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Risk factors predisposing children to food allergies

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KEYWORDS
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Abstract
Background: Food allergies are the most common cause of anaphylaxis in children, and their incidence is increasing globally. The aim of this study was to determine the risk factors leading to food allergies in childhood.
Methods: Children with food allergies and non-atopic healthy children were compared using a questionnaire that included prenatal, neonatal, and postnatal risk factors.
Results: A total of 314 subjects, 155 patients and 159 healthy children for the control group, were enrolled in the study. The median age of patients with a food allergy at diagnosis was 6 months (1-156 months), and 71 patients (45.8%) were males. The median age of the control group was 12 months (1-61 months), and 67.0% were males. Older maternal age (P = 0.023), birth by caesarean section (P = 0.001), birth in the summer or autumn (P = 0.011), crowded housing (P = 0.001), damp houses (P = 0.001), being fed with breast milk and complementary food (P = 0.001), use of synthetic bedding (P = 0.024), and being the oldest child in the family (P = 0.001) were the considered risk factors for an immunoglobulin-E (IgE)-mediated food allergy. A low frequency of yoghurt consumption by mother (P = 0.001) and use of wool bedding (P = 0.018) were identified as risk factors for non-IgE-mediated food allergies. Low socioeconomic status (P = 0.001) played a protective role against both IgE- and non-IgE-mediated food allergies whereas breastfeeding played a protective role against IgE-mediated food allergies (P = 0.030).
Conclusion: The most important aspect of this study was that it separately identified prenatal, neonatal, and postnatal risk factors for IgE- and non-IgE-mediated food allergies.

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Introduction

Food allergy is defined as "an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food," while food intolerance refers to "non-immune reactions that include metabolic, toxic, pharmacologic, and undefined mechanisms." Immune-mediated food reactions are divided into the following three groups according to their mechanism: immunoglobulin-E (IgE)-mediated, non-IgE-mediated, and mixed reactions. In IgE-mediated reactions, clinical manifestations occur within minutes or hours of food ingestion whereas in non-IgE-mediated reactions, manifestations occur within hours or days of food ingestion.[1] Food allergies are the most common cause of anaphylaxis in children, accounting for 81% of cases.[2] The prevalence of food allergies in children is increasing. Recently, it has been reported that various genetic and environmental factors play a role in the development of these allergies.[3]

The aim of this study was to identify the risk factors that may affect the development of food allergies during childhood.

Materials and Methods

This was a multi-centre study in which the patient group (aged 0–18 years) comprised subjects who had been diagnosed with a food allergy and subjected to a food provocation test. Participants were enrolled from facilities throughout Turkey: Başakşehir Çam and Sakura City Hospital, Koç University Hospital, Cemil Taşçıoğlu City Hospital, and the Faculty of Medicine Pediatric Allergy and Immunology Polyclinics, Ondokuz Mayıs University.

All patients were diagnosed with a food allergy using an open food challenge test. While testing was performed in patients with IgE-mediated food allergies in the hospital, testing was performed in patients with non-IgE-mediated food allergies at home. The control group included healthy children aged 0–18 years, who presented to the paediatric department of the Başakşehir Çam and Sakura City Hospital, and neither had chronic diseases or allergic conditions nor family history of atopy.

The study was conducted prospectively. The intake questionnaire form recorded age; gender; clinical findings; eosinophilia; total IgE levels; presence of faecal occult blood; food-specific IgE levels; skin prick, oral provocation, and elimination test results; maternal age; paternal age; and body mass index (BMI). The questionnaire also included information on maternal and paternal educational status, gestational medication use, gestational infections, gestational diseases, birth weight, season of birth, mode of delivery, neonatal ICU hospitalisation, neonatal antibiotic use, neonatal phototherapy use, presence of humidity in the home, smoking exposure, pet exposure, and the timing of transition from exclusive breastfeeding to complementary feeding.

Patients' nutritional habits before the onset of clinical manifestations were compared with those of the control group during the first 6 months of birth. Families with a monthly income of less than $1000 were considered to be of low socioeconomic status.

Patients aged 0–18 years who agreed to participate in the study were diagnosed with an IgE- or non-IgE-mediated food allergy, and did not have a chronic or autoimmune disease as a concomitant condition were enrolled in the study. In the control group, patients with chronic diseases, allergic diseases, a family history of allergic diseases, autoimmune diseases, and patients who did not consent to participate in the study were excluded from the study.

Patients were divided into two groups: IgE- and non-IgE-mediated food allergy patient groups. Risk factors were divided into three categories: effective factors in the prenatal, neonatal, and postnatal periods. The patient groups were statistically compared with the control group in terms of risk factors. Patients with eosinophil count in peripheral blood exceeding 4.0% were considered as eosinophilic.[4] The ImmunoCAP method was used to measure specific IgE measures. Values more than 0.35 kU/L were considered significant.[1,5] Serum total IgE levels were compared with normal IgE levels in healthy children of similar age.[6] Skin prick tests were performed on the volar aspect of the forearm using food allergen solutions, and the reaction was observed after 15 min. The test results were considered positive if the diameter of the wheal was at least 3 mm larger than that of the negative control.[7]

The study was approved by the Ethics Committee of the Başakşehir Cam and Sakura City Hospital, vide number KAEK/2021.10.230.

