

ORIGINAL ARTICLE Epidemiology of Allergic Disease

EpidemAAITO: Features of food allergy in Italian adults attending allergy clinics: a multi-centre study

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Summary

Background Studies of the prevalence of different types of food allergy in adults are lacking. **Objective** To define the prevalence of IgE-mediated food allergies in Italian adults attending allergy clinics and to assess possible differences associated with geographical position and/or dietary habits.

Methods Seventeen allergy outpatient clinics scattered throughout Italy participated to a multi-centre study in 2007. The number of atopic subjects and of food allergic patients along with clinical features were recorded by pre-defined criteria. Patients with unequivocal history of food allergy confirmed by positive skin prick test were included as cases.

Results Twenty five thousand six hundred and one subjects were screened; 12 739 (50%) were atopic, and 1079 (8.5%) had IgE-mediated food allergy. Sixty four percent of patients were females. Overall, the most frequent food allergy was the pollen–food allergy syndrome (55%), which was associated with oral allergy syndrome in 95% of cases and whose frequency decreased southbound. Forty-five percent of patients had a type 1 food allergy, in most cases (72%) caused by fruits and vegetables, and generally associated with a history of systemic symptoms. Type 1 food allergies represented 96% of food allergies in the South. Lipid transfer protein (LTP) accounted for 60% of sensitizations and caused most primary food allergies in all areas.

Conclusion Plant-derived foods cause most food allergies in Italian adults. The pollen–food allergy syndrome is the most frequent type of food allergy followed by allergy to LTP whose frequency increases southbound. The pattern of allergy to certain foods is clearly influenced by specific geographic features such as pollen exposure and dietary habits.

Keywords adults, food allergens, food allergy, Italy

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Introduction

The prevalence of food allergy in adults is still ill defined. In the public perception there is certainly an overestimate of this disease as, in some surveys, up to 25% of interviewed subjects believed that they or one of their relatives

had a food allergy [1–3]. Figures coming from some clinical studies estimate that food allergy affects almost 4% of the adult population in the United States [4], and about 2–4% of European adults [5, 6] seem more realistic. Recent systematic reviews and meta-analyses found a marked heterogeneity in the prevalence of food allergy as

a possible result of differences in study design or methodologies, as well as discrepancies between perception and sensitization [7, 8]. Studies looking at the prevalence of different types of food allergy are lacking.

Italy encompasses many different climate zones ranging from typical Mediterranean to markedly Continental, and from hilly to Alpine environments. This might exert a profound influence on the clinical expression of both respiratory and food allergy. Further, Italy is one of the most renowned countries in the world for food. Such richness stems from the presence on its territory of a

wealth of different populations and traditions that are the heritage of a long and complex history; these variables might also account for differences in the prevalence and type of food allergy. During 2006 several clinical allergy centres in Italy, most of whom adhering to the Associazione Allergologi Immunologi Territoriali e Ospedalieri (AAITO) association, gave birth to the EpidemAAITO consortium, a multi-centre study group whose aim was to define the prevalence of food allergy in Italian adults attending allergy clinics, to detect the prevalence of allergy to different kinds of food, and to assess whether



Fig. 1. Distribution of participating centres.

the environment (geographical position, traditions, habits, behaviours) plays a role in determining the different kinds of food allergy. The present paper summarizes the results of this survey.

Patients and methods

Study design

The study was carried out in 17 allergy outpatient clinics scattered throughout Italy (Fig. 1). Because the large majority of participating centres were devoted to adult patients, the few subjects <12 years old visited in some clinics were excluded from the analysis of general results and analysed separately. In every participating centre the total number of subjects attending for a first visit from January 1 to December 31, 2007, irrespective of the reason for consultation, the number of those found to be atopic (defined as having IgE to common antigens as well as respiratory and/or skin disorders most probably associated with IgE-mediated allergy), the number of patients finally diagnosed as having food allergy, and the clinical features of food allergy (including latency between ingestion and onset of symptoms, and features of allergic reactions) were recorded, as well as the results of skin prick test (SPT) and of specific IgE measurements.

