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Article

Food Sensitization Impact on Asthma Attacks in Children According to Age Group

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Abstract: Introduction: The progression of allergy disorders is termed "atopic march." Having one allergic disorder increases the likelihood of acquiring others. Asthma and food allergies often coexist. There are no thresholds for specific IgE (sIgE) associated with the presence of clinical symptoms. Each allergen shows a particular trend with age. Objective: Our study and analysis aim to identify food sensitization in children with asthma and evaluate its impact on asthma attacks and clinical control. Material and methods: As a part of a bigger study, 56 children (mean age 11.07 years (5.3–17.5), 38 boys, and 18 girls) with bronchial asthma were tested for total IgE and sIgE against food and inhalator allergens. All children performed baseline and post-BD spirometry and were assessed for asthma control. Results: In the studied population of children, sIgE against several food allergens was positive in the same patient. A significant correlation was found between the positive sIgE for milk and soy ($p < 0.0001$), for milk and egg yolk ($p = 0.01$), compared to milk and peanuts ($p = 0.004$), compared to egg yolk and fish ($p < 0.0001$), compared to egg yolk and casein ($p < 0.001$), and soy ($p < 0.0001$). The children who are positive for sIgE antibodies in cats, dogs, Cladosporium, Aspergillus, wormwood from aeroallergens and soy from food allergens have a higher risk of hospitalization for exacerbation of bronchial asthma. ($p < 0.05$). In the studied population, sensitization to food allergens among asthmatics does not contribute to the number of asthma attacks. Conclusions: Food sensitivity is associated with eczema, while mite sensitization is strongly associated with rhinitis and asthma. Food sensitization is not a risk factor for asthma exacerbation in children older than five years old.

Keywords: asthma; food sensitization; asthma attacks; atopic march; age-dependent sensitization

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1. Introduction

Immunoglobulin E (IgE) produced by plasma cells is the main participant in allergic reactions by recognizing antigenic specificities. After initial sensitization, a subsequent exposition to the same allergen follows the release of various cytokines that cause the symptoms of atopic diseases [1].

According to several studies, serum IgE levels during the first few months after birth are usually low (<100 kU/L); therefore, in infants less than six months of age, serum IgE levels may not help predict the development of any allergic disease. Thereafter, IgE production increases with exposure to food allergens [1]. An early sign of sensitization is the appearance of eczema, which is exacerbated by food allergens [1,2]. Prolonged or periodic B-cell activation and differentiation in plasma cells maintain the circulating IgE

antibody pool [3]. In line with this, food-specific IgEs (sIgE) are reduced quantitatively in most, but not all, patients sensitized to eggs and cow's milk after a 3-month elimination diet. The maintenance of clinically relevant IgE titers requires continuous B-cell reactivation in response to allergen exposure [3,4]. It could be speculated that prolonged exposure to food and respiratory allergens causes sensitization to different allergic agents [2,4].

The progression of allergy disorders that are triggered by common genetic and environmental causes also shares common immunological pathways. The term "atopic march" refers to the normal progression of allergy disorders. Atopic diseases of various organs and causative allergens develop progressively with age; some symptoms worsen, while others improve [5,6]. Importantly, having one allergy disorder increases the likelihood of acquiring others [6]. The atopic march typically begins with atopic dermatitis (AD) and progresses to food allergies, allergic rhinitis (AR), and asthma. Each of these disorders has a complex pathophysiology involving several components of the immune response, with Th 2 inflammation playing a prominent role [2,7]. Although most patients with AD have sIgE antibodies to food and/or respiratory allergens, their clinical significance remains unclear [8]. Approximately 35% of children with severe AD have an accompanying food allergy. In comparison, food allergies have a low incidence in adults with AD. Additionally, exposure to seasonal and perennial respiratory allergens has been associated with deterioration in the clinical control of AD [8].

Food sensitivity is associated with eczema, while mite sensitization is strongly associated with rhinitis and asthma. However, total serum IgE levels are considered a highly sensitive predictor of atopic disease, but there are no thresholds for the established amount of IgE to be associated with the presence of clinical symptoms [1,9].

As a part of a bigger observational study assessing the clinical significance of atopic status, spirometry indices, and instruments for clinical control assessment in asthmatic children, the current analysis aims to identify sensitization to certain food and respiratory allergens in children with asthma and evaluate its impact on asthma exacerbations and clinical control [10,11]. The results from the whole data analysis confirmed that pulmonary function, in particular FEV_1% pred., showed a weak correlation with asthma severity and symptoms control. However, despite this weak correlation, our results confirm that the combined use of baseline spirometry with the Asthma Control Questionnaire (ACQ) may better identify children at risk for loss of control, exacerbation, and progressive impairment of pulmonary function. (data in publishing–Lazova S., Priftis S., Petrova G., Naseva E., Velikova Ts. $MMEF_{25–75}$ may predict significant BDR and future risk of exacerbations in asthmatic children with normal baseline FEV_1) It is known that allergic sensitization and viral factors, especially in combination, are the main risk factors for asthma exacerbations in childhood [12].

A number of studies demonstrate that respiratory allergens are predominantly associated with allergic respiratory disease and alimentary allergens with atopic dermatitis throughout childhood [13,14]. According to the literature, children exposed to airborne allergens and different air pollutants, especially in inner-city settings before the age of three, had a significantly greater risk of allergic rhinitis and worse lung function later in life. According to cluster analysis, the risk of allergic rhinitis was most significant in the group exposed to airborne allergens by the age of one year [2,5]. Any sensitization affects the total serum production of IgE. However, the dynamic changes in total serum IgE levels associated with allergy susceptibility are unclear. Therefore, the following two processes overseeing IgE generation are accepted: one that persistently replenishes the IgE and another inducible upon allergen contact [3]. In a 4-year follow-up, Wong C.W. et al. divided a cohort of 258 children without significant baseline characteristics into three groups according to their dynamic changes in serum IgE levels measured at three different time points [1]. Cluster A (n = 106) includes children with serum IgE levels consistently below 100 kU/L throughout the 4-year study period. Cluster B (n = 35) includes children with serum IgE levels between 100 and 200 kU/L from 1 to 4 years, and cluster C (n = 29) inclusion of children with elevated IgE $\geq$ 200 kU/L levels after one year of age. Higher

serum IgE (≥200 kU/L, cluster C) was significantly associated with a higher prevalence of eczema at one year of age and allergic rhinitis and asthma between 2, 3, and 4 years of age [1].

On the other hand, clinical symptoms of food allergy, not only laboratory proven sensitization (serology and/or skin prick tests) are shown to be a significant risk factor for asthma exacerbation in children [15]. These observations raised the question of the impact of food sensitization on asthma control.