Statistical Analyses

The data analysed in the study were processed using SPSS 13. Descriptive statistics were presented as numbers and percentage values for categorical variables and as mean ± standard deviation or median (least maximum value) for continuous variables. Presence of a normal distribution was determined using histograms, Q–Q plots, and normal distribution tests (Kolmogorov–Smirnov or Shapiro–Wilk test). Categorical variables were described using Pearson's Chi-square test or, if assumptions were not met, comparison was done with Fisher's exact test. The Fisher–Freeman–Halton test was used for tables larger than 2×2 if the number of eyes with expected values >5 was high. For comparing continuous variables between two groups, *t*-test or Mann–Whitney U test was used in independent groups, depending on the presence of a normal distribution. For comparing continuous variables between three independent groups, one-way analysis of variance (ANOVA) or Kruskal–Wallis test was used, depending on the presence of a normal distribution. Univariate logistic regression analyses were performed for relationships between independent and dependent variables. Odds ratio (OR), a measure of risk, was reported with a 95% confidence interval (CI). A two-sided P-value of >0.05 were considered statistically significant. Data analyses were performed with R version 4.2.2 (https://www.r-project.org/).

Results

Demographics of all patients with a food allergy

A total of 314 subjects, 155 patients and 159 healthy children in the control group, were enrolled in the study. The median age of patients with a food allergy at diagnosis was 6 months (1–156 months), and 71 (45.8%) patients were males. The median age of the control group at diagnosis was 12 months (1–61 months), and 67.0% were males.

Demographics of patients with an IgE-mediated food allergy

The median age at diagnosis was 7 months (2–156 months) in the IgE-mediated food allergy group. Comparing the patients with an IgE-mediated food allergy with those in the control group, we discovered that maternal and paternal age was higher in the patient groups (P = 0.023, OR=1.06 and P = 0.001, OR = 1.09, respectively).

Demographics of patients with a non-IgE-mediated food allergy

The median age of patients at diagnosis was 4 months (1–11 months) in the group with a non-IgE-mediated food allergy. Comparing patients with a non-IgE-mediated food allergy with those in the control group, we discovered that the median age at diagnosis was lower in the patient group (P = 0.001, OR = 0.69) (Table 1).

Laboratory findings of all patients with a food allergy

The median IgE level for all patients with a food allergy was 94 IU/mL. Eosinophilia was present in 41.9% of the patients, and the median percentage of eosinophils was 3.70 (0–15). An elevated serum IgE level was observed in 61.0% of patients, while the specific IgE level was high in 72.7% of patients. A skin prick test was positive in 70.5% of patients.

Laboratory findings of patients with an IgE-mediated food allergy

The proportion of eosinophilia in patients with an IgE-mediated food allergy was 49.5%; the median proportion of eosinophilia was 4.0%; the proportion of patients with elevated serum IgE was 74.3%; the proportion of patients with an elevated specific IgE was 84.2%; and the proportion of patients with a positive skin prick test was 71.3%.

Laboratory findings of patients with a non-IgE-mediated food allergy

Eosinophilia was found in 27.8% of patients with a non-IgE-mediated food allergy. The median percentage of eosinophils was 2.5 (0–8.8), and the median serum IgE level was 13.2. An elevated specific IgE level was found in 44.4% of patients, and an elevated serum IgE level was found in 35.2% of patients (Table 2).

Characteristics of all patients with a food allergy

Classified by the type of food allergy, 65.2% were IgE-mediated and 34.8% were non-IgE-mediated allergies. Among all the patients, 85.8% had a single food allergy, while 14.2% had multiple food allergies.

Characteristics of patients with a IgE-mediated food allergy

In the IgE-mediated patient group, 83.2% had a single food allergy and 16.8% had multiple food allergies. The most common allergenic nutrient was egg, with 39.6% allergy, while the second most common allergenic food was cow's milk, with 32.7% allergy.

Characteristics of the patients with a non-IgE-mediated food allergy

A vast majority (90.7%) of patients with a non-IgE-mediated allergy had a single food allergy, and only 9.3% had multiple food allergies. Cow's milk was the triggering food in 74.1% of patients, egg was observed as allergic in 16.7% of patients, and the combination of cow's milk and egg caused allergy in 9.4% of patients (Table 3).

Clinical characteristics of patients with an IgE-mediated food allergy

In the IgE-mediated food allergy group, the most common clinical finding upon admission was urticaria, which occurred in 66.3% of patients.

Clinical characteristics of patients with a non-IgE-mediated food allergy

The most common clinical finding in non-IgE-mediated patient group was bloody and mucopurulent stool, observed in 92.6% of patients (Table 4).

Prenatal risk factors in patients with an IgE-mediated food allergy

Comparison between the IgE-mediated food allergy patient group and the control group, in terms of prenatal risk factors, demonstrated that the history of maternal antibiotic use during pregnancy was significantly higher in the patient group than in the control group (P = 0.041, OR = 2.66).

Table 1 Demographics of patient groups and control group.