As one of the aims of the study was to detect possible differences in the features of food allergy between different geographic areas of the country, results coming from the northern, central, and southern part of the country were analysed both as a whole and separately.

Diagnosis of food allergy and exclusion criteria

At each centre, all patients underwent a careful interview by allergy specialist doctors aiming to detect clinical histories possibly associated with IgE-mediated food allergy. A history of oral allergy syndrome (OAS, defined as local itching of lips, tongue, palate, throat, and/or ears and nose, and/or angioedema of the same areas) [9], or of acute systemic symptoms such as generalized urticaria with or without angioedema [10], and/or anaphylaxis [11] occurring some minutes up to 2 h after the ingestion of the offending food(s) was considered as possibly associated with a food allergy. Only patients with unequivocal food allergy diagnosed on the basis of both clear-cut history and positive SPT and/or circulating specific IgE were finally included as cases. Patients whose clinical history, even if suggestive, was not confirmed by either *in vivo* or *in vitro* diagnostic tests were excluded from the analysis, as were patients showing positive SPT and/or elevated food-specific IgE in the absence of any reported adverse reactions to a particular food. Single food positivities (either *in vivo* and/or *in vitro*) were considered as relevant

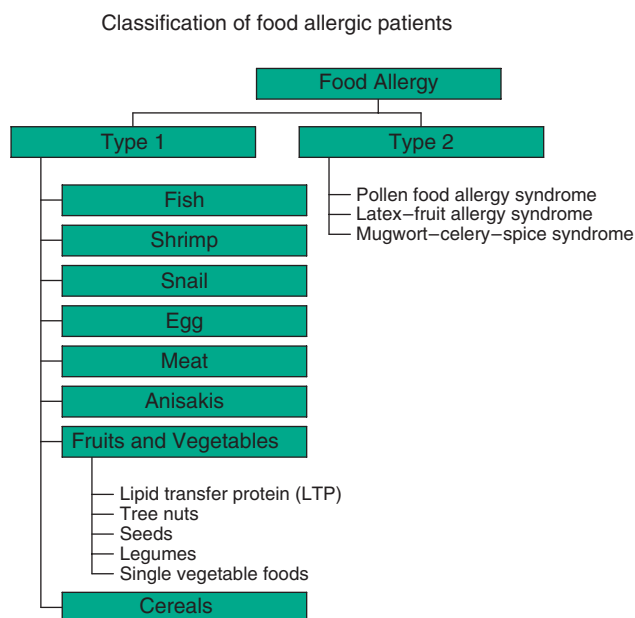


Fig. 2. Classification of food allergic patients.

in patients reporting reactions following the ingestion of several foodstuffs provided that the positive food had been ingested just before the reaction. In patients reporting a clinical reaction to a certain food (positive on SPT) but tolerance afterwards, specialist doctors considered the possible role of exercise or other factors. Patients with a history of clinical reactivity to several foods and positive on SPT with several foods were considered as sensitized to one single cross-reacting allergen [e.g. lipid transfer protein (LTP), seed storage protein, tropomyosin] unless sensitization to distinct allergens was demonstrated by SPT.

Classification of food-allergic patients

The general classification of patients with food allergy adopted in this study is shown in Fig. 2.

In view of the extremely large variety of fruits and vegetables possibly involved in allergic reactions, in order to uniform the recording of clinical data by participating centres and to make the analysis of data easier, patients allergic to these foods were grouped into two general categories:

1. *Type 1 (primary) food allergy*. This category included the following subgroups of patients with primary sensitization to plant-derived foods.
 - (a) *Lipid transfer protein (LTP)*. This group included all patients allergic to LTP irrespective of the offending food(s). LTP hypersensitivity was diagnosed in the presence of a positive SPT with commercial peach extract (ALK-Abello, Madrid, Spain). Previous studies showed that this peach extract virtually contains

only LTP at a concentration of 30 µg/mL, and that a positive SPT with this extract may be used as a clinical marker of sensitization to this protein [12, 13] with only minor exceptions [14]. Offending foods for LTP-allergic patients included all *Rosaceae*, tree nuts, maize, rice, beer, and grapes [13].

