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Food allergy as an asthma comorbidity in children and adolescents: a practical approach through a real-world study

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Abstract
Introduction: Several studies have shown interactions between food allergy (FA) and asthma, but the influence of FA in asthma traits has been scarcely studied.
Methods: A real-world retrospective observational study was conducted among patients between 3 and 18 years old referred to our Asthma Clinic from November 2014 to November 2017. Data were obtained from daily clinical practice. Only patients properly diagnosed with asthma and FA were included.
Results: 815 patients were included: 483 asthmatics and 332 non-asthmatics and 180 FA and 635 no FA. Food allergy was statistically more prevalent among asthma patients (p = 0.014). In a high pollen exposure area, Madrid, among subjects with asthma (121 FA, 362 no-FA), sensitization to lipid transfer protein (LTP) (p = 0.016, OR: 3.064, RR: 2.512) and pollen (p = 0.016, OR: 3.064, RR: 2.512) are risk factors to have a concomitant FA diagnosis, whereas sensitization to profilin is not. Peripheral blood eosinophils were higher in subjects with asthma and FA (≥450 eos/μL) than in asthmatics without FA (≤300 eos/μL) (p = 0.031). Blood eosinophilia, using a cut-off >300 eos/μL, was only present in the FA group. Therefore, this trait should be considered when phenotyping a patient as eosinophilic asthma. Sex had an impact on several variables: height, weight, BMI, blood eosinophils count, sensitization profile, and early-onset asthma.
Conclusions: Asthma and FA are closely related and the presence of FA should be investigated in every asthma patient. This study shows an association between asthma with concomitant FA and sensitization to pollen and LTP, blood eosinophilia, and growth alterations. Differences between boys and girls were also described, so a sex-specific approach is recommended.

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Introduction

Asthma and food allergy (FA) are two common conditions and their prevalence is steadily increasing.[1,2] Backman et al.[3] reported in a Swedish cohort that the prevalence of allergic asthma progressively increased from 1996 until 2016, whereas the prevalence of non-allergic asthma remained stable during that period. Allergic asthma accounted for 67% of the total of asthma cases in the year 2016.[3]

The relationship between FA and asthma has been assessed from different perspectives. Alduraywish et al.[4] studied two different cohorts and they found that FA in the first 2 years of age increased the risk for subsequent rhinitis and asthma, with or without aeroallergen sensitization. Another study showed that patients with asthma and concomitant FA have a higher risk of severe asthma exacerbations.[5] Additionally, Bock et al.[6] reported that patients with concomitant asthma and FA have an increased risk for anaphylactic reactions, especially if asthma is not properly controlled.

Asthma guidelines[1] describe several comorbidities that can influence asthma diagnostic and phenotyping algorithms. For instance, obesity can be related to asthma, either as a comorbidity or with a causal relationship.[7] Although FA is related to asthma incidence and evolution,[4,5] its effects on asthma characteristics have not been sufficiently evaluated.

The frequency of self-diagnosed FA is always higher than the doctor-diagnosed FA.[8–10] McBride et al.[11] conducted the Europrevall food allergy birth cohort study and found a wide range of self-reported FA among nine European countries. This self-reported FA prevalence varied from 30% in Germany to 5–8% in Spain, Greece, Poland, and Lithuania. Another Europrevall-based study analyzed food sensitization by analyzing sera [Immunoglobin E (IgE) against 24 foods] from the second phase of the European Community Respiratory Health Survey. The results once again showed great variability among countries, with a range that went from 24.6% in Portland (USA) to 7.7% in Reykjavik (Iceland).[12] A Europrevall study which looked into the difference between parents' FA diagnosis and a double-blind placebo-controlled food challenge established that this gap is even bigger than with a specific-IgE based diagnosis.[13] This multicentric European study observed a decrease from 16.2% of food consumption adverse reactions reported by parents to 1.4–3.8% diagnosed by the double-blind placebo-controlled food challenge. This technique entails risks, the prevalence is therefore a range because not every patient was eligible to undergo this test and others refused to participate in an oral food challenge.[13] Alergológica 2015, a Spanish nationwide study, performed by selected allergists from the Spanish Allergy Society filling in electronic case reports, diagnosed FA with skin prick tests (SPT), specific IgE and oral challenges in selected patients (approximately a quarter of the total).[14] This study showed that 20% of children had FA, which was the third most important allergic condition, after rhinitis and asthma,[14] while it was the fifth allergic condition in adults, with a 10.4% prevalence.[15]

There are several cross-reactivity syndromes between aeroallergens and food allergens,[16] such as protein family 10 (PR-10),[17] lipid transfer protein (LTP),[18] profilin,[19] tropomyosin,[20] etc., that can explain a direct link between FA and asthma. However, it is unknown whether these syndromes affect asthma features.

The aim of our study is to evaluate the effects of FA in asthma diagnosis and traits. We also aimed to identify specific food allergens that may influence these endpoints. Finally, the relationship between different aeroallergens, asthma, and FA will also be studied.