2. Materials and Methods

2.1. Study Design

An observational study was conducted using complex clinical, functional, and laboratory methods in a cohort of 211 Bulgarian children with asthma [10,11]. We performed the current analysis on randomly selected 56 children from the main asthma group. Selection criteria for inclusion were as follows: complete atopic status assessment, including IgE total and sIgE against food and inhalator allergens, acceptable baseline, and post-bronchodilator (BD) spirometry, and correctly filled ACQ.

2.2. Subjects

In the current study we included 56 children (mean age 11.07 years (5.3–17.5), 38 boys and 18 girls) with diagnosed bronchial asthma, hospitalized due to symptom exacerbation. (Figure 1) All parents and children older than 12 years old signed a written informed consent, following the Commission on Ethics of Research at Medical University Sofia (Ethical approval No. 5/17.04.2013, scientific project identification code 23D/2013) before study enrollment and blood samples collecting. In single analysis concerning asthma control and asthma severity, we included additional 20 children from our main atopy assessment cohort [10] to the current analysis group (n = 56) (Figure 1).

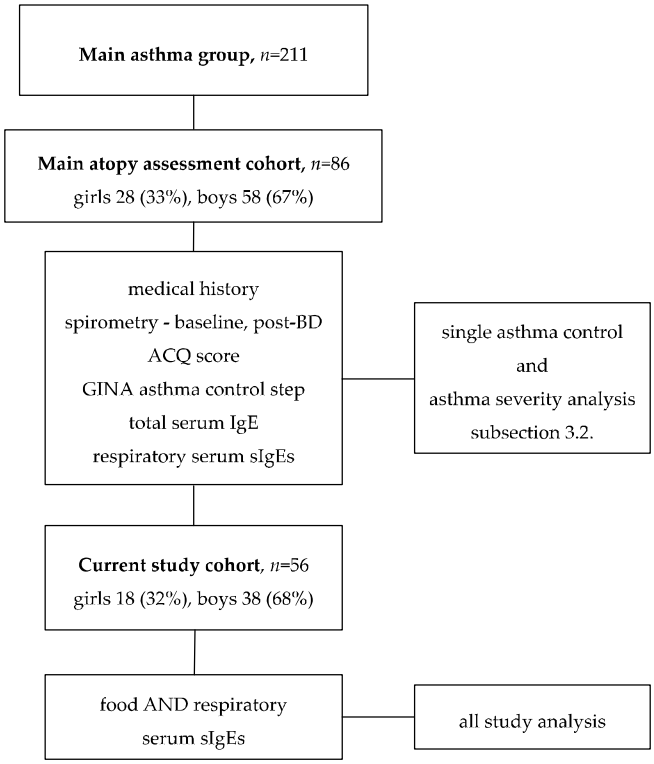

Figure 1. Study design.

2.3. Clinical and Epidemiological Methods

For all children detailed medical history was collected, including clinical asthma course, GINA control treatment step (1 to 5) eight weeks prior to enrolment, and presence of comorbidities [16].

We used a written validated tool to assess the level of asthma control. ACQ questionnaire is validated for children from 6 to 16 years old with an interview-based version (ACQ-IA) for those aged 6–10 years, performed by a trained interviewer. All analyses were performed with 6- and 7-point scale of the questionnaire–with and without the 7th question concerning the FEV_1% predicted value. We used 1.50 points as a threshold for well-controlled asthma. ACQ questionnaire and ACQ-IA were used in the study with the written permission of Prof. Elizabeth Juniper and QOL TECHNOLOGIES Ltd. 2003, who owns the questionnaire's copyright [17,18].

Asthma severity was evaluated using three different approaches–according to GINA asthma control step, baseline FEV_1 percent predicted value, and the presence of asthma symptoms between exacerbation episodes (daytime, nighttime, need for rescue medication, physical activity restriction).

Anthropometric measures were taken (height and weight).

2.4. Lung Function Testing

All 56 children performed acceptable baseline and post-bronchodilator spirometry according to ATS/ERS 2005 criteria for quality, repeatability, and reproducibility [19,20]. All spirometry measurements were performed at the Lung Function Laboratory of the Pediatric Clinic, University Hospital Alexandrovska with Masterscreen Pneumo spirometer 98 (Jager®, Wuerzburg, Germany). According to the local protocol and ERS/ATS 2005 recommendations, the quality control assurance and standard operating procedures were completed [19,20]. Post-bronchodilator spirometry was performed 15 min after administration of 200 μg (two puffs metered-dose inhaler) salbutamol (Ventolin) with a spacer. The result was calculated as a post-BD FEV_1 percentage change compared to the baseline and as an absolute change in mL.

2.5. Immunological Assessment

Atopic status determination included serological assessment of the total IgE and the sIgE antibodies against aero- and food- allergens. Total serum IgE level was evaluated by ELISA (enzyme-linked immunosorbent assay), EUROIMMUN Medizinische Labordiagnostica AG with quantitative result, presented in U/mL. Normal values were determined according to the age-dependent upper limit of normal. Specific IgE testing was performed with Euroline Allergy Profile Pediatrics, Enzyme Allergo Sorbent Test (EAST) of Euroimmune® (Medizinische Labordiagnostica, AG, 2014, Luebeck, Germany), which includes a complex of the most common food and aero-allergens in childhood. EUROLINE provides a semi-quantitative result expressed in the EAST system in seven classes from 0 to 6 (<0.35 kU/L EAST class 0 to >100 kU/L EAST class6). All serological tests were performed in a certified Laboratory of Clinical Immunology.

2.6. Statistical Methods

Statistical analysis was performed with SPSS®, IBM 2009, version 19 (2010), and Microsoft Office Excel 365. Descriptive statistics were used to describe clinical and demographic characteristics of patients, spirometry, and immunological parameters. We used a correlation analysis between category characteristics (χ-square for more than two groups of one of the variables and Fisher's Exact test for tables with dimension 2×2); single-factor analyses and a case-control study to calculate the odds/risk ratio (OR). As a significant level was chosen $\alpha = 0.05$. In case of $p < \alpha$, the null hypothesis is rejected.

3. Results

3.1. Demographic and Clinical Characteristics

Epidemiological and demographic characteristics of the study group are presented in Table 1.

Table 1. Epidemiological and demographic characteristics of the study group.