	Patient n (%)	Control n (%)	*P*	OR
All patients				
Onset age of symptoms (months), Median (min-max)	3 (1-84)			
Diagnosis age (months): median, (min-max)	6 (1-156)	12 (1-61)	**0.001**	**0.96 (0.98-0.93)**
Gender: male	71 (45.8)	67 (42.1)	0.588	(-/-)
Consanguineous marriage	25 (16.1)	18 (11.3)	0.282	1.50 (0.78-2.93)
BMI (m^2/kg), mother, median (min-max)	23.8 (17.6-34.2)	23.8 (16.6-37.7)	0.581	0.96 (1.01-0.90)
BMI (m^2/kg), father, median (min-max)	25.7 (20.1-39.8)	26.6 (19.8-35.2)	**0.008**	0.94 (1.00-0.88)
Maternal age (years)	30 (20-45)	30 (19-43)	0.085	1.04 (1.09-1.00)
Paternal age (years)	33 (23-50)	32 (21-48)	**0.004**	**1.07 (1.11-1.02)**
Maternal education			0.442	
Primary education	24 (21.9)	27 (17.0)		(-/-)
High school	44 (28.4)	43 (27.0)		0.81 (0.42-1.57)
University	77 (49.7)	89 (56.0)		0.69 (0.38-1.24)
Paternal education			0.353	
Primary education	32 (20.6)	23 (14.5)		(-/-)
High school	45 (29.0)	49 (30.8)		0.66 (0.33-1.30)
University	78 (50.3)	87 (54.7)		0.65 (0.34-1.20)
Total	155 (100.0%)	159 (100.0%)		
IgE-mediated				
Onset age of symptoms (months), median (min-max)	5 (1-84)			
Diagnosis age (months), median (min-max)	7 (2-156)		**0.001**	0.98 (0.96-1.01)
Gender: male	54 (53.5)		0.097	(-/-)
Consanguineous marriage	13 (12.9)		0.857	1.16 (0.53-2.49)
BMI (m^2/kg), mother, median (min-max)	24.0 (17.8-34.2)		0.888	0.97 (0.96-1.03)
BMI (m^2/kg), father, median (min-max)	25.6 (20.1-39.8)		**0.026**	0.94 (0.88-1.01)
Maternal age (years)	31 (20-45)		**0.023**	**1.06 (1.01-1.12)**
Paternal age (years)	35 (23-50)		**0.001**	**1.09 (1.04-1.14)**
Maternal education			0.355	
Primary education	23 (22.8)			(-/-)
High school	30 (29.7)			0.82 (0.39-1.71)
University	48 (47.5)			0.63 (0.33-1.23)
Paternal education			0.218	
Primary education	23 (22.8)			(-/-)
High school	30 (29.7)			0.62 (0.29-1.29)
University	48 (47.5)			0.55 (0.28-1.10)
Total	101 (100.0)			
Non-IgE-mediated				
Onset age of symptoms (months), median (min-max)	2 (1-7)			
Diagnosis age (months), median (min-max)	4 (1-11)		**0.001**	**0.69 (0.61-0.79)**
Gender: male	17 (31.5)		0.221	(-/-)
Consanguineous marriage	12 (22.29)		0.078	2.24 (0.97-5.01)
BMI (m^2/kg), mother, median (min-max)	23.5 (17.6-33.7)		0.341	0.94 (0.87-1.02)
BMI (m^2/kg), father, median (min-max)	25.7 (20.4-37.2)		**0.033**	0.92 (0.83-1.02)
Maternal age (years)	29 (21-40)		0.925	1.00 (0.94-1.07)
Paternal age (years)	32 (25-49)		0.461	1.02 (0.97-1.08)
Maternal education			0.854	
Primary education	11 (20.4)			(-/-)
High school	14 (25.9)			0.80 (0.31-2.07)
University	29 (53.7)			0.80 (0.36-1.87)
Paternal education			0.878	
Primary education	9 (16.7)			(-/-)
High school	15 (27.8)			0.78 (0.30-2.13)
University	30 (55.6)			0.88 (0.37-2.21)
Total	54 (100.0)			

Table 2 Laboratory findings of patients with food allergies.

	n (%)
All patients	
Eosinophilia	65 (41.9)
Eosinophil level: median (min-max)	3.70 (0-15)
Serum IgE elevation	94 (61.0)
Serum IgE level: median (min-max), IU/mL	45 (0.10-2790)
Specific IgE elevation	109/150 (72.7)
Specific IgE level: median (min-max), IU/mL	4.69 (0.0-123)
Skin prick test positivity	91/129 (70.5)
Diameter of skin prick test (mm), median (min-max)	5 (0-18)
Total	155 (100.0)
IgE-mediated	
Eosinophilia	50/101 (49.5)
Eosinophil level: median (min-max)	4 (0.1-15)
Serum IgE elevation	75/101 (74.3)
Serum IgE level: median (min-max), IU/mL	65 (3-2790)
Specific IgE elevation	85/101 (84.2)
Specific IgE level: median (min-max), IU/mL	8.7 (0-123)
Skin prick test positivity	72/85 (71.3)
Diameter of skin prick test (mm), median (min-max)	5 (0-18)
Total	101 (100.0)
Non-IgE-mediated	
Eosinophilia	15/54 (27.8)
Eosinophil level: median (min-max)	2.5 (0-8.8)
Serum IgE elevation	19/54 (35.2)
Serum IgE level: median (min-max), IU/mL	13.2 (0.1-492)
Specific IgE elevation	24/54 (44.4)
Specific IgE level: median (min-max), IU/mL	0.25 (0-100)
Skin prick test positivity	19/54 (35.2)
Diameter of skin prick test (mm), median (min-max)	3 (0-8)
Total	54 (100.0)

Prenatal risk factors in patients with a non-IgE-mediated food allergy

Comparison between the non-IgE-mediated food allergy patient group and the control group, in terms of prenatal risk factors, demonstrated that the history of maternal antibiotic use during pregnancy was significantly higher in the patient group than in the control group (P = 0.042, OR = 2.89) (Table 5).

Neonatal risk factors in patients with an IgE-mediated food allergy

Evaluation of the patient groups according to the season of delivery demonstrated that the proportion of food allergies was higher in children born in summer and autumn (P = 0.011, OR = 2.43 and 2.07, respectively).

