

FOOD ALLERGY AND THE DEVELOPMENT OF ASTHMA SYMPTOMS

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Allergies are multifactorial diseases the onset of which depends also on genetic and environmental factors in early life. Thus, environmental factors can affect the immune response and modify lung development, thereby leading to asthma. The role of the factors used to date to predict asthma development is modest, and clinical criteria should always be considered in association with familiarity for atopy. The aim of this study is to evaluate the risk of asthma in a population with positive Skin Prick Test (SPT) (which is a reliable marker of atopy) to food allergens, regardless of clinical manifestations in the early years of life. The cohort of children enrolled in our study who had a positive SPT to food in the first three years of life had a prevalence of asthma after 7–14 years, double that of the general pediatric population. This prevalence increased significantly in patients with SPT positivity for food and inhalant allergens. We identified a correlation between the sensitization profile in children under the age of 36 months and the development of asthma during a period of 7–14 years. This study confirms that early sensitization is an important risk factor for the development of asthma, particularly in association with sensitization to inhalants, and that the persistence of food sensitization in school-age children and adolescents is associated to more severe asthma.

The dramatic increase in the prevalence of asthma and atopic disease over the last 20 years has led to the term ‘allergy epidemic’ (1, 2). Allergies are multifactorial diseases, and their onset depends also on genetic and environmental factors in the first 2–3 years of life, as demonstrated, for example, in asthma (3). In fact, given the predisposing genetic background in the early years of life, environmental factors can affect the immune response and modify lung development, thus leading to asthma (4). Consequently, identification and prevention of such factors is important to forestall the development of asthma. Attention has therefore focused on the first manifestations of the so-called ‘atopic march’, namely atopic dermatitis > food allergy > rhinitis >

asthma. However, atopic dermatitis is IgE-mediated in less than one-third of cases; consequently, it is not always a marker of an immune imbalance towards TH2 dominance. Similarly, food allergy is not always IgE-mediated (5-7). Also wheezing may be caused by various conditions that, unlike atopy, predict the development of asthma (8). Therefore, the predictive role of these conditions as regards asthma development is modest, and clinical criteria should always be considered in association with familiarity for atopy. Furthermore, the production of specific IgE (sIgE) against food allergens in the first years of life and against inhalant allergens later in life is indicative of genetic predisposition, regardless of familial correlation (9).

Key words: food allergy, skin prick test, asthma

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The aim of this study is to evaluate the risk of asthma in a population with early sensitization (which a reliable marker of atopy) to food allergens, regardless of clinical manifestations in the early years of life. We identified a correlation between the sensitization profile in children below the age of 36 months and the development of asthma during a period of 7–14 years. We confirm that early food sensitization is an important risk factor for the development of asthma, particularly in association with sensitization to inhalants, and that the persistence of food sensitization in school-age children and adolescents is associated to more severe asthma.

MATERIALS AND METHODS

Patients and study design

The study population consisted of all 415 children admitted to our Pediatrics Department between 1995 and 2002 who were positive to at least one food allergen of a minimum set of 15 common allergens at SPT carried out before the age of 36 months. Children with malformations or chronic systemic diseases were not included in the study. Parents were contacted by telephone and invited to reply to a questionnaire. They were also invited to bring their child to our Department to participate in a clinical study. The children underwent a clinical examination, another SPT and a spirometry test (FEV_1 , MEF_{50} and PEF) before and after administration of a bronchodilator. The study was conducted in 2009, when the children were between the ages of 7 and 14 years. At this time, the children completed a questionnaire (see below), and underwent a spirometry test.

Questionnaire

The questionnaire consisted of items extrapolated from the Italian Studies on Respiratory Disorders in Childhood and of the Environment (SIDRIA) questionnaire (10). The aim of the questionnaire was to determine the presence/absence of asthma in the child during follow-up and in the year of the study.

Skin prick test

SPTs were carried out with the following allergens (Lofarma, Milan, Italy): lactalbumin, β -lactoglobulin, casein, egg white and yolk, soy, codfish, wheat, dried fruit, *Dermatophagoides pteronissynus* (Der p), *Dermatophagoides farinae* (Der f), dog/cat dander, *Olea europea*, *Lolium perenne*, *Alternaria tenuis*, *Parietaria officinalis*, *Cupressus*, *Pinus sylvestris* according to the

methods adopted by our surgery.