	Index	Value
Number		56
Sex	Male, n, %	38, 68%
	Female, n, %	18, 32%
Age, years, mean		11.07 (5.3–17.5)
Height, cm, mean		111–181 (mean 145.2)
Age, years, mean		11.07 (5.3–17.5)
Age groups	5–8 yrs., n, %	12, 21%
	8–12 yrs., n, %	21, 38%
	12–16 yrs, n, %	15, 27%
	16–18 yrs., n, %	8, 14%
FEV_1 % predicted	>80%, n, %	28, 50%
	<80% and >60%, n, %	18, 33%
	<60%, n, %	10, 17%
Mean BDR (ΔFEV_1%pred., abs.change, mL)		16.59%, 273 mL
Atopic sensitization	Food and respiratory, n, %	31, 55%
	Food, n, %	34, 60%
	Respiratory, n, %	49, 87%
ACQ7 score	Controlled asthma (<0.75)	11, 20%
	Partly controlled asthma (0.75–1.5)	14, 25%
	Uncontrolled asthma (>1.5)	31, 55%
Asthma exacerbations, mean		3.04
Asthma hospitalizations, mean		1.26

According to the immunological assessment, we divided the children into the following two groups: atopic and non-atopic. The atopic group included all children with elevated total IgE above the ULN according to age and or positive sIgE against at least one food or respiratory allergen above EAST class 1. The non-atopic group includes children with normal total IgE, negative sIgE against tested allergens (<0.35 kU/L EAST class 0), and a negative medical history for allergy symptoms or diagnosis.

3.2. Asthma Control and Asthma Severity

For this analysis, we included 86 children from our main cohort [7]. Asthma severity according to GINA treatment step, baseline FEV_1%predicted and presence of asthma symptoms between exacerbation episodes in the groups of atopic and non-atopic children is listed in Table 2. Children in the main group had an average of 2.92 exacerbations and 1.27 hospitalizations in the previous twelve months before the enrollment.

Table 2. Percentage distribution of non-atopics and atopics according to asthma severity and asthma control.

Asthma Control and Severity Classification		Non- Atopics, %	Atopics, %	*p*
GINA step	1	73.7%	54.4%	>0.05
	2	21.1%	32.2%	
	3	5.3%	12.2%	
	4	0.0%	1.1%	
Severity according spirometry (FEV_1 %predicted value)	>80%	50.0%	75.3%	0.030
	<80% and >60%	50.0%	17.3%	
	<60%	0.0%	7.4%	
Asthma control (ACQ7)	Controlled asthma (<0.75)	57.9%	31.1%	0.023
	Partly controlled asthma (0.75–1.5)	21.1%	13.3%	
	Uncontrolled asthma (>1.5)	21.1%	55.6%	

Table 2. *Cont.*

Asthma Control and Severity Classification		Non- Atopics, %	Atopics, %	*p*
Symptom severity	Intermittent asthma	42.1%	23.3%	0.076
	Mild persistent	31.6%	22.2%	
	Moderate and severe persistent asthma	26.3%	54.4%	

We split up all the tested children into three groups as follows: mild, moderate, and moderate to severe persistent asthma, according to the asthma symptoms between exacerbations. Most of the children with moderate and severe persistent asthma are atopic, but without statistical significance (p = 0.076). (Table 2, Figure 2) Additionally, atopic children are more likely to have uncontrolled asthma according to the ACQ score (56%) than children without atopic sensitization (21.1%), p = 0.023 (Table 2, Figure 3).

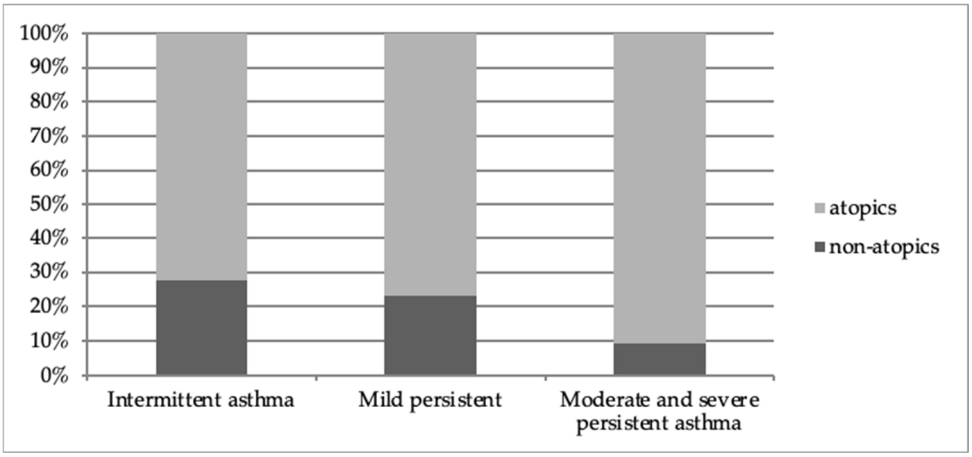

Figure 2. Symptom severity percentage distribution of atopic and non-atopic individuals (*x*–axis–intermittent, mild, moderate, and severe persistent asthma group; *y*–axis–percent patients in the three symptom severity groups).

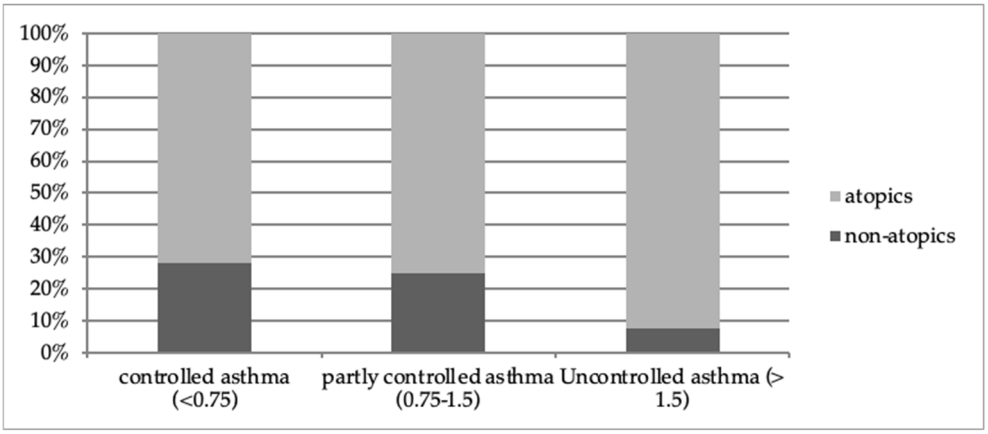

Figure 3. ACQ score percentage distribution of atopic and non-atopic individuals (*x*–axis–controlled, partly controlled and uncontrolled asthma group; *y*–axiss–percent patients in the three asthma control groups according to ACQ score).

3.3. Spirometry Evaluation

Normal baseline spirometry (FEV_1 > 80% predicted) was found in half of the children in the main group (n = 29), (51%). However, significant reversibility (post-BD change in FEV_1 > 12% and or >200 mL) was detected in more than two-thirds (n = 40), (71%).

3.4. Atopic Status Evaluation

3.4.1. Respiratory Allergens Sensitization

In 45 children (78%), there was detected sensitization to one or more allergens and/or elevated total IgE. Sensitization to respiratory allergens was estimated in 27 children (54%), food allergens in n = 4 (8%), and both types of allergens in n= 27 (54%).

