

Population study of food allergy in France

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Background: Food allergy (FA) is an important health problem for which epidemiologic studies are needed.

Objective: We performed an epidemiologic survey in France to determine the prevalence, clinical pictures, allergens, and risk factors of FA.

Methods: This study was conducted on 33,110 persons who answered a questionnaire addressed to a representative sample of the French population on a scale of 1:1000 (44,000 subjects aged ≤ 60 years). One thousand one hundred twenty-nine persons with FA selected during phase 1 received a second questionnaire.

Results: The reported prevalence of FA is 3.52%: 3.24% evolutionary FA; 0.12% asymptomatic cases thanks to eviction diets; and 0.17% cured FA. The subjects were characterized by overrepresentation of city dwellers (80% vs 76%), women (63% vs 50%), and health care personnel (11% vs 4%). Fifty-seven percent (vs 17%) presented with atopic diseases ($P < .01$). FA was often persistent, lasting more than 7 years in 91% of the adults. The most frequent allergens were 14% Rosaceae, 9% vegetables, 8% milk, 8% crustaceans, 5% fruit cross-reacting with latex, 4% egg, 3% tree nuts, and 1% peanut. Sensitization to pollen was significantly correlated with angioedema, asthma, rhinitis, and fruit allergy ($P < .01$). FA was 4 times more frequent in patients with latex allergy. The main manifestations of FA were atopic dermatitis for subjects under 6 years of age, asthma for subjects between 4 and 6 years of age, and anaphylactic shock in adults over 30 years of age ($P < .007$). Shocks were correlated with alcohol or nonsteroidal anti-inflammatory drug intake ($P < .01$ and $P < .04$, respectively).

Conclusion: The prevalence of FA is estimated at 3.24% (range, 3.04% to 3.44%) in France. This study emphasizes the increasing risk of FA in well-developed countries and draws attention to certain FA risk factors, such as the intake of drugs (nonsteroidal anti-inflammatory drugs, β -blockers, and angiotensin-converting enzyme inhibitors) or alcohol, intolerance of latex gloves, and socioprofessional status. (*J Allergy Clin Immunol* 2001;108:133-40.)

Key words: Food allergy, epidemiology, natural history, symptoms, allergens, sensitization to pollen, latex

Food allergy (FA) corresponds to clinical manifestations related to sensitization to food proteins.¹⁻³ At the present time, the emphasis has been mainly placed on the IgE-dependent mechanism.⁴⁻⁶ The diagnosis is established in 2 stages. The first demonstrates an immediate sensitization, with skin prick tests and identification of specific IgEs in the blood. The second requires standardized oral challenge tests. This methodology is the object of a wide consensus on the basis of homogeneous published studies.⁷ The growing number of publications devoted to FA may partly reflect increasing interest in the prevalence of its pathologies. However, it is undeniable that the profound changes in modern eating habits, resulting from the variety of food sources, and the large role played by agronomic and food technologies are responsible for a real increase.⁸ A multicenter study of anaphylactic shock in France indicated that food-induced allergy had increased 5-fold between 1982 and 1995.⁹

There is thus the need to conduct epidemiologic studies to compare the prevalence of FA in different countries and to help food industries concerned about food safety develop relevant strategies. The methodology of population surveys on the basis of questionnaires may be questionable concerning the number of questions asked and their formulation. Indeed, an imprecise formulation gives rise to replies that take into account nonimmunologic reactions to food. This type of survey has led to a rate of adverse reactions of 15% to 33%¹⁰⁻¹³ and a rate of presumed FA of 12% to 15%.¹⁴⁻²¹

Recent studies include validation of answers on the basis of the use of standardized diagnostic methods (skin prick tests and detection of specific IgEs). They frequently included a subgroup that had undergone well-controlled challenge tests. The reference study is an English study conducted on 20,000 subjects.¹⁵ The authors performed challenge tests to 8 everyday foods on a small group of reactive individuals. The prevalence of FA, taking into account these results for a limited number of foods, was evaluated at 1.8%.¹⁵ Other authors have established similar prevalences, from 2.3% to 4.4%.^{14,16,17,22}

This French epidemiologic study was carried out on 33,110 subjects who answered a questionnaire addressed to 44,000 French subjects aged 60 years or less, constituting a representative sample of the French population on a scale of 1:1000.