Evaluation of delivery types demonstrated that the proportion of caesarean sections (C-section) was statistically higher in the patient groups (P = 0.001, OR = 2.20). ICU hospitalisation and antibiotic use during the neonatal period indicated that these parameters were more frequent in the patient groups (P = 0.006, OR = 2.30 and P = 0.027, OR = 2.19, respectively).

Neonatal risk factors in patients with a non-IgE-mediated food allergy

Considering neonatal risk factors, we observed that the median birth weight in the patient groups was lower than that in the control group (P = 0.028). However, no statistically significant difference was determined in the logistic regression analysis (OR = 1.0) (Table 6).

Postnatal risk factors in patients with an IgE-mediated food allergy

Comparison of the groups in terms of postnatal risk factors showed that low socioeconomic status; crowded living conditions; damp homes; exposure to smoking; being the first child in the family; breast feeding and the provision of complementary foods prior to the onset of manifestations; breast feeding, use of infant formula, and the provision of complementary foods prior to the onset of manifestations; using infant formula; and using synthetic bedding were higher in the patient groups than in the control group (P = 0.001, OR = 0.23; P = 0.001, OR = 2.92; P = 0.001, OR = 3.83; P = 0.001, OR = 2.87; P = 0.001, OR = 1.93; P = 0.001, OR = 6.59; P = 0.001, OR = 8.98; P = 0.005, OR = 2.24; P = 0.024, OR = 5.45, respectively). Among these factors, low socioeconomic level decreased the risk, while other factors increased the risk of food allergies. The rate of exclusive breast feeding before the onset of manifestations was higher in the patient groups than in the control group (P = 0.001, OR = 0.40).

Postnatal risk factors in patients with a non-IgE-mediated food allergy

Comparison of the groups in terms of postnatal risk factors showed that damp homes, exposure to cigarette smoke, low socioeconomic level, infant formula feeding, low frequency of maternal yoghurt consumption, and the use of woollen bedding were higher in the patient groups than in the control group (P = 0.005, OR = 3.34; P = 0.016, OR = 2.61; P = 0.001, OR = 0.19; P = 0.002, OR = 2.83; P = 0.001, OR = 5.09; P = 0.018, OR = 3.52, respectively). In both patient groups, low socioeconomic level decreased, while other factors increased the risk of food allergy (Table 7). At least one atopic disease in their family history was discovered in 65.4% of all food-allergic patients, 56.1% of the IgE-mediated patients, and 37.9% of the non-IgE-mediated patients.

Discussion

In recent years, atopic diseases have increased worldwide and represent a major burden on the world's healthcare

Table 3 Characteristics of food allergies.

	n (%)
All patients	
Time of onset of manifestations	
In the first 2 h	101 (65.2)
After 2 h	54 (34.8)
Type of food allergy by mechanism	
IgE-mediated	101 (65.2)
Non-IgE-mediated	54 (34.8)
Type of food allergy by the number of allergen	
Single	133 (85.8)
Multiple	22 (14.2)
Allergenic food	
Cow's milk	73 (47.1)
Egg	49 (31.6)
Cow's milk, and egg	10 (6.5)
Peanut	4 (2.6)
Pistachios	3 (1.9)
Hazelnut	2 (1.3)
Tomato	1 (0.6)
Jevel	1 (0.6)
Sesame	1 (0.6)
Cow's milk, egg, and fish	1 (0.6)
Cow's milk, egg, pistachios, hazelnut, sesame, and walnut	1 (0.6)
Cow's milk, egg, hazelnut, walnut, almond, wheat, and pea	1 (0.6)
Cow's milk, egg, and beef	1 (0.6)
Cow's milk, egg, pistachios, and cashew	1 (0.6)
Egg, wheat, rye, and cashew	1 (0.6)
Egg and hazelnut	1 (0.6)
Egg, hazelnut, and walnut	1 (0.6)
Egg, hazelnut, and fig	1 (0.6)
Egg, peanut, and lentil	1 (0.6)
Egg, peanut, lentil, and fish	1 (0.6)
Total	155 (100.0)
IgE-mediated	
Type of food allergy by the number of allergen	
Single	84 (83.2)
Multiple	17 (16.8)
Allergenic food	
Egg	40 (39.6)
Cow's milk	33 (32.7)
Pistachios	4 (4.0)
Cow's milk and egg	3 (3.0)
Peanut	2 (2.0)
Hazelnut	1 (1.0)
Tomato	1 (1.0)
Jewel	1 (1.0)
Sesame	1 (1.0)
Cow's milk, egg, and fish	1 (1.0)
Cow's milk, egg, pistachios, hazelnut, sesame, and walnut	1 (1.0)
Cow's milk, egg, hazelnut, walnut, almond, wheat, and pea	1 (1.0)
Cow's milk, egg, and beef	1 (1.0)
Cow's milk, egg, pistachios, and cashew	1 (1.0)
Egg, wheat, rye, and cashew	1 (1.0)
Egg and hazelnut	1 (1.0)
Egg, hazelnut, and walnut	1 (1.0)
Egg, hazelnut, and fish	1 (1.0)
Egg, peanut, and lentil	1 (1.0)
Egg, peanut, lentil, and fish	1 (1.0)
Total	101 (100.0)
Non-IgE-mediated	
Type of food allergy by the number of allergen	
Single	49 (90.7)
Multiple	5 (9.3)
Allergenic food	
Cow's milk	40 (74.1)
Egg	9 (16.7)
Cows milk and egg	5 (9.4)
Total	54 (100.0)

systems.[8,9] These diseases can cause life-threatening anaphylactic reactions.[10] In this study, prenatal, neonatal, and postnatal risk factors associated with food allergy were investigated. The study was conducted in four tertiary care research centres in Turkey. In all centres, patients were examined in the paediatric immunology and allergy clinics. Three of the centres were located in Istanbul, and one was in Samsun.