Spirometry under basal conditions and after bronchodilator

The lung function test was carried out with a bell spirometer (Quark PFT-4 Cosmed) according to the procedure indicated by the American Thoracic Society (11, 12). The function test was repeated 20 mins after inhalation of 200 mcg of salbutamol. The bronchodilatation test was considered positive if there was an increase of baseline FEV_1 equal to or greater than 12% of predicted and/or an increase of FEF_{25-75} equal to or greater than 45%.

Statistical analyses

A descriptive analysis included calculating percentages, mean $\pm$ SD for demographic variables, allergens and asthmatic symptoms. *Chi*-squared test was used to compare the prevalence rates of asthma and asthma symptoms vs food and inhalant allergens. Odds ratios (OR) and C.I. 95% were calculated to evaluate the strength of association between asthma symptoms and allergens.

We evaluated the odds ratio (OR), which was chosen instead of relative risk because asthma has a prevalence that is low in the general population and the odds ratio is close to the risk ratio. Positive and negative OR values represent a co-relative positive and negative association between evaluated variables.

Differences between continuous variables were tested for significance using an unpaired *t*-test (two-tailed) or analysis of variance (ANOVA). P values $p < 0.05$ were considered statistically significant. Data were analyzed using SPSS Version 12.0 for windows (Chicago, IL, USA).

RESULTS

Of the 415 children sensitized to food allergens, 54 could not be contacted, 83 declined to participate in the study, and 104 replied only to the telephone questionnaire. The remaining 174 children completed the program (telephone questionnaire, clinical examination, repeat SPT, and spirometry). The main characteristics of these patients and the reason for SPT are reported in Table I.

Sensitization

Table II shows the SPT results in relation to symptoms and diagnosis at the first and second observation, which took place between 7 and 14 years later (mean follow-up 125 months).

Table I. Characteristics of the 174 children with a positive SPT to at least one food allergen.

	At the first observation	At the second observation
M/F (%)	84/90 (48.2)	84/90 (48.2)
Age (months) -mean (range)	7.9 (1-36)	132 (84-168)
SPT+ only to food allergens -n. (%)	65 (37.3)	2 (1.1)
SPT+ food and inhalant allergens -n. (%)	109 (62.6)	60 (34.5)
Reason for the SPT (n.): -Recurrent respiratory infections -Wheezing -Dermatitis -Failure to thrive	 59 42 31 42	- Follow up

Table II. Sensitization to food and inhalants allergens at <36 months and at 7-14 years.

Symptoms	SPT at the first observation			SPT at the second observation				
	F n (%)	F+I n (%)	p	F	F+I	I	Neg	p
Wheezing * (n = 45)	9 (20.0)	36 (80.0)	0.01	2 (4.4)	25 (55.5)	13 (28.9)	5 (11.1)	0.001
Nocturnal dry cough* (n = 60)	22 (36.7)	38 (63.3)	0.89	0 (0)	20 (33.3)	29 (48.3)	11 (18.3)	0.47
Asthma diagnosis (n = 62)	18 (29.0)	44 (71.0)	0.12	0 (0)	31 (50)	24 (38.7)	7 (11.3)	0.007
Total (n = 174)	65 (37.4)	109 (62.6)		2 (1.1%)	60 (34.5)	73 (42.0)	39 (22.4)	

*in the past 12 months

F: Single sensitization to food; F+I; Double sensitization to food and inhalants; I: Single sensitization to inhalants; Neg: Negative.

Food sensitized children presented aspecific gastrointestinal symptoms such as recurrent abdominal pain and constipation. At the first SPT, 65

children (37.4%) had a single sensitization to food (F), and 109 (62.6%) had a double sensitization to food and inhalants (F+I). At the second observation,

Table III. SPT positive for food and inhalants allergens at the first (1) and second (2) observations.