- (b) *Tree nuts*. This group included all patients allergic to tree nuts (including hazelnut, walnut, Brazil nut, pine nut, almond, pistachio, chestnut, peanut, and cashew) but not to LTP. Diagnosis was based on a positive SPT with commercial extract (when available) or with fresh offending nut in the absence of skin reactivity to both commercial peach extract and birch pollen extract. Previous studies showed that commercial walnut extract contains only stable allergens and can therefore be used as a means to rule out sensitization to labile allergens homologous to pollen proteins [13].
 - (c) *Seeds*. Patients allergic to one or more seeds (such as sesame, sunflower, poppy, or other seeds) but not sensitized to tree nuts were included in this group.
 - (d) *Legumes*. This group included subjects allergic to one or more legumes including peanut, bean, string bean, pea, chickpea, lupine, and lentil.
 - (e) *Kiwi*. this category included subjects with single kiwi allergy.
 - (f) *Individuals with allergy to one single vegetable food*. This category included all remaining foods that caused isolated allergic reactions in single individuals.
2. *Type 2 (secondary) food allergy*. This category included patients with plant-food allergy caused by cross-reactivity to a primary sensitizer, and included the following subgroups:
- (a) *Pollen-food allergy syndrome*. This subgroup included patients either mono-sensitized to birch pollen (Bet v 1) or showing sensitization to all seasonal airborne allergens (and, hence possibly sensitized to profilin). Because both Bet v 1-homologous proteins and profilin are heat- and pepsin-labile allergens, a pollen-food allergy syndrome was diagnosed if patients reported good tolerance of the offending foods if these were cooked or otherwise processed, and/or in the presence of positive SPT with fresh offending foods but negative SPT with commercial extract of the same foods [15].
 - (b) *Latex-fruit allergy syndrome*. Patients primarily sensitized to natural rubber latex with a history of allergy to foods known as being potentially cross-reacting, such as chestnut, avocado, kiwi, papaya, and banana.
 - (c) *Mugwort-celery-spice syndrome*. Patients primarily sensitized to mugwort with a history of allergy to

potentially cross-reacting vegetable such as celery, fennel, anise, bell pepper, and other spices [16].

Patients with clinical allergy to cereals (wheat, barley, maize, rice, rye) not sensitized to LTP, as shown by negative SPT with commercial peach extract, were classified as a specific group with type 1 food allergy (group 'cereals').

Patients sensitized to non-plant foods were grouped by allergen. For instance, patients allergic to shrimp, squid, octopus or shellfish were grouped together as possibly sensitized to tropomyosin (group 'shrimp'); similarly, those allergic to different fishes were grouped, as were those allergic to different meats, and so on.

Patients with multiple allergies

Patients co-sensitized to more than one food allergen were considered as single cases when analysing the prevalence of food allergy but as multiple cases in analysing the prevalence of allergy to single foods. As a consequence, the sum of patients allergic to individual allergens or categories exceeds the number of food-allergic individuals.

In vivo and in vitro tests

Allergy to airborne allergens was routinely detected by SPT with commercial extracts of different producers (Allergopharma, ALK-Abello, Lofarma, Stallergenes, etc.) based on each centre preference and experience. Allergens tested in all centres included pollens (grass, mugwort, ragweed, pellitory, plantain, birch, olive, and cypress), moulds (*Alternaria*, *Aspergillus*, *Cladosporium*), house dust mites (*Dermatophagoides pteronissynus*; *Dermatophagoides farinae*), and animals' dander (cat and dog). Each centre was left free to test further allergens (e.g. local causes of seasonal airborne allergy, different dander in specific cases, etc.).

Hypersensitivity to food allergens was detected by SPT with commercial food extracts (ALK-Abello, Spain). The series tested in all patients with suspect food allergy in all participating centres included egg white, egg yolk, cow's milk, shrimp, codfish, wheat, maize, soybean, peanut, sunflower seed, bean, walnut, hazelnut, tomato, carrot, orange, peach, celery, almond, sesame seed, kiwi, and banana (1:20 w/v in all cases, except peach extract containing 30 µg/mL LTP).