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Abbreviations used

FA: Food allergy

NSAID: Nonsteroidal anti-inflammatory drug

This study had 5 objectives: (1) to evaluate the prevalence of FA in France; (2) to identify the relative frequency of the clinical pictures; (3) to specify the natural history of the FA; (4) to note the frequency of allergens; and (5) to investigate associated factors at risk of inducing or worsening food reactions.

The study included 2 questionnaires given 8 months apart. The results of the questionnaires were comparatively analyzed according to whether the diagnosis was confirmed by an allergy evaluation. The results were not significantly different between these 2 groups, leading to an estimation of overall reported prevalence of 3.52% (range, 3.32% to 3.72%), including 3.24% (range, 3.04% to 3.44%) evolutionary FA and 0.28% (range, 0.22% to 0.34%) asymptomatic FA either cured or eliminated by means of an eviction diet. This survey indicates that FA is often a long-lasting phenomenon in adults and is currently not diagnosed in young children.

METHODS

This study used a quantitative approach in the general population implemented by means of a self-administered questionnaire that was distributed to the persons interrogated by a national polling organization (SOFRES). The target population was the polling base established by this organization. It includes 20,000 households with 53,000 individual subjects, representing France on a scale of 1:1000. These people are representative of the French population in terms of region, size of city, profession and social category of the head of household, age of the head of household, and number of people living in the household. The base is renewed at a rhythm of 6000 households per year, one twelfth each month, to avoid the consequences of excessive aging.

This study was limited to persons less than 61 years of age for a total of 44,000 people. It was carried out in 2 phases. Phase 1 took place in May and June 1997. Forty-four thousand persons were contacted, with a response rate of 75.6% for a total of 31,110 individuals. One thousand two hundred sixty-eight individuals responded positively to the questions concerning allergic food reaction.

Phase 2 took place in February 1998. The second questionnaire was sent to 1129 subjects who responded positively to the question concerning allergic food reactions in the first questionnaire. The discrepancy between the numbers of positive responders in phases 1 and 2 is due to the effect of the renewal of some of the panel members every month. Nine hundred forty-seven (83%) responses were obtained. Discrepancies between the answers to the phase 1 and 2 questionnaires led us to contact subjects by telephone to ascertain the reasons for these differences: this was possible for 143 subjects (Fig 1).

Phase 1 questionnaire

The phase 1 questionnaire was composed of 10 questions. Three questions concerning reactions to food were intentionally placed in the seventh, eighth, and ninth positions. The subjects filled in the following answers to questions 1 to 6 in order: (1) sex and age; (2) the existence of eczema, hay fever, allergic rhinitis, or asthma; (3) whether an allergy evaluation was performed; (4) if yes, the allergens retained (pollens, dust mites, animal epithelia, latex, food, and other allergens); (5) frequent use of latex gloves (at least once a week); and (6) if yes, tolerance to the gloves. Question 7 was

designed to detect an allergic reaction after intake of a food or drink; in the case of a positive reply, questions 8 and 9 were designed to determine how many of certain (specifically named) foods and drinks caused such reactions. Question 10 asked whether the person was a health care worker, worked in the food, rubber, or latex industry, or worked in a restaurant.

Phase 2 questionnaire

The phase 2 questionnaire was sent to subjects who answered positively to questions 7 to 9 of the phase 1 questionnaire. It required the following:

1. Confirmation of the positive answer in phase 1.
2. The foods incriminated (up to 3, specifically named).
3. The number of reactions occurring per food.
4. The symptoms (ie, anaphylactic shock, urticaria, angioedema, atopic dermatitis, asthma, rhinitis, diarrhea, vomiting, abdominal pain, migraine, and other symptoms). In all, 13 possibilities were listed in 2 different forms so that they were comprehensible to everyone; for example, rhinitis was also listed as sneezing, runny nose, or stuffy nose; urticaria was listed as redness or red patches; and atopic dermatitis was listed as eczema. Single answers, such as as headache or abdominal pain, were not taken into consideration if these symptoms were not associated with other signs of FA.
5. The type of medical care sought (call to emergency services or the doctor or later visit to the allergist).
6. Exertion or alcohol or drug intake as circumstantial events. Information concerning drugs was organized in 5 questions targeting eye drops, drugs containing aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), β -blockers, and angiotensin-converting enzyme inhibitors. All brand names were listed.
7. The age of onset of allergic reactions.
8. The confirmation obtained by a previous allergy evaluation (or not).