FOOD ALLERGENS		Wheezing		Dry cough		Asthma diagnosis	
		OR	(CI 95%)	OR	(CI 95%)	OR	(CI 95%)
Lactalbumin	1	3.07	1.42-6.62	0.48	0.22-1.08	1.11	0.53-2.30
	2	5.68	2.12-15.23	0.77	0.28-2.13	3.07	1.17-8.05
β -lactoglobulin	1	2.79	1.27-6.11	0.81	0.37-1.78	1.38	0.65-2.92
	2	1.77	0.74-4.26	0.70	0.28-1.70	1.40	0.61-3.22
Casein	1	1.82	0.83-3.99	0.53	0.24-1.19	0.68	0.31-1.48
	2	4.50	1.45-13.92	1.43	0.47-4.38	2.56	0.84-7.80
Egg white	1	1.10	0.53-2.27	0.58	0.30-1.13	1.28	0.66-2.48
	2	1.83	0.62-5.42	0.24	0.05-1.08	1.06	0.36-3.08
Egg yolk	1	0.56	0.26-1.18	0.59	0.30-1.16	0.85	0.44-1.64
	2	3.47	1.32-9.11	0.17	0.04-0.79	1.19	0.46-3.12
Codfish	1	0.45	0.096-2.09	0.28	0.06-1.3	0.26	0.06-1.23
	2	2.00	0.53-7.49	0.44	0.09-2.16	1.18	0.32-4.37
Soy	1	0.59	0.19-1.87	4.02	1.56-10.35	1.0	0.39-2.56
	2	1.47	0.42-5.18	0.34	0.07-1.64	1.84	0.56-6.00
INHALANTS							
<i>Der p</i> or <i>Der f</i>	1	1.14	0.55-2.39	0.96	0.50-1.90	1.11	0.57-2.19
	2	0.79	0.38-1.73	1.47	0.75-2.85	1.64	0.84-3.17
Grass	1	0.74	0.35-1.56	1.30	0.67-2.55	1.18	0.61-2.31
	2	1.92	0.91-4.06	1.95	1.59-2.24	2.03	1.04-4.00
<i>Parietaria O.</i>	1	1.50	0.52-4.30	4.48	1.57-12.73	0.86	0.30-2.43
	2	0.38	0.08-1.73	2.00	0.71-5.70	0.22	0.05-1.02
<i>Alternaria T.</i>	1	4.42	1.60-12.18	1.56	0.58-4.23	1.47	0.54-3.96
	2	1.78	0.74-4.26	1.03	0.44-2.43	2.00	0.87-4.58
Dog dander	1	1.47	0.42-5.18	4.17	1.19-14.60	1.84	0.56-6.00
	2	3.06	0.73-12.85	1.92	0.46-8.00	5.76	1.12-29.60
Cat dander	1	1.47	0.42-5.18	11.14	2.34-52.96	0.86	0.25-3.01
	2	0.94	0.28-3.12	6.86	2.09-22.50	0.55	0.17-1.80
<i>Olea Europea</i>	1	1.57	0.66-3.71	7.91	3.20-19.52	1.21	0.53-2.75
	2	1.08	0.50-2.30	2.06	1.03-4.11	1.15	0.57-2.30

In bold the risk (OR) of developing wheezing or dry cough or of being diagnosed with asthma vs allergens at the first observation.

there was a considerable decrease in the number of children sensitized to food allergens: only two children (1.1%) remained sensitive to food alone, 60 (34.5%) remained sensitive to food allergens and inhalants, and 39 (22.4%) were negative. In addition, a significant number of children [73 subjects (42%)] had positive SPT to inhalants.

As shown in Fig. 1, at the first observation the most frequent food allergens were egg white and yolk, and cow's milk, while the most frequent inhalants were grass and *dermatophagoides* (*Der p*, *Der f*). At the second observation, the most frequent food allergens were always egg and milk and the most frequent inhalants were grass and *dermatophagoides* (*Der p*, *Der f*); *Olea europea* was also frequent (33%).

As shown in Fig. 2, among children with single sensitization to food at the first observation, half lost

sensitization at the second observation and hence were not true atopic (Neg), 10% of children retained sensitization to food and developed sensitization to inhalants (F+I), and 40% no longer showed sensitization to food and developed sensitization to inhalants (I). In the group with double sensitization (F+I) at the first observation, 50% remained positive for food and inhalants (F+I), more than 40% no longer presented sensitization to food (I), and a small percentage became totally negative (Neg). The sensitization profiles differed significantly between the group with a history of single sensitization (F) and the group with a history of double sensitization (F+I).