In the case of suspect allergy to foods not included into this series, commercial extracts (where available) and/or fresh foods were used for skin testing. Fresh foods were tested by the prick-prick technique. All SPT were carried out on the volar side of the forearm using disposable prick lancets (ALK-Abello). SPT with saline and histamine 10 mg/mL were used as negative and positive control,

respectively. Readings were taken at 15 min; weals with a mean diameter of 3 mm or more greater than the negative control were considered positive [17].

In several centres hypersensitivity was confirmed by specific IgE measurements (Uni-CAP, Phadia, Uppsala, Sweden). In these cases specific IgE levels ≥ 0.35 kU/L were regarded as positive.

In view of the observational nature of the study, of the fear of possibly severe adverse reactions, and of the fact that some participating centres lacked the necessary facilities and experience, diagnosis of food allergy was not confirmed by DBPCFC. In the presence of doubt histories or of marked discrepancies between clinical histories and *in vivo* or *in vitro* diagnostic tests single centres carried out open challenges with suspect offending foods.

Statistics

Proportions were compared by χ^2 test with Yates' correction. Probability levels $< 5\%$ were considered statistically significant.

Results

General findings

During 2007, a total of 25 601 subjects underwent allergy screening in the 17 participating centres; 12 739 (50%) of them were diagnosed as being atopic on the basis of hypersensitivity to respiratory and/or food allergens. A total of 1079 patients (8.5% of atopic subjects) were finally diagnosed as having IgE-mediated food allergy. The food

Table 1. Prevalence of different types of food allergy among 1079 food allergic patients and clinical severity of allergic reactions

	No. (%)	No. (%)	Systemic symptoms (%)
Type 1 food allergy	485 (45%)		
Fruits and vegetables		351 (72%)	228 (65%)
			See also Table 2
Cereals		12 (2%)	10 (83%)
Fish		21 (4%)	17 (81%)
Shrimp		64 (13%)	58 (90%)
Milk		15 (3%)	11 (73%)
Egg		17 (3%)	14 (82%)
Meat		4 ($< 1\%$)	3 (75%)
Snail		2 ($< 1\%$)	2 (100%)
Anisakis		3 ($< 1\%$)	3 (100%)
Type 2 food allergy	617 (57%)		
Pollen-food allergy syndrome		598 (97%)	27 (5%)
Latex-fruit allergy syndrome		16 (3%)	9 (56%)
Mugwort-celery-spice syndrome		3 ($< 1\%$)	3 (100%)

Table 2. Frequency and clinical relevance of sensitization to different fruits and vegetables among 351 adult patients with type 1 food allergy

	No. (%)	Systemic symptoms (%)
LTP	210 (60%)	128 (61%)
Tree nuts	75 (21%)	62 (83%)
Hazelnut	38	
Walnut	27	
Pine nut	12	
Peanut	11	
Almond	8	
Pistachio	3	
Chestnut	2	
Brazil nut	1	
Coconut	1	
Cashew	1	
Seeds	5 (1%)	5 (100%)
Sesame	4	
Sunflower	1	
Legumes	18 (5%)	14 (77%)
Peanut	9	
Soybean	8	
String bean	2	
Pea	2	
Lentil	2	
Lupine	1	
Lentil	2	
Bean	1	
Chick pea	1	
Kiwi	23 (7%)	7 (30%)
Other foods		
Buckwheat	4 (1%)	3 (75%)
Pineapple	3 (1%)	2 (67%)
Eggplant	2 ($< 1\%$)	0 (0%)
Spinach	2 ($< 1\%$)	2 (100%)
Tomato	2 ($< 1\%$)	1 (50%)
Watermelon	2 ($< 1\%$)	0 (0%)
Avocado	1 ($< 1\%$)	1 (100%)
Fig	1 ($< 1\%$)	1 (100%)
Mango	1 ($< 1\%$)	1 (100%)
Boletus mushroom	1 ($< 1\%$)	0 (0%)
Fennel	1 ($< 1\%$)	0 (0%)
Garlic	1 ($< 1\%$)	0 (0%)
Onion	1 ($< 1\%$)	0 (0%)
Cherry	1 ($< 1\%$)	1 (100%)

Because some individuals showed multiple sensitizations, the total number of sensitizations exceeds that of patients.