Methods

Subjects

We included all patients from 3 to 18 years of age with a good quality spirometric maneuver who attended the Asthma Clinic at the Allergy Department, Hospital General de Villalba (Madrid, Spain), over a 3-year period (November 2014–November 2017). The demographic data of the study patients are shown in Table 1. All the included patients were referred to our clinic by their general practitioners or other specialists for asthma evaluation, regardless of their FA history.

All patients' charts were examined and only those with clear information on asthma and FA diagnosis were included. No other inclusion criteria were considered. Patients who were not capable of producing a good quality spirometric maneuver were excluded from the study. All the included histories were analyzed, and the collected data were introduced into a database. This study was approved by the hospital's ethics committee.

Food allergy

Food allergy diagnosis required an unequivocal allergic reaction upon the ingestion of the incriminating food and demonstration of IgE-mediated sensitization. Sensitization was confirmed by a positive SPT, positive prick-by-prick test, and/or specific IgE measurements with the suspicious food. If the patient had a convincing allergic history with positive sensitization to a clearly identified food, an oral challenge was not performed according to our daily practice protocol. When more than one food was involved, the reaction was unclear, or the test results were not robust; in such case an oral open food challenge was performed to confirm FA diagnosis.

The SPT used was a panel of commercially available allergens, including peach Pru p 3 (LTP) and palm tree Pho d 2 (profilin) (from different suppliers). Fresh foods were used for prick-by-prick tests. Specific IgE assays were performed by ImmunoCAP® (ThermoFisher-Phadia, Uppsala, Sweden) using commercially available extracts. SPT and prick-by-prick tests were considered positive if the wheal's orthogonal diameters were larger than 3x3. Specific IgE measured by ImmunoCAP® was considered positive if values were over 0.35 kU/L.

Hospital approved written informed consent was obtained for all open food challenges. Patients underwent these challenges in the day hospital clinic.

Asthma

All medical charts were carefully reviewed for proper asthma diagnosis. Patients were diagnosed with asthma

Table 1 Patients with asthma.

	Food allergic	No-food allergic	Food allergic vs no-food allergic	ANCOVA (age as covariate)	Odds Ratio	Relative Risk
Sample size	121	362	-	-	-	-
Female	57 (47%)	151 (42%)	0.299	-	1.245	1.178
Male	64 (53%)	211 (58%)	0.299	-	1.245	0.946
Age (Years)	11.39 ± 3.68	11.54 ± 3.68	0.698	-	-	-
Weight (kg)	44.53 ± 17.01	46.72 ± 18.43	0.248	0.141	-	-
Height (cm)	147.4 ± 18.29	149.87 ± 18.43	0.202	**0.026***	-	-
BMI	19.68 ± 4.21	19.94 ± 4.15	0.555	0.653	-	-
Rhinitis	118 (98%)	340 (94%)	0.156	-	2.545	2.147
Asthma diagnosis before 12 years old	110 (91%)	306 (85%)	0.890	-	1.797	1.587
Allergic asthma	103 (85%)	300 (83%)	0.603	-	1.164	1.122
Persistent asthma	17 (14%)	52 (14%)	0.923	-	0.971	0.978
FEV1 (L)	2.41 ± 0.91	2.51 ± 0.95	0.324	0.205	-	-
FEV1 (%)	99.74 ± 13.55	99.22 ± 15.19	0.737	0.747	-	-
FVC (L)	2.87 ± 1.12	3.01 ± 1.15	0.250	0.117	-	-
FVC (%)	100.60 ± 12.96	100.85 ±	0.854	0.843	-	-
FEV1/ FVC	84.60 ± 6.42	83.57 ± 7.82	0.188	*0.194*	-	-
FEF25-75 (L/s)	2.53 ± 1.03	2.64 ± 1.13	0.361	*0.355*	-	-
FEF 25-75 (%)	83.99 ± 21.27	84.89 ± 24.19	0.717	0.738	-	-
Pollen sensitization	116 (96%)	318 (88%)	**0.016***	-	**3.064**	**2.512**
Dander sensitization	70 (58%)	184 (51%)	0.199	-	1.313	1.227
Mold sensitization	34 (28%)	79 (22%)	0.167	-	1.390	1.273
Mite sensitization	33 (27%)	57 (16%)	**0.005****	-	**1.993**	**1.629**
Profilin sensitization	21 (17%)	47 (13%)	0.240	-	1.399	1.275
LTP sensitization	21 (17%)	15 (4%)	**<0.001*****	-	**4.830**	**2.596**
FeNO (ppb)	30.8 (29.24)	29.9 (36.56)	0.635	0.708	-	-
Eosinophil (eos/μL)	450 (400)	300 (300)	0.052	**0.031***	-	-
Total IgE (kU/L)	535 (973)	379 (691)	0.118	0.541	-	-

Data are presented as n (%), mean ± standard deviation, and median (interquartile range).
ANCOVA: negative for the Levene test.
BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF25-75: forced expiratory flow between 25 and 75% of the spirometry; LTP: lipid transfer protein; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; Vol: Volume; %: Percentage.
*p < 0.05, **p < 0.01, ***p < 0.001.
NS: not significant.