As far as we know, there are no data in the literature on the prevalence of food allergies among children in Istanbul. In a study of children aged less than 5 years in Edirne, a city near Istanbul, the prevalence of food allergies was reported to be 12.3%. In this study, the prevalence of food allergies was determined based on information provided by children's families.[11] In a study conducted in a nursery and kindergarten in Samsun, the prevalence of food allergies was 7.7%.[12] In this study, the median age of the patient groups at diagnosis was 6 months whereas it was 12 months in the control group, and this was a statistically significant difference between the two main groups. At first glance, one might think that the age difference was a disadvantage when making comparisons; however, the age difference was crucial for the control group's inclusion and exclusion criteria. To be included in the control group, a participant had to have both personal and familial atopy. Familial atopy could be easily detected through a detailed medical history, but a period of more than 6 months was required for follow-up in case of diseases such as recurrent wheezing, food allergy, and atopic dermatitis, which are common atopic diseases among infants. For this reason, the median age of participants in the control group was assumed to be higher in order to exclude personal atopy.

In the present study, in case of patients with an IgE-mediated allergy, we found that both paternal and maternal age was higher, compared with subjects of the control group. One study examined the association between maternal age and food allergies, but no statistically significant relation was discovered.[13] By contrast,

Table 4 Clinical characteristics of patients with food allergy.

	n (%)
IgE-mediated	
Skin	
Urticaria	67 (66.3)
Erythema	60 (59.4)
Pruritis	43 (42.6)
Redness around the mouth	31 (30.7)
Angioedema	20 (19.8)
Eczema	17 (16.8)
Gastrointestinal tract	
Vomiting	19 (18.8)
Refuse food	15 (14.9)
Abdominal pain	4 (4.0)
Perianal rash	3 (3.0)
Constipation	2 (2.0)
Stool with blood and mucus	2 (2.0)
Discomfort/colic	2 (2.0)
Diarrhea	2 (2.0)
Respiratory tract	
Shortness of breath	18 (17.8)
Cough	14 (13.9)
Persistent rhinitis	9 (8.9)
Wheezing	5 (5.0)
Stridor	0 (0.0)
Cardiovacular tract	
Weakness	8 (7.9)
Syncope	3 (3.0)
Bradycardia	2 (2.0)
Palpitation/tachycardia	1 (1.0)
Hypotension	0 (0.0)
Anaphylaxis	32 (31.7)
Total	101 (100.0)
Non-IgE-mediated	
Gastrointestinal tract	
Stool with blood and mucus	50 (92.6)
Perianal rashes	17 (31.5)
Refuse food	14 (25.9)
Diarrhea	13 (24.1)
Discomfort/colic	9 (16.7)
Consipation	9 (16.7)
Abdominal pain	7 (13.0)
Vomiting	4 (7.4)
Weight loss	3 (5.6)
Skin	
Eczema	5 (9.3)
Pruritis	4 (7.4)
Redness around the mouth	4 (7.4)
Erythema	4 (7.4)
Total	54 (100.0)

another study reported that maternal age was significantly related to food allergies, and mothers of allergic children tended to belong to older age groups.[14] In Turkey, educated people generally marry at a later age than less-educated people. In parallel, increase in socioeconomic level and a more hygienic lifestyle may increase the incidence of food allergies in these groups.

In the study conducted by Karpa et al., the incidence of food allergy was found higher in the patients treated in ICU during neonatal period, and in children who were born by C-section.[14] The fact is that an infant not exposed to mother's vaginal and perineal flora is generally recognised as a risk factor for food allergies.[15] One cohort study reported that IgE-mediated food allergies increased in infants born by C-section.[16] Another study established that the incidence of gastrointestinal manifestations, atopic dermatitis, and food allergies increased during the first year of birth following a delivery by C-section.[17] In a study conducted in 2019, caesarean delivery was found to be directly associated with childhood allergic diseases, particularly asthma and food allergies.[18] In this study, caesarean delivery was determined as significantly more common in the IgE-mediated patient group than in the control group.

Some studies have emphasised the season of birth as a factor in the development of food allergies. One study reported that food allergies were more common in children born in winter and autumn than in children born in summer. Some animal studies demonstrated that allergen sensitivity of the skin, which worsens with increase in the frequency of skin dryness, is associated with atopic dermatitis during winter months.[19] There are conflicting data in the literature that deficiency or excess of vitamin D causes food allergies.[3] It has been depicted in the literature that births in winter and autumn are associated with insufficient synthesis of vitamin D, insufficient induction of specialised regulatory T cells (Tregs), and exacerbation of eczema, which can lead to food allergies by increasing allergen sensitivity in intestinal barrier.[20] However, in the present study, IgE-mediated food allergies occurred more frequently in patients born in summer or autumn. This could be because the earliest 3–6 months of birth, which is one of the most common periods for a food allergy to present, coincide with winter months in these patients. As a result, these patients could not receive sufficient sunlight during this critical period, and endogenous vitamin D production could decrease.

In a study conducted by Karpa et al., food allergies were found to occur more frequently in patients with perinatal antibiotic use.[14] Our knowledge of the importance of microbiota in the development of food allergies is increasing day by day. The deterioration of microbiota due to various reasons is called dysbiosis. One of the possible conditions that may cause dysbiosis is the use of antibiotics. It has been reported that use of antibiotics in the past is a risk factor for future food allergies and irritable bowel syndrome.[21] Another study reported that the frequency of food allergy diagnosis at the age of 3 years was significantly higher among children who had taken antibiotics during the first year of birth.[22] In this study, the use of antibiotics in neonates was higher in the IgE-mediated food allergy group than in the control group.