The main respiratory sensitization is against grass (n = 23) and Dermatophagoydes pteronyssimus, followed by Dermatophagoydes farinae (n = 20) and cats (n = 20). The distribution of respiratory allergen sensitization among tested children is presented in Figure 4.

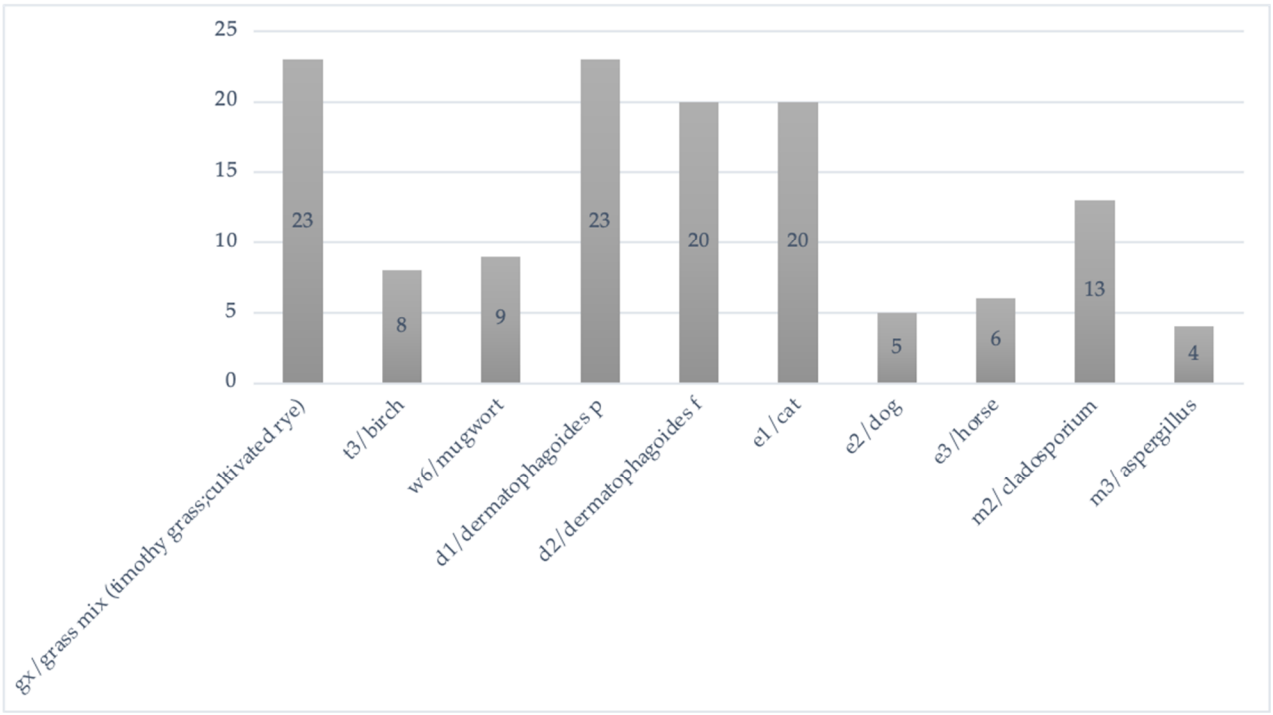

Figure 4. Distribution of respiratory allergen sensitization. (x–axis–aeroallergens, y–axis–patient numbers).

Respiratory sensitization is most often in children from 8 to 12 years old (n = 19), followed by adolescents aged from 12 to 16 years old (n = 12), 5–8 years old (n = 10), and above 16 (n = 4).

3.4.2. Food Allergens Sensitization

In the studied population, the main food allergens causing sensitization are potato (n = 19), carrot (n = 12), peanut (n = 10), and apple (n = 9). (Figure 5).

The vast majority of children (n = 51, 91%) with food sensitization have positive sIgE against more than one food allergen. We found a significant correlation between the positivity of sIgE against milk and soy ($p < 0.0001$), against milk and egg yolk ($p = 0.01$), against milk and peanuts ($p = 0.004$), against egg yolk and fish ($p < 0.0001$), against egg yolk and casein ($p < 0.0001$), and soy ($p < 0.0001$).

We divided all patients (n = 56) into five groups according to the number of asthma exacerbations in the previous twelve months. Without asthma exacerbation, they were as follows: n = 8 (15%), from 1 to 2 attacks in n = 17 (33%), from 3 to 4 attack n = 18 (35%), from 5 to 6 n = 17 (33%) and more than 6 in n = 3 (6%). The single factor analyses showed that food sensitization does not relate to the number of asthma attacks (Table 3).

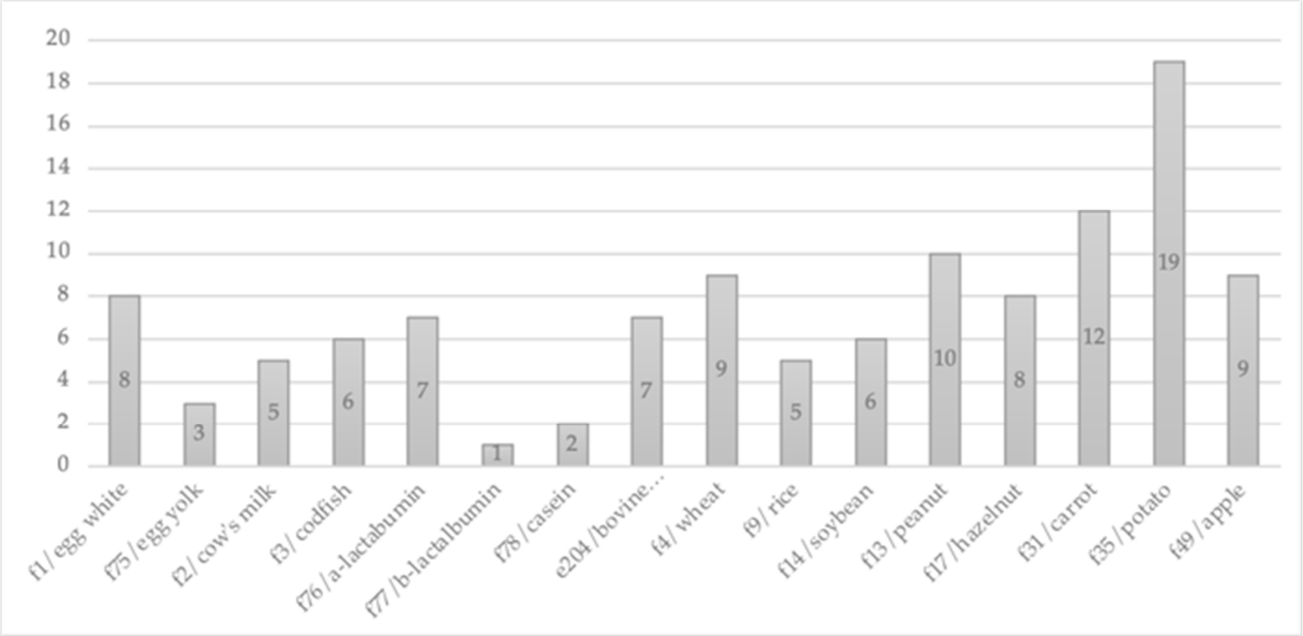

Figure 5. Distribution of food allergen sensitization. (*x*–axis–food allergens, *y*–axis–patient numbers.