if they had compatible symptoms and a positive bronchodilation test, or if they showed a positive clinical response to bronchodilator and/or controller asthma treatment.[1] For the purposes of the study, however, only the first clinical visit of every patient was recorded and evaluated. Eighty-six percent of the patients presented non-persistent asthma (Table 1), and 140 (17%) were symptomatic. One hundred patients (12%) were on corticosteroid treatment at the first visit when the spirometry was performed and the clinical information obtained. Asthma was treated according to current asthma management guidelines.[1]

Allergological work-up in patients evaluated for asthma included SPT and/or specific IgE measurements by ImmunoCAP® to common aeroallergens (pollen, dust mites, molds, animals, LTP, and profilin) following the same standards as that of FA diagnosis.

Database

Included patients were referred to our Allergy department for asthma evaluation between November 2014 (when the hospital opened) and November 2017.

This study is observational and retrospective, thus all tests and diagnoses were based on daily practice hospital's protocols. The information was retrieved from the visits registered in the electronic patients' charts. Only good quality histories, where asthma and FA allergy diagnosis were robustly supported or rejected, were included. Medical histories that could be misinterpreted or did not have the necessary information were excluded, deleting the patient from the database. Atopy was defined in this database as having any allergic sensitization or allergic disease. Atopy was defined as having any allergic sensitization to common inhalant or food allergens.

Data analysis

Descriptive statistics were performed with all collected variables included in the database. Patients were classified as asthmatic or non-asthmatic, as well as FA or no-FA. Discrete variables were described with its frequency and percentage, whereas continuous variables were defined as parametric or non-parametric. Variables with a normal distribution were described with their mean ± standard deviation and non-parametric variables with their median and interquartile range. Since the sample size was over 800 patients, Kolmogorov–Smirnov and Shapiro–Wilk tests were too sensitive and consequently unable to establish the normality of a variable. Therefore, gaussian distribution was analyzed by comparing the variable's histogram and the normal curve. Finally, asthmatics and non-asthmatics were compared in each category to evaluate if any statistically significant difference existed. The same procedure was applied for FA and no-FA.

To analyze the effects of FA in asthma, all asthmatic patients were divided into two groups, according to FA presence or absence and then compared. Student t-tests were used for continuous gaussian variables. Mann-Whitney U-test was used to compare continuous non-parametric variables.

Sex and age are important confounders both in FA[14,21] and asthma.[22,23] Nevertheless, to verify this possibility in our database several linear models were designed to examine the effect of our predictors on the dependent variables. Comparing the effect of all the predictors on the other predictors' linear regression coefficients confirmed that age and sex were the two confounding variables present in our database. Therefore, normalization for these confounders was necessary.

Stratification by age could have led to a big loss of information, therefore, this normalization was obtained by applying an ANCOVA test with age as a covariant for every continuous variable. For this matter, we ensured that all residual distributions were normal and checked variance equality with the Levene test. The literature suggests that both FA[21] and asthma[22,23] have different traits in boys and girls when studied separately. Consequently, normalization for sex was obtained through stratification into boys and girls. Therefore, to obtain a better understanding of these interactions, samples were studied with and without sex stratification and both analyses were normalized by age. Thereby, a sex-specific approach for this relationship could be analyzed.

Discrete variables were compared using the Chi-square test when large sample sizes were present. Whenever a sample size was under five, Fisher's exact test was selected. Since discrete variables were dichotomous and two variables were used in every comparison, Odds Ratio (OR) and Relative Risk (RR) were also calculated. Whenever OR or RR 95% confidence interval contained 1 these values were stated as not significant. Categorical variables were not normalized by age, since no cut-off points have been established for these two diseases. Thus, no stratification could be scientifically determined, and stratification would have led to an unnecessary power loss in the statistic tests. Sex was also normalized by stratification in boys and girls, obtaining a sex-specific approach, with individual tables for boys and girls.

Finally, in order to analyze the influence of different food allergies in asthma, the aforementioned comparisons were repeated among asthmatics with FA for every different food group allergy registered (milk, egg, nut and peanut, seafood, fruit, fish, and legumes). No normalization method was applied to this study due to the insufficient sample sizes to properly carry out these techniques.

IBM® SPSS® statistics 25 was the software used for the data analysis.

Results

General population

A total of 815 patients were included in the study, of whom 483 were diagnosed with asthma and 180 with FA.

Among FA patients there were 121 (67%) asthmatics and 59 (57%) non-asthmatics, while in the no-FA group we found 362 (57%) asthmatics and 121 (25%) non-asthmatics. This comparison showed a statistically significant difference ($p = 0.014$) and a directly proportional risk increase, OR 1.547. Relative Risk was also analyzed, determining that an asthmatic is 1.410 more likely to have concomitant FA and for a FA patient it is 1.179 times more probable to be asthmatic.