LTP, lipid transfer protein.

allergic group showed a mean age of 31 years (range 12–79 years) and a clear prevalence of female patients (64%; M/F 384/695) with no difference between the different centres (data not shown).

Different types of food allergy

The overall prevalence and the clinical features of the different types of food allergy are shown in Table 1. Four

hundred and eighty-five patients (45%) were diagnosed as having a type 1 food allergy. Fruits and vegetables represented by far the most frequent cause of this type of food allergy (351/485; 72%). Among the remaining allergen sources, shrimp allergy was the most frequent (13%); allergy to fish (4%), milk (3%), egg (3%), cereals (2%), meat, snail, and *Anisakis* (<1%) were recorded in few cases. Notably, the large majority of patients with primary food allergy had a clinical history of systemic symptoms following exposure to offending foods (Tables 1 and 2); the only exception was kiwi, which induced local symptoms in a majority of allergic patients.

Type 2 food allergy was diagnosed in 617 (57%) cases. The pollen-food allergy syndrome represented the most frequent type 2 food allergy (97% of cases) and also the most frequent food allergy in general (55% of all patients); both the latex-fruit allergy syndrome and the mugwort-celery-spice syndrome were very uncommon. In patients with latex-food allergy syndrome offending foods included banana ($n = 4$) avocado (3), chestnut (3), kiwi (3), bell pepper (2), and peach (1). Among patients with type 2 food allergy, the large majority of those with pollen-food allergy syndrome had only mild local symptoms and reported systemic symptoms only in a very little proportion of cases (5%), whereas both the latex-fruit allergy syndrome and the mugwort-celery-spice syndrome were frequently associated with systemic symptoms (Table 1).

Eleven patients were diagnosed as having food-dependent exercise-induced anaphylaxis. In these subjects offending foods included peach ($n = 4$), almond and lettuce in six patients sensitized to LTP, pistachio ($n = 2$), squid, kiwi, and wheat (one case each). No centre reported alcoholic drinks as triggers, although five LTP-allergic

patients experienced at least one episode of food allergy after drinking alcoholics containing this allergen (beer and wine in two and three cases, respectively).

Type 1 food allergy to fruits and vegetables

The frequency of sensitization to the various allergen sources among 351 patients with type 1 allergy to fruits and vegetables is shown in Table 2. Sensitization to LTP alone accounted for 60% of sensitizations, followed by far by tree nuts (21%), kiwi (7%), legumes (5%), seeds, buckwheat, and pineapple (1%). Allergies to all other fruits and vegetables were uncommonly seen (<1%).

In keeping with the wide cross-reactivity of this allergen, the 210 LTP-allergic patients reported a large number of offending foods, peach being by far the most frequent one ($n = 178$), followed by apple (74), walnut (43), hazelnut (42), cherry (38), and peanut (22). Offending foods included also other *Rosaceae* (apricot, plum, pear, almond, strawberry), cereals (maize, beer, rice), kiwi, grapes, lettuce, cauliflower, broccoli, and many others foods in a little proportion of subjects.

Similarly, patients with tree nuts allergy reported a variety of offending nuts (Table 2), sometimes isolated, more frequently in different combinations, and in some cases associated with plant foods from other groups (peanut, soybean, seeds) suggesting that tree nut allergens show variable cross-reactivity patterns with legumes and seeds.

The co-existence of different type 1 food allergies was rare in adult patients, limited to 6/485 (1%) cases: nuts+*Amarillidaceae* ($n = 1$), milk+legumes ($n = 1$), nuts+milk+egg ($n = 1$), nuts+cereals ($n = 1$), peanut+egg

Table 3. Overall prevalence of food allergy and frequency of the main types of food allergy in the three geographical areas of Italy