A study conducted in Italy reported that a high socioeconomic level increased the incidence of atopy.[23] A study conducted in Sweden found that food sensitivity decreases with increase in socioeconomic level.[24] A more recent study has demonstrated that the incidence of food allergy increases and minority groups and individuals with low socioeconomic status are disproportionately affected and

Table 5 Prenatal risk factors for food allergy.

	Patient n (%)	Control n (%)	*P*	OR
IgE-mediated				
Drugs used by the mother during pregnancy				
Analgesic/antipyretic	19 (18.8)	20 (12.6)	0.233	1.61 (0.80-3.21)
Antibiotic	14 (13.9)	9 (5.66)	**0.041**	**2.66 (1.11-6.69)**
Maternal infection during pregnancy	26 (25.7)	30 (18.9)	0.246	1.49 (0.81-2.71)
Type of maternal infection during pregnancy			0.507	
URTI	9 (8.9)	14 (8.8)		0.70 (0.22-2.18)
UTI	13 (12.8)	14 (8.8)		(-/-)
Other	4 (3.9)	2 (1.2)		2.05 (0.32-18.8)
Disease of mothers during pregnancy	18 (17.8)	16 (10.1)	0.105	1.93 (0.93-4.05)
Type of diseases of mothers during pregnancy			0.637	
Pre-eclampsia	4 (3.9)	6 (3.7)		0.36 (0.05-2.18)
Gestational diabetes	10 (9.9)	6 (3.7)		(-/-)
Other	5 (4.9)	4 (2.5)		0.71 (0.12-4.25)
Total	101 (100.0)	159 0.233		
Non-IgE-mediated				
Drugs used by mothers during pregnancy				
Analgesic/antipyretic	12 (22.2)	20 (12.6)	0.135	1.99 (0.87-4.38)
Antibiotic	8 (14.8)	9 (5.66)	**0.042**	**2.89 (1.01-8.09)**
Maternal infection during pregnancy	16 (59.6)	30 (18.9)	0.142	1.81 (0.88-3.66)
Type of maternal infection during pregnancy			0.701	
URTI	5 (9.2)	14 (8.8)		0.51 (0.13-1.88)
UTI	10 (18.5)	14 (8.8)		(-/-)
Other	1 (1.0)	2 (1.2)		0.75 (0.02-10.4)
Disease of mothers during pregnancy	10 (1.8)	16 (10.1)	0.162	2.03 (0.83-4.79)
Type of diseases of mothers during pregnancy			0.687	
Pre-eclampsia	2(3.7)	6 (3.7)		0.24 (0.01-2.38)
Gestational diabetes	6 (11.1)	6 (3.7)		(-/-)
Other	2 (3.7)	4 (2.5)		0.77 (0.09-5.78)
Total	54 (100.0)	159 0.233		

are more at risk of allergies because of the difficulty of having allergen-free foods.[25]

In the present study, a low socioeconomic level was found to be higher in both patient groups than in the control group. This factor appeared to play a protective role against food allergies. In IgE-mediated food allergy group, crowded living conditions, damp homes, and use of synthetic bedding were the risk factors. In non-IgE-mediated food allergy group, wool bedding was identified as a risk factor. These results could be due to their higher incidence in the patient groups than in the control group for other atopic diseases, especially respiratory and skin allergies.

It is recommended that infants must be exclusively fed with breast milk for the first 6 months, although Gustafsson et al. noted that the early discontinuation of breast feeding and early initiation of complementary feeding did not cause allergic manifestations.[26] Another study failed to provide information on whether antigenic structures in breast milk induce sensitisation or induce tolerance against food allergies.[27] Still another study showed that exclusive breast feeding during the first 6 months protects infants from proctocolitis and food allergies.[28]

However, in the present study, we found no significant association between the timing of initiation of breast feeding both supplementation and the development of food allergies in either the patient groups or the control group. Examining of diet before the onset of manifestations demonstrated that infants in the IgE-mediated patient group consumed less breast milk than the control group. Although protection through breast milk was delivered in the IgE-mediated patient group, the condition was not observed in the non-IgE-mediated patient group. Similarly, we observed that the consumption of foods in addition to breast milk triggered food allergies more frequently in the IgE-mediated patient group. Considering the use of infant formula, it was common in both patient groups.

It is well known that health of the gut plays an important role in the development of allergic diseases.[29] Although not enough evidence in the literature is found to make a definitive statement, previous studies have shown that probiotic supplementation accelerates tolerance in the patients of food allergies.[30] The pathogenesis of allergic proctocolitis is not fully known, but it is observed that non-IgE-mediated food allergies develop due to subacute

Table 6 Neonatal risk factors for food allergy.