Table 3. Food sensitization and asthma attacks.

ANOVA	Title 2	Title 3				
Source of Variation	SS	Df	MS	F	*p*-value	F crit
Between groups	44.66667	2	22.33333	0.643715	0.547911	4.256495
Within groups	312.25	9	34.69444			
Total	356.9167	11				

3.4.3. Respiratory and Food Allergens Sensitization

The positivity of sIgE against hazelnuts showed a significant correlation with the positivity of sIgE against birch wood pollen and grass mix. Sensitization to carrot correlates with birch sensitization and to apple and potato with the fungal spore Cladosporium (Table 4).

Table 4. Significant correlation between food and respiratory allergen sensitization.

Food Allergen Positivity	Respiratory Allergen Positivity	Correlation Coefficient	*p* Value
Hazelnuts	Birch	0.489	0.000
Carrot	Birch	0.303	0.003
Hazelnuts	Grass mix	0.301	0.004
Apple	*Cladosporium*	0.326	0.000
Potato	*Cladosporium*	0.413	0.000

Specific IgE antibodies to cats, *Cladosporum*, *Aspergillus*, wormwood, and soybean were associated with a higher hospitalization risk due to exacerbation among asthmatics. ($p < 0.05$). In case of dog sensitization, the relationship is insignificant (trend $p = 0.052$) (Table 5). Soybeans are the single food allergen that correlates with the hospitalization risk. *Cladosporum* sensitization correlates with both hospitalizations and exacerbation risk. ($p = 0.005$ and $p = 0.048$s respectively).

Table 5. Type of sensitization * and risk of hospitalization/exacerbation.

Clinical Outcome	Specific IgE	*p*
Risk of hospitalization	Cat	0.002
	Dog	0.052
	Cladosporum	0.005
	Aspergillus	0.054
	Wormwood	0.013
	Soybean	0.013
Risk of exacerbation	*Cladosporium*	0.048

* sIgE antibodies in serum (EUROIMMUN pediatric).

4. Discussion

Asthma and atopy are associated with epithelial damage, which, in turn, contributes to both susceptibilities to viral infections and sensitization to aeroallergens [21]. It is proven that viral infections increase interleukin-4 (IL-4) and may elicit the inflammatory Th2 response [21]. In our cohort of patients, most of the children with moderate and severe persistent asthma are atopic, without statistical significance ($p = 0.076$). Additionally, atopic children are more likely to have uncontrolled asthma according to the ACQ score (56%) than children without atopic sensitization (21.1%), $p = 0.023$. Our results are in line with other research in this field. According to a study in Korea, children with allergic sensitization showed the same number of viral infections, but more severe than non-atopics.[21] In another Korean study, it was found that an association between rhino and influenza virus infection and asthma exacerbation in atopic sensitized children (elevated total serum IgE), but not in non-atopics [22].

Childhood asthma is often associated with allergies. The incidence of allergic asthma varies and is highest in the age group of 0–9 years and lowest in the age group of 50–59 years [23]. On the other hand, the prevalence of non-allergic asthma increases significantly after middle age and is highest in the age group of 50–59 years [23]. In our patient group, non-atopic asthmatics are a minority, ranging from 5 to 13% according to the assessment method (total IgE or serum sIgE).

There are no specific features that could distinguish allergic from nonallergic asthma, except a positive skin prick test (SPT). Sinisgalli et al. reported that approximately a third of 321 pediatric asthma patients had negative SPT to any of the tested aeroallergens [24]. A small amount of data is addressed to nonatopic asthma phenotype. A significant portion of nonatopic children with persistent asthma treated with inhaled corticosteroids as first-line therapy demonstrate a less robust response to treatment compared to atopic children [25]. The main comorbidities in asthmatic children are AR, gastroesophageal reflux, obesity, depressive disorders, and food allergies [26,27].

Asthma and food allergies often coexist. Several studies have shown that children with asthma are more sensitive to food allergens than the general population, and this sensitization is associated with increased severity of asthma [28–30]. Schroeder et al. and Roberts et al. reported that children with food allergies are more often diagnosed with asthma [28,29]. Friedlander et al. reported a high prevalence of food allergies in inner-city school-age children with asthma. Additionally, the authors conclude that food allergies are associated with increased asthma morbidity and health resource utilization with decreased lung function, especially in children with multiple food allergies [30]. On the other hand, a United Kingdom study demonstrated that wheezing before the age of two was not related to adult asthma. Positive SPT to egg or milk in the first year of life has a strong positive correlation with adult asthma [31].

In 2008, the dual allergen exposure hypothesis arose [32]. According to this, oral antigen exposure tends to induce tolerance. In contrast, skin exposure induces allergic sensitization and subsequent food allergy manifestation—up to 10% in the pediatric population and from 1 to 3% in the adult population. According to the literature, the prevalence ranges from 1–2% to 11% in food allergy-reported patients, and several studies report even higher

rates, reaching up to 35% [2,4]. The most common food allergens in children are milk (2.5%), eggs (1.3%), peanuts (0.8%), wheat (0.4%), soy (0.4%), wood nuts (0.2%), fish (0.1%), and mussels (0.1%) [2,4]. At the age of 5, most of them outgrow allergic reactions to milk, eggs, wheat, and soybeans. Emran H. et al. noted that the most prevalent aeroallergens in the Brunei study were *Dermatophagoides pteronyssinus*, followed by *Dermatophagoide farinae* [33]. Shrimp was the most common food allergen, followed by peanut and egg white [33]. Atta et al. reported the prevalence of food allergy in asthmatic children from 4 to 18 years about 38.9% [34]. Food allergy in this study was suspected by the presence of sIgE (detected either by skin prick test or by serum sIgE) and confirmed by a food challenge test. Detected food allergens are cow milk and casein 68 (77%), followed by chicken 56 (65%), egg 52 (59%), banana 52 (59%), fish 52 (59%), wheat 48 (54%) and peanut 28 (31%) [34]. It is necessary to emphasize that in the mentioned group food allergy is confirmed by a food challenge test [34]. In our study, only serum sIgE was used, and we did not perform an oral food challenge (OFC). According to our results the main food allergens sIgE are potato (n = 19), carrot (n = 12), peanut (n = 10) and apple (n = 9). These may be due to different food habits, genetic backgrounds, and environmental conditions among different populations.

