma in the univariate analysis, whereas the association for paternal asthma was slightly insignificant. In the multivariate analysis, we also established parental asthma (asthma in any parent) as a risk factor for asthma in children with grass pollen sensitization and allergic rhinitis.

Along with prematurity and parental asthma, major reviews and guidelines have indicated that maternal smoking during pregnancy and the infant's early life has been associated with childhood wheezy illnesses and also with an increased risk of delivering a preterm infant.^{4,11,22–24} However, we could not find an association between either maternal smoking during pregnancy or smoke exposure after birth and asthma. The plausible explanation for this lack of association may be that our study group consisted exclusively of children with grass pollen sensitization, although Strachan and Cook²⁵ did not find an association between parental smoking and allergic sensitization in children, either before or after birth. Our sample size may also be too small to identify the significance of this variable.

Breast-feeding is also one of the most investigated parameters in previous studies. A reasonable number of epidemiologic studies have investigated the effects of breast-feeding on the development of wheezing disorders and asthma during childhood. However, there is still not a consensus regarding the relationship between breast-feeding and allergy risk. Although there is evidence that breast-feeding protects against atopic dermatitis, wheeze in early childhood, and allergy to cow's milk, data are inconclusive about the role of breast-feeding in protection against asthma.^{12,13,26,27} In our study, the frequency of exclusively of children who were breast-fed was lower and the duration of exclusive breast-feeding was shorter (although slightly insignificant) in children with asthma. Moreover, the introduction of cow's milk-based formulas to infants earlier than 6 months of age was revealed as an independent risk factor in our study.

In contrast to our findings, Gustafsson *et al.*²⁸ reported that feeding with cow's milk-based formula does not increase the risk of atopic disease development. Wegienka *et al.*²⁹ surprisingly established an increased risk of childhood allergies in children who were exclusively breast-fed when compared with children who were breast-fed and formula fed. Nwaru *et*

Table 2 Demographic and perinatal characteristics of children with grass pollen allergy and allergic rhinitis according to asthma presence

	Children with asthma (n = 109)	Children without asthma (n = 184)	p
Parental characteristics			
Mother's age at birth, median (IQR), y	27.9 (24.1–31.4)	27.8 (25.0–31.7)	0.64
Father's age at birth, median (IQR), y	30.8 (27.1–33.4)	31.2 (28.8–34.6)	0.12
Nulliparous mother (first child)%	57.4	48.4	0.14
Maternal asthma%	15.7	7.6	0.03
Paternal asthma%	10.2	4.3	0.051
Parental asthma (any)%	25.0	11.4	0.002
History of asthma in both parents%	0.9	0	0.37
Children's characteristics			
Current age, median (IQR), y	8.8 (6.9–11.6)	11.3 (8.0–13.3)	0.001
Boys%	73.4	65.2	0.15
Duration of follow-up, median (IQR), y	1.8 (1.0–2.9)	2.3 (1.0–2.8)	0.92
Age at start of AR symptoms, median (IQR), y	5.3 (4.0–8.0)	7.0 (5.0–10.0)	0.001
Rhinitis duration, median (IQR), y	3.6 (1.8–5.6)	2.8 (1.8–4.6)	0.26
Time between AR symptoms and diagnosis, median (IQR), y	1.1 (0.5–2.5)	1.5 (0.9–2.8)	0.20
Conjunctivitis%	69.7	81.0	0.027
Atopic dermatitis%	10.1	4.3	0.054
Birth season%			0.36
Winter%	28.4	22.3	
Spring%	23.9	33.2	
Summer%	25.7	23.9	
Autumn%	22.0	20.7	
Multiple births (twins <i>etc.</i>)%	3.7	3.8	0.95
Caesarean section%	58.3	51.6	0.27
Gestational age, median (IQR), wk	38 (37–39)	39 (38–40)	0.015
Birth weight, median (IQR), g	3200 (2800–3600)	3400 (3100–3650)	0.016
Prematurity%	16.7	6.5	0.006
LBW < 2500 g	11.4	6.0	0.11
Birth weight ≤ 2000 g	5.6	1.6	0.08
Postmaturity%	1.8	4.3	0.25
Prenatal exposures%			
Maternal smoking during pregnancy%	9.3	8.7	0.87
Gestational diabetes mellitus%	2.8	3.8	0.75
Oligohydramnios%	2.8	1.6	0.51
Preeclampsia%	5.5	0	0.001
Postnatal exposures%			
NICU admission%	15.1	6.0	0.01
Mechanical ventilation%	3.8	1.1	0.20
Phototherapy%	17.9	7.1	0.004
Breast-feeding%	83.5	90.2	0.09
Breast-feeding duration, median (IQR), mo	12 (6–24)	15 (7–24)	0.09
Exclusively breast-fed%	57.8	67.8	0.09
Exclusive breast-feeding duration, median (IQR), mo	5 (3–6)	6 (4–6)	0.07
Weaning time, median (IQR), mo	6 (5–6)	6 (5–6)	0.22
Early formula feeding%	58.7	42.1	0.006
Cow's milk before 1 y of age%	12.0	15.8	0.37
Daycare before 2 y of age%	8.3	8.2	0.97
Elder sibling%	42.6	51.6	0.14