	Patient n (%)	Control n (%)	*P*	OR
IgE-mediated				
Birth weight (g)	3190 (1750-5040)	3300 (2100-5030)	0.144	1.00 (1.00-1.00)
<2500 g	6 (5.94)	3 (1.89)		3.47 (0.67-22.2)
2500-4000 g	88 (87.1)	143 (89.9)		1.13 (0.44-3.16)
>4000 g	7 (6.93)	13 (8.18)		(-/-)
Birth season			**0.011**	
Spring	10 (9.9)	37 (23.3)		(-/-)
Summer	42 (41.6)	46 (28.9)		**3.32 (1.51-7.87)**
Fall	31 (30.7)	38 (23.9)		**2.97 (1.30-7.23)**
Winter	18 (17.8)	38 (23.9)		1.73 (0.71-4.42)
Type of birth, C/S	73 (72.3)	81 (50.9)	**0.001**	**2.50 (1.47-4.32)**
Hospitalization in ICU in the neonatal period	31 (30.7)	22 (13.8)	**0.002**	**2.74 (1.48-5.15)**
Antibiotic use in the neonatal period	21 (20.8)	15 (9.43)	**0.016**	**2.50 (1.22-5.24)**
Phototheraphy in the neonatal period	17 (16.8)	15 (9.43)	0.115	1.94 (0.91-4.14)
Total	101 (100.0)	159 (100.0)		
Non-IgE-mediated				
Birth weight (g)	3115 (2300-4600)	3300 (2100-5030)	**0.028**	1.00 (1.00-1.00)
<2500 g	5 (9.3)	3 (1.89)		9.15 (1.26-101)
2500-4000 g	47 (87.0)	143 (89.9)		2.01 (0.52-14.4)
>4000 g	2 (3.7)	13 (8.18)		(-/-)
Birth season			0.235	
Spring	11 (20.4)	37 (23.3)		(-/-)
Summer	22 (40.7)	46 (28.9)		1.59 (0.69-3.84)
Fall	14 (25.9)	38 (23.9)		1.23 (0.49-3.15)
Winter	7 (13.0)	38 (23.9)		0.63 (0.21-1.79)
Type of birth, C/S	35 (64.8)	81 (50.9)	0.107	1.76 (0.94-3.40)
Hospitalization in ICU in the neonatal period	11 (20.4)	22 (13.8)	0.353	1.60 (0.69-3.53)
Antibiotic use in the neonatal period	8 (14.8)	15 (9.43)	0.397	1.68 (0.63-4.16)
Phototheraphy in the neonatal period	7 (13.0)	15 (9.43)	0.633	1.44 (0.52-3.68)
Total	54 (100.0)	159 (100.0)		

or chronic intestinal inflammation and are generally present with localised manifestations in the intestine.[31] At the same time, fermented dairy products, such as yoghurt, have been reported to regulate homeostasis in the intestinal mucosa and protect the intestinal barrier.[32] However, in the present study, we found that the risk of a non-IgE-mediated food allergy increased with the decreasing frequency of maternal consumption of yoghurt.

A study concerning egg allergies noted that the presence of an older sibling decreased the risk of such allergies.[33] In the current study, most children with an IgE-mediated food allergy were first-born child in their family. The reason why most patients we observed happened to be the first-born child in the family might be because some mothers made changes in their diets and nutritional habits after the diagnosis of a food allergy.

Istanbul is one of the few metropolises in the world in terms of population density and industrialisation.[34] In recent years, it has been observed that change in climate is leading to rise in temperatures, especially in industrialised cities. In particular, increase in carbon dioxide, methane, and nitrous oxide gases play a major role in climate changes. Increased exposure to pollen products and aeroallergens exacerbates respiratory allergies, such as asthma and allergic rhinitis. Increased sensitivity to aeroallergens also increases the incidence of food allergies.[35] It has been reported that increased exposure to indoor and outdoor aeroallergens at an early age increases the incidence of food allergy. Furthermore, it has been suggested that the gut, skin, and respiratory tract may increase sensitivity to foods.[36]

In addition, according to the Köeppen-Geiger system of climate classification, Istanbul is described as having climate-smart agriculture (CSA) climate. This type of climate corresponds to typical Mediterranean climate, with warm summers and very cold winters.[37] In Istanbul, the lowest temperature throughout the year is ¤11°C, the highest temperature is +40°C, and the average relative humidity is 75%. Although all months of the year are humid in Istanbul, maximum humidity has been reported in December and January, with a rate of 80-85% (http://www.istanbul.gov.tr/istanbul-iklim. Accessed July 22, 2023). This high humidity also poses a risk for the emergence of food allergies and other allergic diseases.

For the control group, presence of atopic diseases other than food allergies and the use of atopy in the family

Table 7 Postnatal risk factors for food allergy.