Asthma symptoms

Table II shows the symptoms and the diagnosis

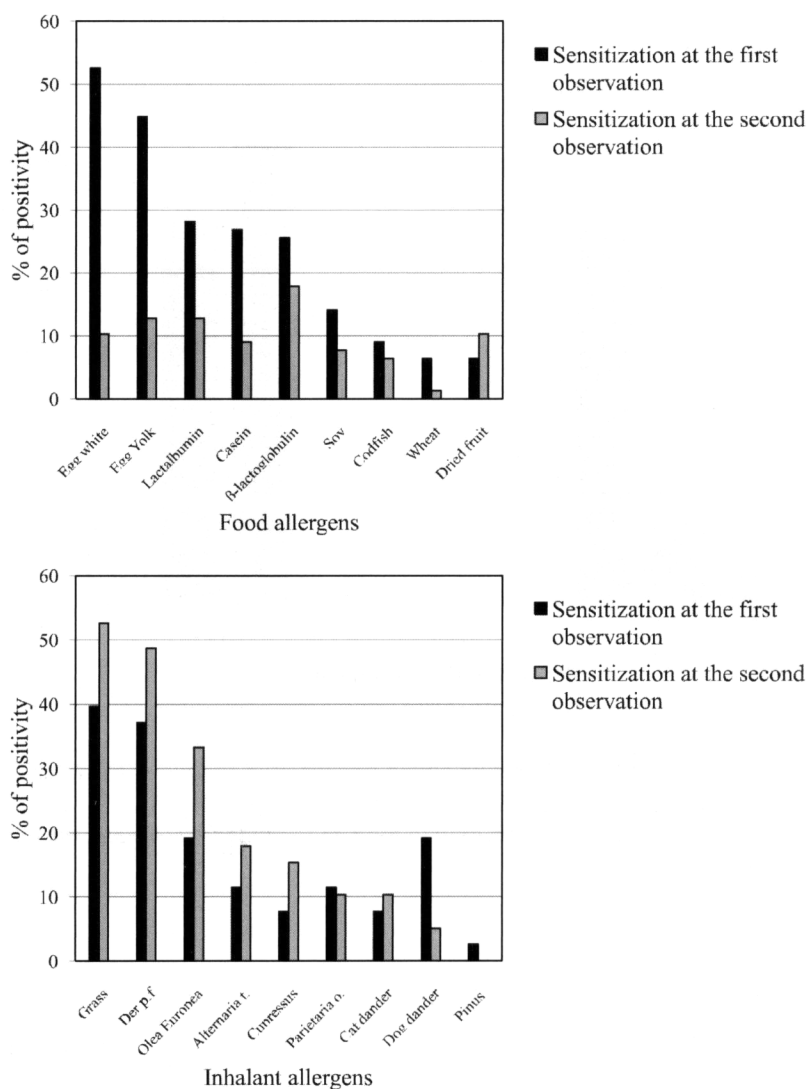


Fig. 1. Prevalence (%) of sensitization to specific food and inhalant allergens at the first and second observation.

of asthma of the children studied based on the replies to the questionnaire, the clinical history and/or clinical examination between 7 and 14 years after the first SPT. Over one-third of children reported a diagnosis of asthma (62/174) and had nighttime dry cough (60/174); almost a quarter reported wheezing (45/174). Moreover, 87 children (50%) had been treated with bronchodilators and 85 (48.8%) had been referred to emergency due to asthma during the previous year (data not shown). Sensitization to inhalant allergens at < 36 months (SPT at the first observation; $p=0.01$) and sensitization to food and inhalant allergens at the second observation

($p=0.001$) were significantly more frequent in children with reported wheezing than in the entire study population. A diagnosis of asthma was not correlated with early sensitization to inhalants, but it was correlated, at an almost significant level ($p=0.007$), with double sensitization to F+I at the second SPT.

Table III shows the allergens found to be positive in our patients at the first and second observations in relation to symptoms and diagnosis of asthma. The risk of wheezing was increased only with milk sensitization (lactalbumin and β -lactoglobulin, OR 3.07 and 2.79, respectively), and in the presence