Another main question is addressed to the following two different immunological phenomena: cross-reactivity and age-related characteristics of sIgE in the course of the atopic march. Cross-reactivity occurs when IgE antibodies directed against certain allergen bind to an allergen from another allergen source as a result of shared B-cell epitopes of homologous proteins [35]. In order to exhibit cross-reactivity, identification of at least 50% homology between allergens is required. IgE responses against a wide variety of N-glycans, defined as cross-reactive carbohydrate determinants (CCD), cannot cause mast cell or basophilic degranulation but are ubiquitous in helminthic, insect, plant, and animal species as structural components of their glycoproteins [35]. The clinical manifestation of this phenomenon is known as oral allergy syndrome (OAS), an immediate allergic symptom of the oral mucosa owing to food antigens [36]. The term pollen-food allergy syndrome (PFAS) is defined as patients with pollen allergy who develop OAS after eating fruits and vegetables. PFAS is caused by cross-reactivity between pollen allergens and fruit and/or vegetable allergens. The most common causal foods of PFAS are kiwi fruit and pineapple (39.0%), followed by peach (28.8%), apple (22.0%), tomato (18.6%), melon (16.9%), mango (13.6%), cherry (11.9%), watermelon (8.5%), and pear (6.8%) [36].

On the other hand, sensitization to respiratory allergens in our group of patients is most often in children from 8 to 12 years old (n = 19), followed by adolescents aged from 12 to 16 years old (n = 12), 5–8 years (n = 10), and above 16 (n = 4). In n= 27, (54%) patients' sensitizations to both food and respiratory allergens were detected. As mentioned above, potato (n = 19), carrot (n = 12), peanut (n = 10), apple (n = 9) and wheat (n = 9) sIgE are detected in our asthmatics. We did not collect data on clinical manifestations of OAS/PAFS.

The relationship between food components and asthma control is well described but unclear. Different types of aspects need to be considered. Histamine is a crucial inflammatory mediator in asthmatic patients, triggering airway hyper-responsiveness and remodeling as well as worsening asthma symptoms [37]. Plasma histamine concentrations of 7–12 ng/mL can lead to bronchospasm. A study performed by James et al. shows that 7 out of 12 patients experience chest symptoms after a food challenge [37]. Bronchial hyperresponsiveness (BHR) increased under methacholine inhalation in the same group. In addition, Roberts et al. reported asthma attacks after inhalation exposure to food [38]. Other dietary factors may also influence asthma, such as a high-fat diet, low whole-grain consumption, low fiber intake, and saturated-unsaturated fat imbalance [39–43]. More data are needed to clarify this link. Foods are a rich source of both allergenic components and pharmacological substances, manifested by identical clinical manifestations. The clinical manifestation of sensitization to food components demonstrates differences in different age periods [44]. On the other hand, restrictive diets have demonstrated a different impact on the course of the atopic march [45].

Zicari A.M. et al. reported that persistence of sensitization to food allergens at school age is associated with more severe asthma [46]. We find that sIgE antibodies to cats, Cladosporium, Aspergillus, wormwood, and soy were associated with a higher risk of hospitalization for exacerbation among asthmatics. ($p < 0.05$). In case of dog sensitization, the relation is insignificant (trend $p = 0.052$). We performed a single factor analysis and found that food sensitization does not relate to the number of asthma attacks during the past twelve months. This finding could be due to the particular trend of each allergen with age. House dust mites induce the earliest IgE response, with clinically significant IgE levels detected in early childhood. This early reaction can result from the ubiquitous presence of mites and their persistence over time throughout the year. Alternaria's response is typical in adolescents and young adults but declines rapidly after 25–27 years [47]. Pollens and grasses cause early IgE production, which decreases after 30 years, even though these allergens cause the highest levels of IgE. For example, birch-sIgE peaked in adolescence and young adulthood, while IgE against ragweed and artemisia peaked later [7,47].

On the other hand, allergic manifestations tend to decrease with age [47,48]. The available data indicates that serum IgE levels are lower among people aged between 45–70 years [49]. In addition, sIgE levels for different allergens differ significantly between different age groups of patients. A peak is reported in 19- to 21-year-olds, followed by a corresponding peak in the range of 28–30 years. An unexpected peak is also described in the age group > 85 years, and this trend is more evident in women. A possible explanation for this surprising observation is the probable impaired regulatory function of IgE production. It is not uncommon to detect autoantibodies in adult patients [49]. The limit in these studies is related to their duration. In addition, they are focused on the particular clinical constellation, and the age transition in the light of the clinical significance of sensitization remains unclear.

The limitations of our study are the small group of children and the lack of observation of sIgE production's dynamic. Additionally, we assessed the impact of the detected sensitization to the studied components of food allergens without performing an oral food challenge. However, our observations affirm the need for more serious attention to food sensitization in the light of the clinical control of another concomitant allergic disease such as bronchial asthma.

5. Conclusions

In the studied population, isolated sensitization to food allergens without evidence of clinical symptoms of food allergy among asthmatic children does not contribute to the number of asthma exacerbations and hospital admissions. The single food allergen sensitization that correlates with the hospitalization but not exacerbation risk in our school-age asthmatics is soybean.

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Informed Consent Statement: Before the study enrolment, all parents and children over 12 years old signed written informed consent and child assent, according to the Ethics Committee on Scientific Research requirements at the Medical University of Sofia.

Data Availability Statement: The data presented in this study are available only on request from the corresponding author, due to restrictions, e.g., privacy or ethics.