Atopy was also more frequent in subjects with asthma (95%) than in non- asthmatics (77%) ($p < 0.001$), and in FA (100%) than no-FA subjects (84%) ($p < 0.001$). Subjects with asthma were more likely to be atopic than subjects without asthma (RR: 2.797 and OR: 6.039) and all aeroallergen groups were more prevalent among asthma and FA patients.

The study biomarkers, total IgE, fractional exhaled nitric oxide (FeNO), and blood eosinophils, were significantly elevated both in asthma and FA. Subjects with asthma also showed a higher prevalence of rhinitis and lower spirometric values than non-asthmatics.

Asthma subjects

Among 483 subjects with asthma, 121 had FA and 362 were no-FA (Table 1). Statistically significant differences were found in the frequency of aeroallergen sensitization between both groups. Pollen sensitization was found in 96% of FA and 88% of no-FA patients ($p = 0.016$, OR: 3.064, RR: 2.512). Mite sensitization was found in 27% of asthmatics with FA and in 16% of asthmatics without FA ($p = 0.005$).

Sensitization to LTP was present in 17% of FA asthmatics and 4% of no-FA asthmatic patients ($p < 0.001$, OR: 4.830, RR: 2.596) (Figure 1), whereas sensitization to profilin was observed in 17% of asthmatic FA patients and 13% of asthmatic no-FA subjects ($p = 0.240$).

ANCOVA test was performed with age as a covariate, and two new statistically significant differences appeared, height and peripheral blood eosinophil count (Table 1). Height could not be fully evaluated at this moment, since it is very gender-dependent.

We also observed that asthmatic subjects with FA had a higher median blood eosinophil count (450 eos/μL) than no-FA (300 eos/μL). Peripheral blood eosinophil count almost reached statistical significance in the first analysis ($p = 0.052$), and when this variable was normalized by age it became significant ($p = 0.031$).

Stratification by sex

In the asthma population, there were 208 girls and 275 boys. Raw statistical results were obtained from both groups, and data were also normalized by age. Asthmatic girls (Table 2) and boys (Table 3) were divided into FA (57 girls, 64 boys) and no-FA (151 girls, 211 boys) groups. Results were consistent with pre-stratified analysis, but some differences were found.

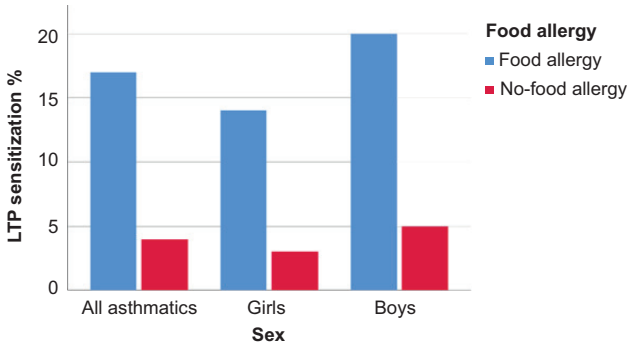

Figure 1 LTP sensitization analysis.

No-FA asthmatic girls (151.18 cm) were taller than FA asthmatic girls (145.86 cm) with raw data (p = 0.027), and after being normalized by age (p = 0.0497). Weight and BMI did not show statistically significant differences in this group. On the contrary, boys did not show any statistically significant difference among these biometric parameters when raw data were analyzed. Conversely, when studying boys and treating age as a covariant, we could observe a statistically significant difference in weight (p = 0.012), whereas no-FA asthmatics had a higher weight than FA asthmatic patients. Height and BMI did not show a significant difference but were close to significance (p = 0.072 and p = 0.060, respectively).

Another difference between sexes was that FA asthmatic girls (91%) tended to develop asthma at the earlier onset, prior to 12 years old than asthmatic no-FA

Table 2 Girls with asthma.