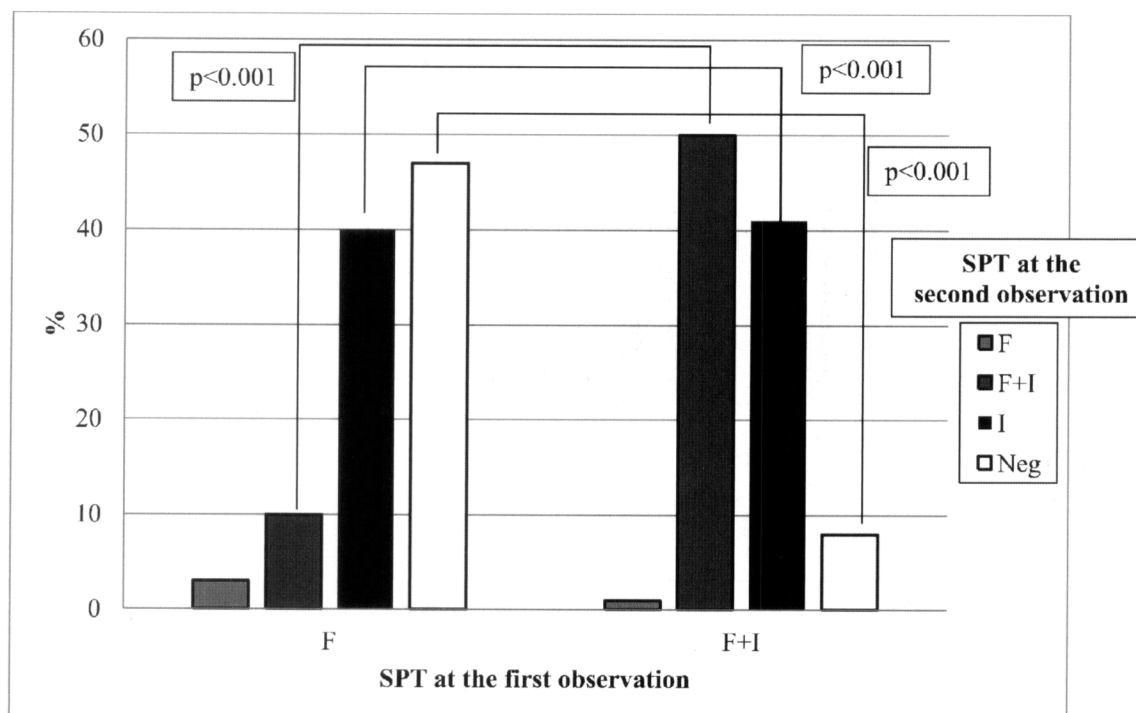


Fig. 2. Sensitization at 7–14 years in 65 children with single sensitization to food (F), and in 109 children with double sensitization to food and inhalants allergens (F+I) at <36 months of age.

F: Single sensitization to food; F+I: Double sensitization to food and inhalants; I: Single sensitization to inhalants; Neg: Negative.

of sensitization to *Alternaria tenuis* (OR 4.42). Sensitization to cat epithelium at the first observation increased the risk of dry cough by 11.14-fold, whereas sensitization to *Olea europea* by 7.91, dog dander by 4.17-fold and *Parietaria officinalis* by 4.48-fold and soy (OR 4.02).

Spirometry before and after bronchodilation

FEV₁ and MEF₅₀ were significantly lower in school age children and in adolescents who had double sensitization to F+I at < 36 months of age than in the group with single sensitization to F (Fig. 3). This result is in line with the results of spirometry testing after bronchodilatation: most (80%) of the 22 children positive to the bronchial reversibility test at the second observation had double sensitization (F+I) at <36 months of age ($p=0.009$) (data not shown). During school age and adolescence, the mean spirometry values of FEV₁, MEF₅₀ and PEF were lower, albeit not significantly so, in the group with double sensitization than in any other group

(Fig. 4).

DISCUSSION

This is the first study conducted in a cohort of children selected for the presence of sensitization to food at <36 months of age, regardless of the familiarity for atopy and the presence of symptoms, with the aim of evaluating the prognostic role of food sensitization for the development of other sensitizations and asthma after 7–14 years. Three findings emerge from this study: 1) already in the early years of life, food sensitization is frequently associated with inhalant sensitization and the trend of sensitivity variations differs between children affected by food allergy alone and children affected by co-sensitization; 2) children with single sensitization to food at <36 months of age have a modest risk of developing asthma after 10 years (mean) and the presence of double sensitization to food and inhalant allergens significantly increases