Food allergy type/allergy source	Northern Italy (A)	Central Italy (B)	Southern Italy (C)	P		
				A vs. B	B vs. C	A vs. C
Subjects visited	19 144	2513	3944			
No. of atopic subjects	9738 (51%)	1282 (51%)	1719 (43%)			
Individuals with food allergy	886 (9%)	98 (8%)	95 (6%)	NS	<0.05	<0.001
Type 1 food allergy	323 (36%)	71 (72%)	91 (96%)			
Fruits and vegetables	222 (69%)	48 (68%)	80 (88%)	NS	<0.05	<0.01
Cereals	9 (3%)	3 (4%)	0 (0%)	NS	NS	NS
Fish	17 (5%)	3 (4%)	1 (1%)	NS	NS	NS
Shrimp	51 (16%)	9 (13%)	4 (4%)	NS	NS	<0.01
Snail	1 (<1%)	1 (1%)	0 (0%)	NS	NS	NS
Milk	13 (4%)	0 (0%)	2 (2%)	NS	NS	NS
Egg	11 (3%)	0 (0%)	4 (4%)	NS	NS	NS
Meat	3 (<1%)	0 (0%)	0 (0%)	NS	NS	NS
<i>Anisakis</i>	2 (<1%)	0 (0%)	0 (0%)	NS	NS	NS
Type 2 food allergy						
Pollen-food allergy syndrome	568 (64%)	24 (24%)	6 (6%)	<0.001	<0.01	<0.001
Latex-fruit allergy syndrome	13 (1%)	3 (3%)	0 (0%)	NS	NS	NS
Mugwort-celery-spice syndrome	2 (<1%)	0 (0%)	1 (1%)	NS	NS	NS
Prevalence of birch pollen sensitization	51% (452/886)	33% (32/98)	2% (2/95)	<0.001	<0.001	<0.001

($n = 1$), and fish+egg+fruits ($n = 1$). In these cases milk and egg allergy lasted since childhood. By contrast the co-existence of types 2 and 1 plant-food allergy (particularly to LTP) was more frequently recorded (Table 1).

Geographic differences in sensitization patterns

The overall prevalence of all food allergies in patients attending the allergy clinics as well as the prevalence of the main types of food allergy in the three geographical regions of Italy is shown in Table 3. Food allergy was more frequently found among patients attending the allergy clinics in northern and central Italy than in southern Italy ($P < 0.001$ and $P < 0.05$, respectively), but such difference was totally due to the pollen-food allergy syndrome whose frequency progressively decreased southbound. By contrast, both latex-fruit allergy syndrome and mugwort-celery-spice syndrome showed the same, low prevalence in all three macro-regions. The prevalence of birch pollen sensitization in patients from the three regions clearly paralleled to prevalence of pollen-food allergy syndrome (Table 3). Type 1 food allergies represented 96% of all food allergies in the southern part of the country vs. 36% in the north ($P < 0.001$). Fruits and vegetables caused most type 1 food allergies in all three regions although they were significantly more frequent as offending food in southern Italy (80/91, 88% of all allergies) than in central and northern Italy ($P < 0.05$ and $P < 0.001$, respectively). In contrast, shrimp allergy was more frequently detected in the northern part of the country. The three macro-regions did not differ in the prevalence of allergy to fish, milk, egg, snail, meat, cereals, and Anisakis.

The main type 1 plant-food allergies in the three areas are further analysed in Table 4. LTP was by far the most frequent allergen in all three areas, although it caused $> \frac{3}{4}$ of type 1 plant-food allergies in the south vs. about $\frac{1}{2}$ in the remaining areas ($P < 0.05$ and $P < 0.001$ vs. central and northern Italy, respectively). No statistically significant difference in the prevalence of allergy to tree nuts, kiwi, legumes, and buckwheat was detected between the

different areas, although allergy to pine nut or buckwheat occurred more frequently in the north.

Finally, also among the 34 patients < 12 years old visited in some clinical centres those living in southern Italy showed a significantly higher prevalence of allergy to LTP than those living in the north (9/12 vs. 1/22; $P < 0.001$), whereas tree nut allergy was more frequent in the north although the difference did not reach statistical significance (7/22 vs. 0/12; $P = \text{NS}$).