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References

1. Wong, C.-Y.; Yeh, K.-W.; Huang, J.-L.; Su, K.-W.; Tsai, M.-H.; Hua, M.-C.; Liao, S.-L.; Lai, S.-H.; Chen, L.-C.; Chiu, C.-Y. Longitudinal Analysis of Total Serum IgE Levels with Allergen Sensitization and Atopic Diseases in Early Childhood. *Sci. Rep.* **2020**, *10*, 21278. [CrossRef] [PubMed]
2. Tham, E.H.; Leung, D.Y.M. Mechanisms by Which Atopic Dermatitis Predisposes to Food Allergy and the Atopic March. *Allergy. Asthma Immunol. Res.* **2019**, *11*, 4. [CrossRef] [PubMed]
3. Eckl-Dorna, J.; Villazala-Merino, S.; Campion, N.J.; Byazrova, M.; Filatov, A.; Kudlay, D.; Karsonova, A.; Riabova, K.; Khaitov, M.; Karaulov, A.; et al. Tracing IgE-Producing Cells in Allergic Patients. *Cells* **2019**, *8*, 994. [CrossRef] [PubMed]
4. Satitsuksanoa, P.; Daanje, M.; Akdis, M.; Boyd, S.D.; Veen, W. Biology and Dynamics of B Cells in the Context of IgE-mediated Food Allergy. *Allergy* **2021**, *76*, 1707–1717. [CrossRef]
5. Tsuge, M.; Ikeda, M.; Matsumoto, N.; Yorifuji, T.; Tsukahara, H. Current Insights into Atopic March. *Children* **2021**, *8*, 1067. [CrossRef]
6. Wahn, U.; Nickel, R.; Grüber, C.; Lau, S.; Illi, S. The Atopic March. *Asthma Prev.* **2005**, *120*, 313–331. [CrossRef]
7. Togias, A. Rhinitis and Asthma: Evidence for Respiratory System Integration. *J. Allergy Clin. Immunol.* **2003**, *111*, 1171–1183. [CrossRef]
8. Upton, E.; Martin, B.; Wehmeyer, A. Allergic Rhinitis: To Sneeze or to Wheeze. Pollen Is the Question, What Is the Answer? *South African Pharm. J.* **2018**, *85*, 37–42.
9. Migueres, M.; Dávila, I.; Frati, F.; Azpeitia, A.; Jeanpetit, Y.; Lhéritier-Barrand, M.; Incorvaia, C.; Ciprandi, G. Types of Sensitization to Aeroallergens: Definitions, Prevalences and Impact on the Diagnosis and Treatment of Allergic Respiratory Disease. *Clin. Transl. Allergy* **2014**, *4*, 16. [CrossRef]
10. Lazova, S.; Baleva, M.; Priftis, S.; Naseva, E.; Velikova, T. Atopic Status in Children with Asthma and Respiratory Allergies—Comparative Analysis of Total IgE, ImmunoCAP Phadiatop/Fx5 and Euroimmun Pediatric Immunoblot. *Sinusitis* **2021**, *6*, 1. [CrossRef]
11. Lazova, S.; Velikova, T.; Priftis, S.; Petrova, G. Identification of Specific IgE Antibodies and Asthma Control Interaction and Association Using Cluster Analysis in a Bulgarian Asthmatic Children Cohort. *Antibodies* **2020**, *9*, 31. [CrossRef] [PubMed]
12. Gern, J.E. Virus/Allergen Interaction in Asthma Exacerbation. *Ann. Am. Thorac. Soc.* **2015**, *12* (Suppl. S2), S137–S143. [CrossRef] [PubMed]
13. Spergel, J.M. From Atopic Dermatitis to Asthma: The Atopic March. *Ann. Allergy Asthma Immunol.* **2010**, *105*, 99–106. [CrossRef] [PubMed]
14. Wang, Y.-H.; Lue, K.-H. Association between Sensitized to Food Allergens and Childhood Allergic Respiratory Diseases in Taiwan. *J. Microbiol. Immunol. Infect.* **2020**, *53*, 812–820. [CrossRef] [PubMed]
15. Wan, K.-S.; Wu, W.-F.; Liu, Y.-C.; Huang, C.-S.; Wu, C.-S.; Hung, C.-W.; Chang, Y.-S. Effects of Food Allergens on Asthma Exacerbations in Schoolchildren with Atopic Asthma. *Food Agric. Immunol.* **2017**, *28*, 310–314. [CrossRef]
16. 2021 GINA Report, Global Strategy for Asthma Management and Prevention. Available online: https://ginasthma.org/gina-reports/ (accessed on 1 January 2022).
17. Juniper, E.F.; Gruffydd-Jones, K.; Ward, S. Asthma Control Questionnaire in Children: Validation, Measurement Properties, Interpretation. *Eur. Respir. J.* **2010**, *36*, 1410–1416. [CrossRef]
18. Juniper, E.F.; Bousquet, J.; Abetz, L.; Bateman, E.D.; Goal Committee. Identifying "well-Controlled" and "Not Wellcontrolled" Asthma Using the Asthma Control Questionnaire. *Respir. Med.* **2006**, *100*, 616–621. [CrossRef]
19. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am. J. Respir. Crit. Care Med.* **1995**, *152*, 1107–1136. [CrossRef]
20. Pellegrino, R. Interpretative Strategies for Lung Function Tests. *Eur. Respir. J.* **2005**, *26*, 948–968. [CrossRef]
21. Costa, L.D.C.; Costa, P.S.; Camargos, P.A.M. Exacerbation of Asthma and Airway Infection: Is the Virus the Villain? *J. Pediatr. (Rio. J.)* **2014**, *90*, 542–555. [CrossRef]
22. Kwon, J.-M.; Shim, J.W.; Kim, D.S.; Jung, H.L.; Park, M.S.; Shim, J.Y. Prevalence of Respiratory Viral Infection in Children Hospitalized for Acute Lower Respiratory Tract Diseases, and Association of Rhinovirus and Influenza Virus with Asthma Exacerbations. *Korean J. Pediatr.* **2014**, *57*, 29. [CrossRef] [PubMed]
23. Pakkasela, J.; Ilmarinen, P.; Honkamäki, J.; Tuomisto, L.E.; Andersén, H.; Piirilä, P.; Hisinger-Mölkänen, H.; Sovijärvi, A.; Backman, H.; Lundbäck, B.; et al. Age-Specific Incidence of Allergic and Non-Allergic Asthma. *BMC Pulm. Med.* **2020**, *20*, 9. [CrossRef] [PubMed]
24. Sinisgalli, S.; Collins, M.S.; Schramm, C.M. Clinical Features Cannot Distinguish Allergic from Non-Allergic Asthma in Children. *J. Asthma* **2012**, *49*, 51–56. [CrossRef] [PubMed]