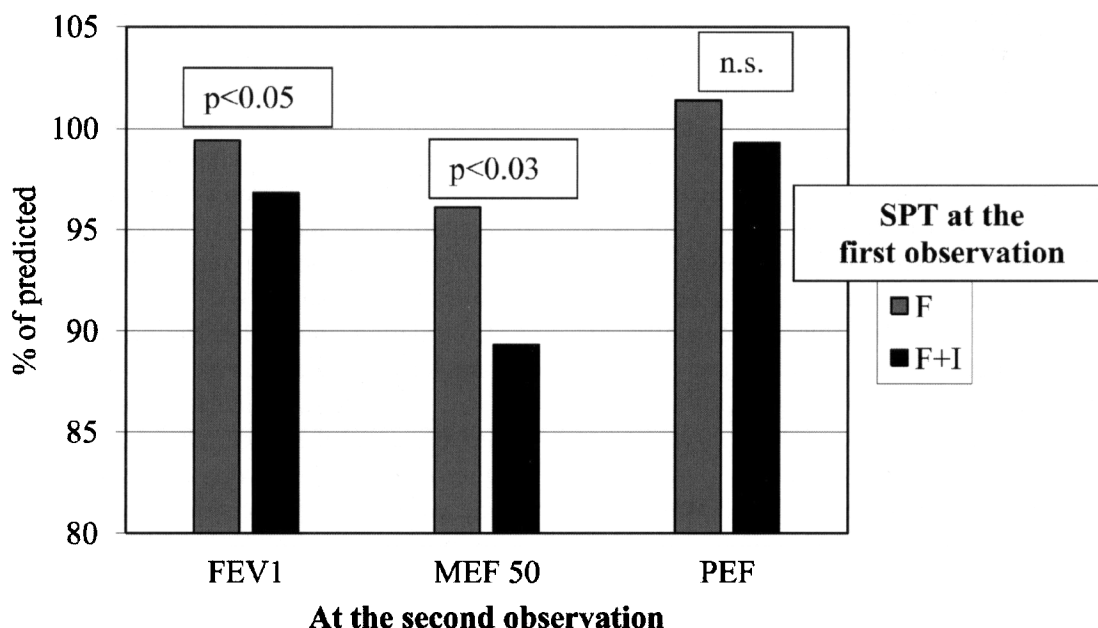


Fig. 3. Mean FEV_1 , MEF_{50} and PEF values in children aged between 7 and 14 years with single sensitization (F) or with double sensitization (F+I) at < 36 months of age.

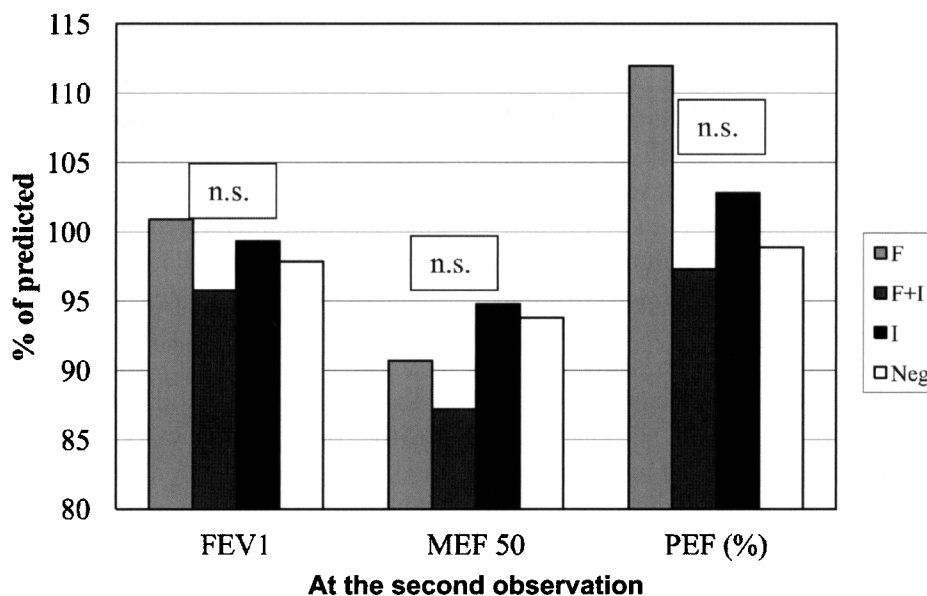


Fig. 4. Mean FEV_1 , MEF_{50} and PEF values in relation to sensitization at the second observation (7-14 years).

this risk; 3) the persistence of sensitization to food allergens at school age is associated with more severe asthma.