Questions 2 to 7 were asked for each of the first 3 incriminated foods.

Validation of study methods

Phase 1 and 2 questionnaires were tested on a pilot sample of 15 subjects to make sure that the questions were intelligible and comprehensible and to verify the capacity of those interviewed to respond. We verified that these subjects understood the question correctly and gave a response that corresponded to the information sought. We made certain that within the prompted lists, the subjects' situations were precisely described. We tested the correspondence and evaluated the relevance of the filters by verifying the correlation of the answers by crossing the different items. We verified the correspondence of interquestion responses that were related. We therefore adapted our questionnaire to resolve any problems.

On receipt of the phase 2 questionnaires, we verified that there was no structural bias between the 943 subjects and the reactive phase 1 sample (1268 subjects) concerning the parameters for the construction of the sample.

No personally identified information was transmitted. Because we were not allowed to perform subsequent allergy testing to confirm FA in accordance with French law governing protection of privacy (94-548, July 1, 1994), the only solution that could be envisaged was to introduce question 7 to validate the diagnosis of FA by means of a previous allergy evaluation.

Statistical analysis

The statistical evaluation was carried out by the national polling organization by using the *t* test to compare the proportions in the different study groups and to compare the means of these groups.

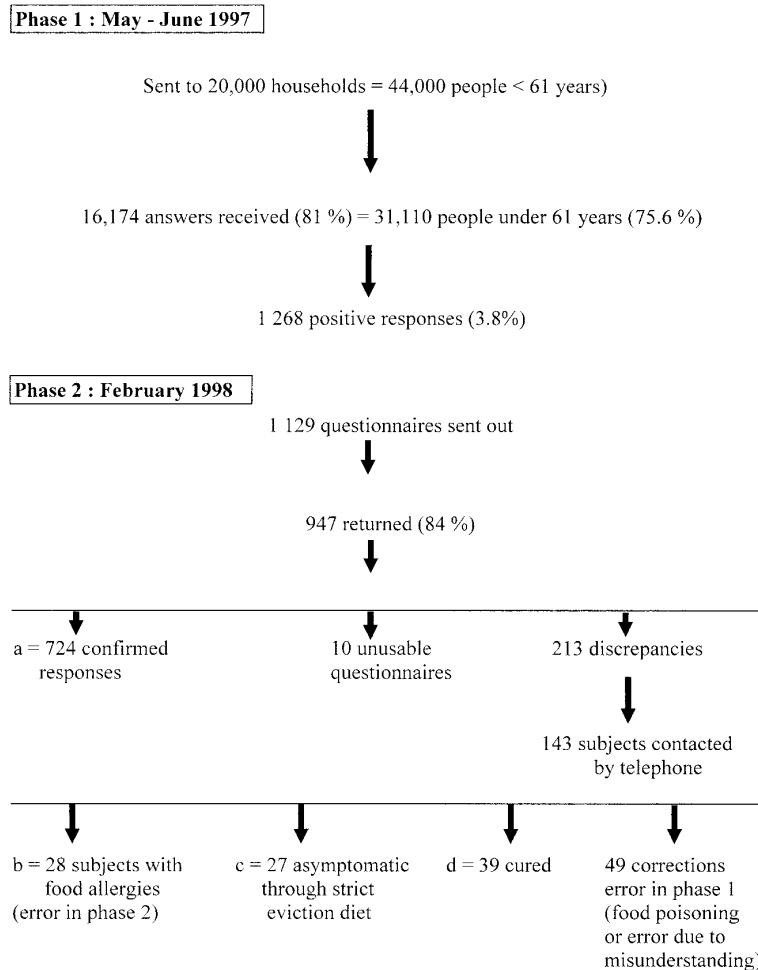


FIG 1. Study design: data for phase 1 and 2 questionnaires.