25. Vazquez Garcia, G.; Blake, K. Considerations for the Child with Nonatopic Asthma. *Pediatr. Allergy. Immunol. Pulmonol.* **2020**, *33*, 39–42. [CrossRef] [PubMed]
26. Bahreinian, S.; Ball, G.D.C.; Colman, I.; Becker, A.B.; Kozyrskyj, A.L. Depression Is More Common in Girls with Nonatopic Asthma. *Chest* **2011**, *140*, 1138–1145. [CrossRef] [PubMed]
27. Ullmann, N.; Mirra, V.; Di Marco, A.; Pavone, M.; Porcaro, F.; Negro, V.; Onofri, A.; Cutrera, R. Asthma: Differential Diagnosis and Comorbidities. *Front. Pediatr.* **2018**, *6*, 276. [CrossRef]
28. Schroeder, A.; Kumar, R.; Pongracic, J.A.; Sullivan, C.L.; Caruso, D.M.; Costello, J.; Meyer, K.E.; Vucic, Y.; Gupta, R.; Kim, J.S.; et al. Food Allergy Is Associated with an Increased Risk of Asthma. *Clin. Exp. Allergy* **2009**, *39*, 261–270. [CrossRef]
29. Roberts, G.; Patel, N.; Levi-Schaffer, F.; Habibi, P.; Lack, G. Food Allergy as a Risk Factor for Life-Threatening Asthma in Childhood: A Case-Controlled Study. *J. Allergy Clin. Immunol.* **2003**, *112*, 168–174. [CrossRef]
30. Friedlander, J.L.; Sheehan, W.J.; Baxi, S.N.; Kopel, L.S.; Gaffin, J.M.; Ozonoff, A.; Fu, C.; Gold, D.R.; Phipatanakul, W. Food Allergy and Increased Asthma Morbidity in a School-Based Inner-City Asthma Study. *J. Allergy Clin. Immunol. Pract.* **2013**, *1*, 479–484. [CrossRef]
31. Emons, J.A.M.; Gerth van Wijk, R. Food Allergy and Asthma: Is There a Link? *Curr. Treat. Options Allergy* **2018**, *5*, 436–444. [CrossRef]
32. Kulis, M.D.; Smeekens, J.M.; Immormino, R.M.; Moran, T.P. The Airway as a Route of Sensitization to Peanut: An Update to the Dual Allergen Exposure Hypothesis. *J. Allergy Clin. Immunol.* **2021**, *148*, 689–693. [CrossRef] [PubMed]
33. Emran, H.; Chieng, C.S.E.; Taib, S.; Cunningham, A.C. House Dust Mite Sensitisation and Association with Atopic Dermatitis in Brunei. *Clin. Transl. Allergy* **2019**, *9*, 65. [CrossRef] [PubMed]
34. Atta, A.; Elbehady, R.; El Shobaky, A.; El Shabrawy, R. The Effect of Food Elimination and Probiotic Supplementation in Asthmatic Children with Food Allergy. *Egypt. J. Pediatr. Allergy Immunol.* **2021**, *19*, 19–26. [CrossRef]
35. Twaroch, T.E.; Curin, M.; Valenta, R.; Swoboda, I. Mold Allergens in Respiratory Allergy: From Structure to Therapy. *Allergy. Asthma Immunol. Res.* **2015**, *7*, 205. [CrossRef]
36. Kiguchi, T.; Yamamoto-Hanada, K.; Saito-Abe, M.; Sato, M.; Irahara, M.; Ogita, H.; Miyagi, Y.; Inuzuka, Y.; Toyokuni, K.; Nishimura, K.; et al. Pollen-Food Allergy Syndrome and Component Sensitization in Adolescents: A Japanese Population-Based Study. *PLoS ONE* **2021**, *16*, e0249649. [CrossRef] [PubMed]
37. James, J.M.; Eigenmann, P.A.; Eggleston, P.A.; Sampson, H.A. Airway Reactivity Changes in Asthmatic Patients Undergoing Blinded Food Challenges. *Am. J. Respir. Crit. Care Med.* **1996**, *153*, 597–603. [CrossRef]
38. Roberts, G.; Lack, G. Relevance of Inhalational Exposure to Food Allergens. *Curr. Opin. Allergy Clin. Immunol.* **2003**, *3*, 211–215. [CrossRef]
39. Vassilopoulou, E.; Konstantinou, G.N.; Dimitriou, A.; Manios, Y.; Koumbi, L.; Papadopoulos, N.G. The Impact of Food Histamine Intake on Asthma Activity: A Pilot Study. *Nutrients* **2020**, *12*, 3402. [CrossRef]
40. Kim, J.-H.; Choi, G.-S.; Kim, J.-E.; Ye, Y.-M.; Park, H.-S. Three Cases of Rice-Induced Occupational Asthma. *Ann. Allergy, Asthma Immunol.* **2010**, *104*, 353–354. [CrossRef]
41. Hanson, C.; Brigham, E. Maternal Nutrition and Child Respiratory Outcomes: Paradigms of Lung Health and Disease. *Eur. Respir. J.* **2020**, *55*, 1902437. [CrossRef]
42. Alwarith, J.; Kahleova, H.; Crosby, L.; Brooks, A.; Brandon, L.; Levin, S.M.; Barnard, N.D. The Role of Nutrition in Asthma Prevention and Treatment. *Nutr. Rev.* **2020**, *78*, 928–938. [CrossRef] [PubMed]
43. Calcaterra, V.; Verduci, E.; Ghezzi, M.; Cena, H.; Pascuzzi, M.C.; Regalbuto, C.; Lamberti, R.; Rossi, V.; Manuelli, M.; Bosetti, A.; et al. Pediatric Obesity-Related Asthma: The Role of Nutrition and Nutrients in Prevention and Treatment. *Nutrients* **2021**, *13*, 3708. [CrossRef]
44. Kim, H.Y.; Shin, Y.H.; Han, M.Y. Determinants of Sensitization to Allergen in Infants and Young Children. *Korean J. Pediatr.* **2014**, *57*, 205. [CrossRef] [PubMed]
45. Carucci, L.; Nocerino, R.; Paparo, L.; Di Scala, C.; Berni Canani, R. Dietary Prevention of Atopic March in Pediatric Subjects With Cow's Milk Allergy. *Front. Pediatr.* **2020**, *8*, 440. [CrossRef] [PubMed]
46. Zicari, A.M.; Indinnimeo, L.; De Castro, G.; Zappalà, D.; Tancredi, G.; Bonci, E.; Celani, C.; Duse, M. Food Allergy and the Development of Asthma Symptoms. *Int. J. Immunopathol. Pharmacol.* **2012**, *25*, 731–740. [CrossRef]
47. De Amici, M.; Ciprandi, G. The Age Impact on Serum Total and Allergen-Specific IgE. *Allergy Asthma Immunol. Res.* **2013**, *5*, 170. [CrossRef]
48. Hong, S.-N.; Won, J.Y.; Nam, E.-C.; Kim, T.S.; Ryu, Y.-J.; Kwon, J.-W.; Lee, W.H. Clinical Manifestations of Allergic Rhinitis by Age and Gender: A 12-Year Single-Center Study. *Ann. Otol. Rhinol. Laryngol.* **2020**, *129*, 910–917. [CrossRef]
49. Badloe, F.M.S.; De Vriese, S.; Coolens, K.; Schmidt-Weber, C.B.; Ring, J.; Gutermuth, J.; Kortekaas Krohn, I. IgE Autoantibodies and Autoreactive T Cells and Their Role in Children and Adults with Atopic Dermatitis. *Clin. Transl. Allergy* **2020**, *10*, 34. [CrossRef]