	Patient n (%)	Control n (%)	*P*	OR
IgE-mediated				
Pet exposure	8 (7.9)	7 (4.40)	0.361	1.86 (0.64-5.57)
Low socioeconomic status	23 (22.8)	10 (6.29)	**0.001**	**0.23 (0.10-0.50)**
Crowded housing	30 (29.7)	20 (12.6)	**0.001**	**2.92 (1.55-5.59)**
Living in a damp house	29 (28.7)	15 (9.43)	**0.001**	**3.83 (1.95-7.80)**
Smoking exposure	32 (31.7)	22 (13.8)	**0.001**	**2.87 (1.56-5.38)**
Time to start breastfeeding			0.333	
0-4 h	78 (77.2)	136 (85.5)		(-/-)
4-12 h	15 (14.9)	18 (11.3)		1.45 (0.68-3.06)
12-24 h	4 (4.0)	2 (1.26)		3.35 (0.60-27.6)
1-3 days	3 (3.0)	2 (1.26)		2.54 (0.38-22.3)
After the 3rd day	1 (1.0)	1 (0.63)		1.74 (0.04-68.4)
Patient's number in his family, first	1 (1-4)	1 (1-4)	**0.001**	**1.93 (1.35-2.76)**
Time to complementary foods, month	6 (6-8)	6 (5-8)	0.514	0.77 (0.46-1.31)
Patients diet before manifestations, breast milk	40 (39.6)	99 (62.3)	**0.001**	**0.40 (0.24-0.66)**
Patients diet before manifestations, infant formula	3 (3.0)	2 (1.26)	0.380	2.34 (0.35-20.4)
Patients diet before manifestations, breast milk and infant formula	19 (18.8)	45 (28.3)	0.113	0.59 (0.32-1.07)
Patients diet before manifestations, breast milk and complementary foods	29 (28.7)	9 (5.66)	**0.001**	**6.59 (3.06-15.6)**
Patient's diet before manifestations, infant formula and complementary foods	0 (0.0)	1 (0.63)	1.000	(-/-)
Patient's diet before manifestations, breast milk, infant formula, and complementary foods	11 (10.9)	2 (1.26)	**0.001**	**8.98 (2.30-64.4)**
Using formula milk	41 (40.6)	37 (23.3)	**0.005**	**2.24 (1.31-3.88)**
Formula start time, day	1 (1-7)	2 (1-15)	0.237	0.86 (0.70-1.06)
Formula start time, month	2.5 (1-7)	2 (1-5)	0.384	1.32 (0.87-2.01)
Frequency of mother's diet with yogurt			**0.001**	
Every day	30 (29.7)	43 (27.0)		(-/-)
2-3 days a week	42 (41.6)	90 (56.6)		(-/-)
Once per week	18 (17.8)	19 (11.9)		(-/-)
For more than a week	11 (11.9)	7 (4.50)		2.22 (0.77-6.77)
Bed/quilt			**0.024**	
Wool	7 (6.9)	4 (2.52)		1.60 (0.52-4.71)
Fiber	47 (46.5)	9 (5.66)		1.34 (0.78-2.32)
Cotton	36 (35.6)	72 (45.3)		(-/-)
Synthetic	11 (10.9)	74 (46.5)		**5.45 (1.70-21.5)**
Total	101 (100.0)	159 (100.0)		
Non-IgE-mediated				
Pet exposure	4 (7.4)	7 (4.40)	0.476	1.76 (0.43-6.23)
Low socioeconomic status	14 (25.9)	10 (6.29)	**0.001**	**0.19 (0.08-0.47)**
Crowded housing	6 (11.1)	20 (12.6)	0.965	0.88 (0.30-2.23)
Living in a damp house	14 (25.9)	15 (9.43)	**0.005**	**3.34 (1.47-7.58)**
Smoking exposure	16 (29.6)	22 (13.8)	**0.016**	**2.61 (1.23-5.48)**
Time to start breastfeeding			0.426	
0-4 h	48 (88.9)	136 (85.5)		(-/-)
4-12 h	3 (5.6)	18 (11.3)		(-/-)
12-24 h	2 (3.7)	2 (1.26)		(-/-)
1-3 days	1 (1.9)	2 (1.26)		(-/-)
After the 3rd day	0 (0.0)	1 (0.63)		(-/-)
Patient's number in his family, first	1 (1-4)	1 (1-4)	0.263	1.22 (1.94-0.77)
Time to complementary foods, month	6 (5-8)	6 (5-8)	0.538	0.63 (1.38-0.29)
Patient's diet before manifestations, breast milk	30 (55.6)	99 (62.3)	0.477	0.76 (0.40-1.43)
Patient's diet before manifestations, infant formula	1 (1.85)	2 (1.26)	1.000	1.57 (0.05-19.8)
Patient's diet before manifestations, breast milk and infant formula	19 (35.2)	45 (28.3)	0.435	1.38 (0.70-2.65)

(continues)

Table 7 Continued.

	Patient n (%)	Control n (%)	*P*	OR
Patient's diet before manifestations, breast milk and complementary foods	3 (5.6)	9 (5.66)	1.000	1.01 (0.21-3.62)
Patient's diet before manifestations, infant formula and complementary foods	0 (0.0)	1 (0.63)	1.000	(-/-)
Patient's diet before manifestations, breast milk, infant formula, and complementary foods	1 (1.9)	2 (1.26)	1.000	1.57 (0.05-19.8)
Using formula milk	25 (46.3)	37 (23.3)	**0.002**	**2.83 (1.47-5.45)**
Formula start time, day	1 (1-15)	2 (1-15)	0.311	0.97 (1.13-0.84)
Formula start time, month	3 (1-6)	2 (1-5)	0.220	1.55 (2.66-0.91)
Frequency of mother's diet with yogurt			**0.001**	
Every day	14 (25.9)	43 (27.0)		(-/-)
2-3 days a week	22 (40.7)	90 (56.6)		(-/-)
Once per week	6 (11.1)	19 (11.9)		(-/-)
For more than a week	12 (23.3)	7 (4.50)		**5.09 (1.70-16.5)**
Bed/quilt			**0.018**	
Wool	10 (18.5)	4 (2.52)		**3.52 (1.26-10.1)**
Fiber	18 (33.3)	9 (5.66)		0.81 (0.40-1.62)
Cotton	23 (42.6)	72 (45.3)		(-/-)
Synthetic	3 (5.6)	74 (46.5)		2.41 (0.42-12.4)
Total	54 (100.0)	159 (100.0		

as exclusion criteria appeared to be limiting aspects of our study. It is well known that allergic diseases are usually multimorbid conditions that coexist;[38] therefore, these exclusion criteria were applied so that risk factors related to allergic diseases other than food allergies could not influence the study's results.

Conclusion

Although some prior studies have addressed risk factors for food allergies in childhood, this study is the first, to our knowledge, to examine the prenatal, neonatal, and postnatal risk factors that are important for both mother and child.

Conflict of Interest

The authors declare no potential conflict of interest with respect to research, authorship, and/or publication of this study.

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