Various prospective studies conducted on the general population or on a population selected based on risk factors have demonstrated that

sensitization to food allergens is a precursor of sensitization to inhalants and to the development of asthma (13-15). Therefore, it is important to diagnose allergies in early life, particularly food allergies, since sensitization to food allergens is considered a prognostic factor for the development

of other sensitizations and of asthma. Holt et al. (16) demonstrated that sensitization to ubiquitous antigens is a dynamic phenomenon that involves different levels of oral and inhalant tolerance. The sensitization, in particular to food antigens, may be transitory, especially at concentrations below 0.20 or 0.34 KU/L. Thus, sensitization to inhalants is a risk factor for asthma, whereas sensitization to food allergens is a less reliable predictor. The results of our study are consistent with this concept: 50% of children with single sensitization to food at <36 months of age were negative to allergen tests between 7 and 14 years later; thus these children were not true atopic. Differently, only a small percentage (7%) of children with double sensitization to food and inhalant allergens lost sensitization and were not atopic. The difference between the two groups is statistically significant. Therefore, positivity of SPT to food allergens in early life is not a marker of an atopic condition and cannot, by itself, be considered a marker of the risk of developing asthma. Without other important risk factors (symptoms, positive SPT to inhalant allergens and familiarity), children with SPT positivity for food allergens should not be subject to specific preventive measures.

In a prospective study of 1,314 children observed from birth to the age of 13 years, Illi et al. (17) observed a strong relationship between sensitization to perennial allergens (*dermatophagoides*, cat and dog) in the first three years of life and asthma in school age; the relation was even stronger if sensitization to perennial allergens was associated with IgE for food allergens. Priftis et al. (18), in a study of 69 children with food allergy, found that sensitization to perennial allergens and to pollens (but not to animal dander) is highly predictive of developing asthma at school age (OR 12.5 and 7.2, respectively).

The cohort of children enrolled in our study who had a positive SPT to food at <36 months of age had a prevalence of asthma after 7–14 years double that of the general population. Over 25% of children reported wheezing and almost one-third was diagnosed with asthma. These frequencies are significantly higher ($p < 0.001$) than those reported in the SIDRIA study which evaluated the pediatric population of Southern Italy (9.0–10.8% of wheezing, and 11.1–12.7% for asthma) (19). In our study, the prevalence increased significantly in patients with

double sensitization to food and inhalant allergens at <36 months of age. Almost half developed asthma within 10 years and spirometry values in this group were significantly lower (mean MEF_{50} and FEV_1) than in children with single sensitization to food. In addition, 80% of children with a positive bronchial reversibility test and 80% of patients with recurrent wheezing had a double sensitization (F+I) at <36 months of age ($p = 0.009$).

Considering single allergens, early sensitization to cat dander increased the risk of dry cough at school age by 11.14-fold, whereas sensitization to olea pollen increased the risk by 8-fold and sensitization to *Alternaria tenuis* and dog dander by about 4-fold. In the case of food allergens, cow's milk and soy were positively correlated with the development of asthma; no significant correlation was found for egg. The different role of specific food sensitization with respect to other studies (20–22) may depend on different dietary habits between countries; for example, the minor role of egg sensitization in our study with respect to other studies may depend on the late introduction of egg in the Mediterranean diet.

Finally, another interesting finding of our study is the relationship between symptoms of asthma and the persistence of positivity to food allergens. Wheezing was significantly more frequent in children with double sensitization to food and inhalants than in children positive to inhalants alone (55% vs 28%; $p < 0.001$). This significant difference suggests that the persistence of sensitization to food allergies may be an aggravating factor in asthma. Also MEF_{50} and FEV_1 were lower in the group with double sensitization (F+I) than in the group positive only for inhalants in whom positivity for food allergy disappeared. Our results are in line with studies conducted in the USA and in China that showed a high prevalence of sensitization to food allergens among Asiatic children that, when present, was associated with more severe asthma (23, 24).

In conclusion, our study highlights the importance of conducting Skin Prick Test with a wide range of inhalants and food allergens in early life. In preschool infants, sensitization to inhalants and food allergens is highly predictive of the development of asthma and in school age/adolescence it is related to more severe asthma. In early life, the lung is not fully developed, and any inflammatory episode (infections

or allergies) at that age may contribute to developing irreversible functional limitations (25). Also in our experience, the subjects most at risk are the ones that, also without important clinical manifestations, had sensitization to inhalants and food allergens. Secondary and tertiary preventive measures should be considered for these children.

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