	Food allergic	No-food allergic	Food allergic vs no-food allergic	ANCOVA (age as covariate)	Odds Ratio	Relative Risk
Sample size	57	151	-	-	-	-
Age (Years)	11.39 ± 3.85	12.20 ± 3.44	0.143	-	-	-
Weight (kg)	45.25 ± 17.18	47.51 ± 16.26	0.380	0.626	-	-
Height (cm)	145.86 ± 16.24	151.18 ± 15.07	**0.027***	**0.050***	-	-
BMI	20.39 ± 4.54	20.17 ± 4.19	0.743	0.157	-	-
Rhinitis	56 (98%)	143 (95%)	0.449	-	3.133	2.533
Asthma diagnosis before 12 years old	52 (91%)	118 (79%)	**0.035***	-	**2.820**	2.264
Allergic asthma	50 (88%)	118 (79%)	0.137	-	1.937	1.658
Persistent asthma	6 (11%)	19 (13%)	0.673	-	0.811	0.856
FEV1 (L)	2.30 ± 0.81	2.49 ± 0.74	0.114	0.525	-	-
FEV1 (%)	100.33 ± 14.33	100.15 ±	0.934	0.842	-	-
FVC (L)	2.71 ± 0.98	2.91 ± 0.84	0.150	0.713	-	-
FVC (%)	101.96 ± 13.59	101.70 ±	0.891	0.872	-	-
FEV1/ FVC	85.42 ± 6.17	85.14 ± 7.28	0.796	0.811	-	-
FEF25-75 (L/s)	2.43 ± 0.92	2.74 ± 1.01	**0.039***	*0.148*	-	-
FEF 25-75 (%)	82.28 ± 22.76	87.32 ± 23.32	0.163	0.201	-	-
Pollen sensitization	55 (97%)	130 (87%)	**0.44***	-	4.231	3.270
Dander sensitization	32 (56%)	80 (53%)	0.717	-	1.120	1.086
Mold sensitization	13 (23%)	28 (19%)	0.504	-	1.287	1.196
Mite sensitization	15 (26%)	25 (17%)	0.116	-	1.786	1.491
Profilin sensitization	6 (11%)	19 (13%)	0.673	-	0.811	0.856
LTP sensitization	8 (14%)	5 (3%)	**0.005****	-	**4.735**	**2.436**
FeNO (ppb)	26.95 (29.33)	28.9 (34.9)	0.669	0.405	-	-
Eosinophil (eos/µL)	400 (400)	300 (300)	0.200	0.311	-	-
Total IgE (kU/L)	532 (874.5)	339.5 (366.25)	0.316	0.871	-	-

Data are presented as n (%), mean ± standard deviation, and median (interquartile range).
ANCOVA: Negative for the Levene test.
BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF25-75: forced expiratory flow between 25 and 75% of the spirometry; LTP: lipid transfer protein; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; Vol: Volume; %: Percentage.
*p<0.05, **p<0.01.
NS: not significant.

Table 3 Boys with asthma.

	Food allergic	No-food allergic	Food allergic vs no-food allergic	ANCOVA (age as covariate)	Odds Ratio	Relative Risk
Sample size	64	211	-	-	-	-
Age (Years)	11.39 ± 3.56	11.07 ± 3.78	0.543	-	-	-
Weight (kg)	43.88 ± 16.97	46.16 ± 19.85	0.408	**0.012***	-	-
Height (cm)	148.77 ±19.97	148.93 ± 20.49	0.955	0.072	-	-
BMI	19.05 ± 3.82	19.77 ± 4.16	0.211	0.060	-	-
Rhinitis	62 (97%)	197 (93%)	0.293	-	2.203	1.915
Asthma diagnosis before 12 years old	58 (91%)	188 (89%)	0.728	-	1.183	1.140
Allergic asthma	53 (83%)	182 (86%)	0.494	-	0.768	0.820
Persistent asthma	11 (17.2%)	33 (15.6%)	0.767	-	1.119	1.090
FEV1 (L)	2.51 ± 0.99	2.52 ± 1.07	0.930	0.169	-	-
FEV1 (%)	99.2 ± 12.90	98.55 ± 15.97	0.764	0.707	-	-
FVC (L)	3.01 ± 1.23	3.08 ± 1.33	0.714	**0.038***	-	-
FVC (%)	99.38 ± 12.36	100.24 ± 13.28	0.645	0.681	-	-
FEV1/ FVC	83.88 ± 6.60	82.44 ± 8.01	0.193	0.173	-	-
FEF25-75 (L/s)	2.63 ± 1.21	3.40 ± 12.07	0.613	0.592	-	-
FEF 25-75 (%)	85.52 ± 19.91	83.15 ± 24.70	0.484	0.505	-	-
Pollen sensitization	61 (95%)	188 (90%)	0.159	-	2.379	2.041
Dander sensitization	38 (59.4%)	104 (49.5%)	0.167	-	1.490	1.359
Mold sensitization	21 (32.8%)	51 (24.3%)	0.175	-	1.523	1.370
Mite sensitization	18 (28%)	32 (15%)	**0.019***	-	**2.177**	**1.753**
Profilin sensitization	15 (23%)	28 (13%)	0.052	-	1.990	**1.645**
LTP Sensitization	13 (20%)	10 (5%)	**<0.001*****	-	**2.115**	**1.802**
FeNO (ppb)	38.65 (31.53)	30.8 (39.4)	0.262	0.741	-	-
Eosinophil (eos/μL)	500 (400)	400 (400)	0.096	**0.032***	-	-
Total IgE (kU/L)	542 (1544.5)	415 (858)	0.131	0.276	-	-

Data are presented as n (%), mean ± standard deviation, and median (interquartile range).
BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEF25-75: forced expiratory flow between 25 and 75% of the spirometry; LTP: lipid transfer protein; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; Vol: Volume; %: Percentage.
*p<0.05, ***p<0.001.
NS: not significant.

(79%) (p = 0.035, OR: 2.820), while boys did not show this difference.

Once more, we observed the statistically significant difference in mite sensitization and pollen sensitization, as in non-sex-stratified data. LTP and profilin also had similar behavior as in the previous analysis (Figure 1). Eosinophils were another difference between sexes. No difference was found among girls, but boys-once normalized by age-showed higher blood eosinophil counts when FA was present (500 eos/μL) than with its absence (400 eos/μL) (p = 0.032) (Figure 2).