Table 2 Continued

	Children with asthma (n = 109)	Children without asthma (n = 184)	p
Current indoor smoking%	22.0	20.1	0.70
Mother a current smoker%	19.3	17.4	0.70
Father a current smoker%	30.3	29.3	0.87
Both parents were current smokers%	11.9	9.2	0.46
Any parent was current smoker%	40.4	39.1	0.83

IQR = Interquartile range; AR = allergic rhinitis; LBW = low birth weight; NICU = neonatal intensive care unit.

Table 3 Laboratory features of children according to asthma presence)*

	Children with asthma (n = 109)	Children without asthma (n = 184)	p
Eosinophils percentage	3.7 (2.1–5.8)	4.1 (2.4–6.3)	0.08
Eosinophil counts, no./mm ³	260 (150–460)	270 (190–490)	0.45
Total IgE level, kU/L	73 (23–164)	78 (28–150)	0.73
FEV ₁ %	86 (78–96)	103 (97–113)	<0.001
FVC%	91 (79–98)	96 (90–107)	<0.001
FEV ₁ :FVC	88 (82–92)	91 (88–95)	<0.001
PEF%	81 (71–88)	95 (83–103)	<0.001
FEF _{25–75} %	77 (65–90)	106 (94–122)	<0.001

IgE = Immunoglobulin E; FEV₁ = forced expiratory volume during first second; FVC, forced vital capacity; PEF = peak expiratory flow; FEF_{25–75} = forced expiratory flow between 25% and 75%; IQR = interquartile range.

*Values are median (IQR).

Table 4 Multivariable logistic regression analysis for asthma (N = 293)

	OR (95% CI)	p
Prematurity	2.78 (1.24–6.24)	0.013
Early formula feeding	1.81 (1.09–3.01)	0.022
Parental asthma (any)	2.37 (1.22–4.63)	0.011

OR = Odds ratio; CI = confidence interval.

*al.*³⁰ concluded that the nature of infant feeding during the first 6 months does not influence the long-term risk of asthma risk in children. However, there also are several well-designed studies and guidelines that report the higher incidence of asthma and wheezing disorders in children who were fed with cow's milk-based formulas when compared with children who were exclusively breast-fed.^{4,12,31–33}

To achieve better results regarding the relationship between nutritional patterns and asthma, Dogaru *et al.*¹² recommend performing prospective and longitudinal studies that recruit women during pregnancy and that assess the duration of breast-feeding and incidence of asthma symptoms. They also recommend the addition of several confounders, including exposure during pregnancy (e.g., tobacco smoke), perinatal

confounders, family's socioeconomic status, and family's history of asthma and/or atopy. Unfortunately, we could not include the socioeconomic status of the family in our analyses.

To our knowledge, this is the first study that investigated asthma risk factors exclusively in children with grass pollen sensitization and allergic rhinitis. Although we followed up the patients for a reasonable period (median, 3.3 years) asthma symptoms can start anytime during the childhood. However, the median age of children with asthma was younger in our study. Therefore, it can be said that our follow-up duration was long enough to detect the children with newly diagnosed asthma. Nevertheless, prospective studies with a longer follow-up duration may better help to identify the risk factors for childhood and adolescent asthma in children with grass pollen sensitization and allergic rhinitis.

Along with the perinatal factors, several environmental variables during infancy and early childhood (e.g., vitamin D, folate, microbiome, infections, medications) that we did not investigate can also affect the asthma development in children. However, our relatively high patient number enabled us to include several confounders in our multivariate analysis. Pediatric allergy specialists performed the diagnostic proce-

dures and longitudinal follow-up of the patients. The outcome data were assessed with a standardized instrument and were based on physician-confirmed diagnosis. We believed that these strengths of our study design increased the reliability of our results. Nevertheless, when interpreting our results, it must be kept in mind that our study group exclusively consisted of children with grass pollen sensitization and allergic rhinitis. Therefore, it may not be suitable to directly generalize our findings to the general population.

CONCLUSION

Our results revealed that prematurity, early formula feeding, and parental asthma were associated with asthma in school-age children with allergic rhinitis. Therefore, close monitoring of patients with these risk factors may help with an earlier diagnosis of asthma and prompt initiation of therapeutic interventions to prevent morbidities in children with allergic rhinitis and monosensitized to grass pollen.

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