Discussion

The present study is probably the first one that attempts to assess the frequency and features of food allergy in Italy. More than 8% of patients diagnosed as being atopic at 17 allergy offices scattered throughout the Italian territory were found to have food allergy. Although this was not a population-based epidemiological survey, and accurate estimates of the prevalence of food allergy cannot be carried out using a biased population such as the one seen in allergy clinics, if one assumes a prevalence of allergic diseases of about 20% in the general Italian population (similar to other developed countries) it turns out that about 2% of Italian adults (corresponding to about 10% of atopic individuals) are likely to have some kind of food allergy, which is in keeping with existing estimates of food allergy in 2–4% European adults [5, 6].

In this study, food allergy was more commonly observed in female than in male patients; this finding confirms similar observations in other studies [6]. The majority of our patients with food allergy had a pollen-food allergy syndrome, suggesting the relevance of the increased prevalence of airborne allergies in causing an overall increase in the prevalence of food allergies in areas where certain pollen species play a relevant role; in fact, most of these subjects lived in Northern Italy, where allergy to birch pollen is rather common (Table 3). As expected, the large majority of patients with pollen-food allergy syndrome reported mild local symptoms (OAS) [9] due to the pepsin-sensitivity of allergenic proteins homologous to the major pollen allergen, Bet v 1, in fruits and vegetables. It is also likely that a proportion of patients with pollen-food allergy syndrome were sensitized to profilin, another labile plant-food pan-allergen whose clinical relevance has been recently demonstrated [18]. The other type 2 plant-food allergies, namely the latex-food allergy syndrome and the mugwort-celery-spice syndrome, were diagnosed in a small minority of patients. In our population the importance of the latex-food allergy syndrome was much more limited than in another survey carried out in France in 2000 [6], possibly as a result of the declining prevalence of latex allergy in the general population, particularly healthcare workers, following the implementation of preventive measures [19]. The low prevalence of the so-called mugwort-celery-spice

Table 4. Frequency of type 1 allergy to the main fruits and vegetables in the three geographical areas of Italy

	A ($n = 222$)	B ($n = 48$)	C ($n = 80$)	P		
				A vs. B	A vs. C	B vs. C
LTP	121 (55%)	27 (56%)	62 (78%)	NS	< 0.001	< 0.05
Tree nuts	50 (23%)	13 (27%)	12 (15%)	NS	NS	NS
(total)						
(Pine nut only)	11 (5%)	1 (2%)	0	NS	NS	NS
Legumes	12 (5%)	3 (6%)	3 (4%)	NS	NS	NS
Kiwi	16 (7%)	3 (6%)	4 (5%)	NS	NS	NS
Buckwheat	4 (2%)	0	0	NS	NS	NS

A: northern Italy; B: central Italy; C: southern Italy.

syndrome in our population is not surprising, as this type of food allergy has been mostly reported in Switzerland probably as a result of a significant prevalence of primary mugwort pollen allergy (rare in Italy) and of particular dietary habits such as the use of celery root (that is not consumed in Italy) [16, 20].

Although allergen extracts from different producers were employed to detect sensitization to airborne allergens, in view of the good standardization grade reached by current commercial extracts it seems unlikely that this may have somehow biased the results.

Type 1 food allergies were associated with a clinical history of systemic symptoms in the large majority of cases, suggesting that most allergens involved in these reactions are pepsin stable and heat stable. The only exception to this rule was kiwi allergy that was associated with local (though in some cases unusually severe) symptoms in 70% allergic patients. Plant-derived foods were by far the commonest cause of sensitization in the general population with type 1 food allergy, causing about $\frac{3}{4}$ of cases. Interestingly, the LTP alone caused 60% of all primary plant-food allergies, confirming the extreme relevance of this allergen in Mediterranean countries. Tree nuts represented the second cause of primary plant-food allergy, suggesting their clinical importance as food allergens also in Italian adults [21]. Peanut allergy was rare (only 6% of primary plant-food allergies) as in other European surveys [6] but, interestingly, occurred in several distinct contexts: isolated peanut allergy, variably associated with allergy to different tree nuts, associated with allergy to other legumes, and in LTP-allergic patients, probably as a result of cross-reactivity. All these observations confirm the profound differences in food allergy patterns between Italy and both the United States and the British Islands where peanuts represent one of the main causes of food allergy [22]. Differences in dietary habits (e.g. the absence of peanut butter from the Italian market) might explain this difference. Seeds (sesame, sunflower), although clinically relevant due to the severity of the reactions caused, were involved in a very limited proportion of patients (about 1% of plant-food allergic individuals). With the exception of shrimp (13% of all primary food allergies), individual animal-derived foods were involved in <5% of cases of food allergy.