Food allergy groups

When we analyzed all asthmatic FA patients (121) depending on if they were allergic to the most prevalent food groups in our region (Table 4), we observed that sample sizes were small: milk (4), egg (10), nut and peanut (48), seafood (17), fruit (74), fish (11), and legumes (6).

A statistically significant decrease in weight (p = 0.03) was observed among fruit allergic patients. Differences in height (0.054) and BMI (p = 0.027) were not statistically significant but were close to reaching significance. Moreover, fruit allergic patients had a decreased FEV1 value (p = 0.030) and percentage (p = 0.003). These patients were also more commonly sensitized to profilin (p = 0.002, OR: 7.773, RR: 1.645).

Finally, seafood allergic patients were more commonly sensitized to mites (p = 0.010, OR: 3.750, RR: 3.000) and less commonly associated with early-onset asthma (p = 0.026, OR: 0.235, RR: 0.325). Only 52% of seafood allergic patients were sensitized to dust mites and 10% of house dust-mite sensitized patients were allergic to seafood. Nine percent of these dust-mite sensitized patients were monosensitized to dust mites (91% were also sensitized to other aeroallergens).

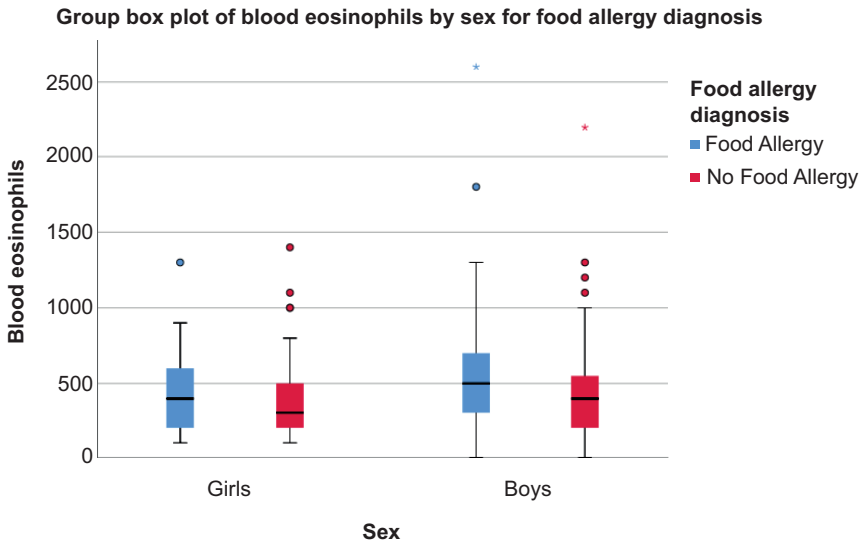

Figure 2 Blood eosinophils in asthmatic patients.

Discussion

Our study confirms that asthma and FA are a mutual risk factor, indicating that both conditions are intimately connected.

This study population has some specific characteristics that should be considered when analyzing the gathered data. Studied patients were sent to an Allergy clinic in Madrid and underwent an evaluation for asthma diagnosis. Hence, all studied patients had reported at least one episode of shortness of breath, wheezing, or a cough that suggested asthma, including those subjects in whom asthma was not confirmed. In addition, allergy was investigated in all cases as a cause or comorbidity of asthma. Thus, all these patients had symptoms consistent with asthma that were potentially related to allergen exposure. This could be the explanation for the increased allergic asthma prevalence in our study among the total of asthmatic patients (84%) compared to the 67% reported in 2016 among asthmatic patients in a Swedish Cohort.[3] Non-asthmatic patients also had at least one episode suggestive of asthma or bronchospasm. Moreover, Madrid is a high pollen area, and FA is common among patients with respiratory allergy. Lipid transfer protein[13,24] and profilin[13,25] have been reported as the main panallergens causing sensitization in this area.

Finally, a high proportion of asthma was due to pollen allergy,[14] which means that an important number of patients were only exposed to their main asthma trigger during the pollen season, remaining asymptomatic for the rest of the year. Thus, most patients included in our study were evaluated whilst asymptomatic. FA and asthma are mutual risk factors and atopy is more common among both conditions. This higher prevalence of atopy among asthma and FA patients appears to be related to the higher rate of sensitizations in these groups.

Lipid transfer protein and profilin are very prevalent allergens in the area,[13,24,25] and they are considered as panallergens responsible for cross-reactivity syndromes between aeroallergens and food allergens.[18,19] Surprisingly, when sensitization to these two panallergens was analyzed, only sensitization to LTP had a statistically significant difference among asthma subjects with or without FA (Figure 1). These results show that LTP sensitization is more common among asthma patients with FA than those without FA, whereas this association was not found for profilin sensitization. Our findings suggest that FA should be investigated in every patient with asthma sensitized to LTP because it is a risk factor for their concomitant existence. However, when focusing on profilin we observed that it is a risk factor for FA patients to have a concomitant asthma diagnosis, but not the other way around. Thus, it means that its sensitization is not a risk factor for asthmatics to have concomitant FA.

Despite the fact that the level of exposure to mites in Madrid is very low, a significant association was found between sensitization to dust mites and asthma, with and without FA. Seafood allergy rates were very low among those dust-mite sensitized and only half of those allergic to seafood were also sensitized to mites, showing that this effect cannot be attributed to tropomyosin.[20] A very small proportion of mite-sensitized patients were monosensitized to mites, whereas 91% were sensitized to more than one aeroallergen group, pointing out that mite sensitization could be a marker of high atopic patients and consequently FA is increased in this patient group.

It is accepted that FA can affect childhood and adolescent growth, with stunting being the most common effect.[26] This condition is described during elimination diets, but also at the time of diagnosis, irrespective of whether they are under a dietician's control or if their nutritional requirements were fulfilled.[26] Asthmatic persons' growth is always a concern in this population, especially due to its treatment, corticosteroids.[27] Growth affectation by these two diseases combined has been scarcely evaluated. It is particularly interesting that this effect seems to be sex-dependent, being more important in boys. This may be congruent with the different sex-hormone-dependent development that sexes describe during this period, but it has been rarely explored.[21,28]

Table 4 Allergy to different food groups in asthmatic and food allergic patients.

Food group	Studied variable	Food allergic	No-food allergic	Food allergic vs no-food allergic	Odds Ratio	Relative Risk
Fruit allergy		74	47			
	Weight	47.11 ± 15.88	40.46 ± 18.08	**0.035***	-	-
	Height	149.95 ± 16.70	143.38 ± 20.07	0.054	-	-
	BMI	20.35 ± 4.24	18.61 ± 3.98	**0.027***	-	-
	FEV1 (L)	2.55 ± 0.84	2.18 ± 0.98	**0.030***	-	-
	FEV1 (%)	120.64 ± 11.97	95.17 ± 14.71	**0.003****	-	-
	Profilin sensitization	19 (26%)	2 (4%)	**0.002****	**7.773**	**1.645**
	Fish allergy	3 (4%)	8 (17%)	**(-) 0.016***	**0.206**	0.423
	Milk allergy	0 (0%)	4 (9%)	**(-) 0.011***	-	-
	Egg allergy	2 (3%)	8 (17%)	**(-) 0.005****	**0.135**	0.308
	Nut and peanut allergy	20 (27%)	28 (60%)	**(-) <0.001*****	**0.251**	**0.563**
Nut and peanut allergy		48	73			
	Profilin sensitization	4 (8%)	17 (23%)	**(-) 0.034***	**0.299**	0.433
	Fruit allergy	20 (42%)	54 (74%)	**(-) <0.001*****	**0.251**	**0.454**
	Legumes allergy	5 (10%)	1 (1%)	**0.025***	8.372	**2.229**
Egg allergy		10	111			
	Milk allergy	2 (20%)	2 (2%)	**0.002****	**13.625**	**7.31**
	Fruit allergy	2 (20%)	72 (65%)	**(-) 0.005****	**0.135**	**0.159**
Milk allergy		4	117			
	Egg allergy	2 (50%	8 (7%)	**0.002****	**13.625**	**11.100**
	Fruit allergy	0 (0%)	74 (63%)	**(-) 0.011****	-	-
Legumes allergy		6	115			
	LTP allergy	4 (67%)	17 (15%)	**0.001****	**11.529**	**9.524**
	Nuts and peanut allergy	5 (83%	43 (37%)	**0.025***	8.372	7.604
Seafood allergy		17	104			
	Asthma diagnosis before 12 years old	13 (77%)	97 (93%)	**(-) 0.026***	**0.235**	**0.325**
	Mite sensitization	9 (53%)	24 (23%)	**0.010***	**3.750**	**3.000**
	Fish allergy	8 (47%)	3 (3%)	**<0.001*****	**29.926**	**8.889**
	Legumes allergy	3 (17%)	3 (3%)	**0.009****	**7.214**	**4.107**
Fish allergy		11	110			
	Seafood allergy	8 (73%)	9 (8%)	**<0.001*****	**29.926**	**16.314**
	Fruit allergy	3 (27%)	71 (65%)	**(-) 0.016***	**0.206**	**0.238**

Data are presented as n (%), mean ± standard deviation, and median (interquartile range).
BMI: Body mass index; FEV1: forced expiratory volume in one second; LTP: lipid transfer protein; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; %: Percentage; (-): Protective factor.
*p<0.05, **p<0.01, ***p<0.001.
NS: not significant.

Lung function may also be affected by FA, particularly early age sensitization to food allergens, leading to spirometry alterations.[29] Nevertheless, no significant differences were found in this study among FEV1, FVC, FEV1/FVC, and FEF25-75 in total volumes nor percentages.