The analysis of geographical differences of food allergy patterns produced several surprising results. The prevalence of primary plant-food allergy increased progressively southbound; this fact could be totally ascribed to LTP sensitization, as the prevalence of allergy to tree nuts, legumes, seeds, and kiwi did not show any difference between northern, central, and southern Italy. The reason for the strange geographical distribution of allergy to LTP, which is nearly exclusive of the Mediterranean countries [23], has long been a matter of debate. Some studies suggested that the fuzz of untreated peaches might be a

relevant source of LTP and that sensitization may occur through the skin [24] or through the airways [25], but this still remains an open question. The findings in our small population of patients <12 years old confirm that LTP sensitization is typically found in southern Italy and clearly suggest that it may occur early in life.

Some geographical differences in the prevalence of certain food allergies observed in this study were clearly associated with particular dietary habits. Shrimp allergy was less frequent in southern than in northern or in central Italy; this seemingly odd finding can be explained both by geographic and socio-economic differences, as southern centres were located in the inland, far away from the sea, and cared for a mostly rural population that very rarely eat fish, crustaceans, and molluscs. Although the difference did not reach the statistical significance due to the small numbers of subjects involved, pine nut and buckwheat allergies were more frequent in northern than in southern Italy. Again, geographic differences and eating habits may have played a role, as one half of pine nut allergic patients were from the area of Genoa where home made pesto sauce (traditionally made using pine nuts) is extremely popular; it is interesting to notice that, due to lower costs, most industrial pesto sauces sold in the supermarkets are produced using almonds or other fruit kernels rather than pine nuts. Buckwheat is typically used in certain Alpine areas of the country to prepare a special type of pasta ('pizzoccheri') that is virtually absent in southern Italy. It has been also suggested that in northern Italy pizza flour used in some pizza restaurants may contain a variable proportion of buckwheat flour [26]; there are presently no data suggesting that this is the case also in southern Italy.

It is possible that the design adopted in this study has led to some bias. For instance, the fact that allergy to seed storage proteins (i.e. genuine allergy to tree nuts, seeds, or peanut) or to cereals was diagnosed by exclusion of LTP sensitization may have led to an underestimate of this type of allergies and to an underestimate of the number of co-sensitized patients. We are aware that component-resolved diagnosis (either *in vivo* or *in vitro*) would have been a much preferable means to get more reliable diagnoses. However, these tests are not yet routinely available and, even if they were, using them on a large scale (>1000 patients) would have represented an intolerable cost for most patients. Nonetheless, because, to the best of our knowledge there are no data suggesting a preferential co-sensitization LTP/seed storage proteins or LTP/cereal proteins, we are quite confident that the study design did not significantly alter the results of our study.

It is also possible that the lack of positive *in vivo* and/or *in vitro* tests has led to the exclusion of a limited number of patients sensitized to 'difficult' allergens that often score falsely negative on routine diagnostic investigation (e.g. oleosins), though it seems unlikely that this may have

somehow biased the general results of this study. It is also possible that the overall prevalence of some particular type of food allergy has been slightly incorrectly estimated due to the imbalance between the numbers of patients from the three macro-regions studied.

In conclusion, in keeping with previous surveys [6], the co-existence of different type 1 food allergies in the same subject seems extremely rare in adults which is clearly in contrast with airborne allergies where co-sensitization to multiple allergens is frequent [27]. Whether this difference between food and respiratory allergy reflects a different interplay between environment and gut rather than airway mucosa [28] remains to be established. Finally, this nationwide survey performed in specialty settings confirms that the pattern of allergy to certain foods is clearly influenced by specific geographic features such as pollen exposure and dietary habits [29].

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