Notwithstanding, girls with asthma and FA have a higher rate of early-onset asthma. Boys showed no difference. This might be important for future asthma traits, since it is described that obesity affects asthma diversely in early- or late-onset asthma, with 12 years of age being considered as the cut-off point for early- and late-onset asthma.[30]

Asthma is commonly classified according to its inflammatory profile into eosinophilic and non-eosinophilic variants, having different clinical features and therapeutic implications.[31,32] Longo et al.[33] studied the association between asthma and FA and the differences in peripheral blood eosinophil count, observing a higher eosinophil count in patients with asthma and concomitant FA. Eosinophilic esophagitis or gastroenteritis has also been related to FA, and dietary restriction is a common therapeutic approach in these disorders.[34,35] Other biomarkers such as total IgE[36] or FeNO[37,38] can also be modified or influenced by FA.

Despite these studies, the influence that FA has on these biomarkers among asthmatics has been scarcely studied.

No differences existed in FeNO and total IgE in our study. On the contrary, peripheral blood eosinophils were not statistically significantly different with raw data but became significant when normalized by age in every no-sex-stratified analysis. Once again, sex differences were identified. Girls did not show this significant difference, even after age normalization, but boys did (Figure 2). Interestingly, boys seem to have a higher blood eosinophil rise when FA is concomitant to asthma but that is the only group where the median of eosinophils in asthmatics without FA is above 300 eos/μL.[39] This means that it is the only group where both groups are considered eosinophilic, whereas, both, in girls and all asthmatics together, patients with no-FA were non-eosinophilic asthmas and FA median should be classified as eosinophilic asthma.

It is also important to highlight that FA is a heterogeneous condition with different etiological agents and clinical features. Depending on the incriminating food or the implicated protein family FA reactions can be more or less severe.[40] This is why FA allergy was divided into several groups to examine the different effects that each food group could cause. Food allergies were organized as fruit, nuts and peanuts, milk, egg, fish, seafood, legumes, and other foods.

Our FA groups had small sample sizes, diminishing the statistical power of the tests and conclusions.

Most of the findings refer to the interaction between food groups, but other interesting associations were also observed.

Mite sensitization is a risk factor for seafood allergy, even in a low exposure area like Madrid and it is also related to late-onset asthma, after 12 years of age.

As expected, an association between profilin sensitization and fruit allergy was obtained. Interestingly, fruit allergy is related to a decrease in weight, BMI and FEV1 (volume and %).

Fruit allergy is the only food group associated with a reduction in FEV1 and biometric parameters (height, weight, and BMI), suggesting that its influence on asthma is more pronounced than other food groups. This may be due to the high pollen exposure in the area, which is strongly related to food allergy.[24,25]

It is also important to comment on the strengths and limitations of the present study. The sample size and sex stratification, when analyzing the data, are considered as strengths, since it allowed us to identify sex-dependent abnormalities. The type of study population can be a limitation, since this population has a specific regional allergen exposure profile, where pollen concentrations are very high, and there is a high prevalence of LTP and profilin sensitization. On the other hand, other aeroallergens, such as dust mites or PR-10 containing pollen concentrations are very low. It is known that populations from different environments and allergen exposures can have different asthma traits and sensitization profiles. However, these possible differences may only influence some specific findings.

We would also like to highlight that pre- and post-normalization data has been presented and analyzed to emphasize the need for this statistical tool. Moreover, a sex-specific approach is recommended in the literature for FA and asthma in children and adolescents,[14,21-23] but it is usually mentioned as a sub-analysis, not included in the primary study design. We can observe in this study how statistically significant differences appear after age and sex normalization that were not present before applying these corrections. Therefore, it is emphasized how data should be normalized for these criteria in FA and asthma, despite the fact that childhood and adolescence are already age strata.

Finally, we consider that it is positive to evaluate most patients when they were asymptomatic. Thus, we are able to analyze markers or alterations that are stable or permanent in the study patients, and not dependent on acute exposure to asthma triggers.

In conclusion, FA increases asthma prevalence and affects its characteristics. FA in asthmatic patients is associated with lower height and weight. It is also associated with a higher blood eosinophil count, which should be taken into account when phenotyping a patient as eosinophilic asthma.

Food allergy should be included in the regular asthma anamnesis and it should be considered in asthma patients with blood eosinophilia, growth alteration, LTP or mite sensitization, since they are risk factors for the coexistence of FA and asthma. The anamnesis should be sex-specific.

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Conflicts of interest

Ignacio Esteban-Gorgojo, co-founder of IgncyErto, served as a consultant to Orion, Allergy Therapeutics, Merck, ALK, given lectures for AstraZeneca, Allergy Therapeutics, Leti, Novartis, Shire, Chiesi, as well as received grant support from Merck, ALK.

Joaquin Sastre reports having served as a consultant to Thermofisher, MEDA, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GSK, having been paid lecture fees by Novartis, GSK, Stallergenes, Leti, and Faes Farma, as well as received grant support for research from Thermofisher, Sanofi, and ALK.

Santiago Quirce served in ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Sanofi, Teva–organization of educational events, advisory boards, and speakers' honoraria.

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