RESULTS

Fig 1 shows the study design and the overall figures. In phase 1, 1268 of 16,174 subjects answered positively to the question about food reactions. Eighty-eight percent of subjects reporting that they had FA were the only ones to be affected in their household. The number of individuals affected per household correlates with the size of the household: 0.43% of 2-person households showed 2 persons with FAs; 1.04% for 3-person households; 1.37% for 4-person households; and 1.72% for households of 5 persons or more. This finding refers to a partly probabilistic distribution of the individuals affected. There appears to be no systematic correlation with responses linked to shared practices or genetic predisposition in certain households, and the results recorded testify to the importance of other factors in the development of FA.

FAs were precisely estimated by the sum (a + b + c + d) of patients (818), corresponding to 86.3% (818/947) of responses to phase 2 questionnaires. The comparison of this phase 2 group with the group of 1268 phase 1 subjects was performed for sex, age, geographic location, socioprofessional category, and the frequency of

the different foods. The groups were homogeneous, except for slight overrepresentation in phase 2 of adults between the ages of 31 and 61 years and inhabitants of rural areas. Thus a corrective factor was applied to the answers to the phase 1 questionnaire that took into account this rate of 86.3%. Consequently, the overall reported prevalence of FA was estimated at 3.52% (range, 3.32% to 3.72%), including 3.24% (range, 3.04% to 3.44%) of present FAs, 0.17% (range, 0.13% to 0.21%) of cured FAs, and 0.12% (range, 0.08% to 0.16%) of asymptomatic subjects after strict elimination diets in the 9-month period separating the 2 surveys.

The group of subjects reporting allergic food reactions was characterized by overrepresentation of city dwellers (80% vs 76%) and women (63% vs 50%). Distribution of age groups of symptomatic and nonreactive subjects was equivalent for the 1- to 6-year and the 16- to 30-year age groups. In symptomatic subjects there was a slight decrease in representation in the 7- to 15-year age group (12% vs 15% for the set) and overrepresentation of adults over 31 years of age (54% vs 49% of the total). Health care personnel were also overrepresented (11% vs 4%; all test statistics had *P* values of less than .001).

TABLE I. Atopic diseases in subjects with FA (n = 1253 in phase 1 and n = 724 in phase 2)

Subjects	n	Eczema (%)	Pollinosis (%)	Allergic rhinitis (%)	Asthma (%)	Atopic disease (>1, %)
Symptomatic	1253 or 724	29*	19*	24*	16*	57*
Nonsymptomatic	31,857	7	5	6	4	17

P* < .01.TABLE II.** Clinical symptoms of FA according to pollen sensitization

FA symptoms (n = 290)	Sensitized to pollens (n = 126)	Not sensitized (n = 164)	<i>P</i> value
Angioedema	37.3	22	.004
Asthma	18.3	7.9	.009
Rhinitis	17.5	6.7	.005
Urticaria	60.3	62.2	NS
Digestive symptoms	19.8	20.7	NS
Anaphylactic shock	1.6	4.3	NS
Atopic dermatitis	8.7	14	NS
Headache	9.5	9.8	NS

NS, Not significant.

Most often, subjects with FAs presented with past or evolutionary atopic diseases (57% vs 17%). An atopic disease was noted in 19% (range, 18.6% to 19.4%) of the general population: atopic dermatitis in 8%, allergic rhinitis in 6%, pollinosis in 6%, and asthma in 5%. All of the atopic diseases were overrepresented in the group with FA (*P* < .01, Table I).

The incriminated allergens, clinical signs, particularities induced by pollen and latex sensitization, natural history of FA, factors at risk of inducing or worsening allergic reactions, and type of medical care sought were analyzed for the 724 completed phase 2 questionnaires. In these 724 patients, 1153 FAs were observed: 58.1% of the subjects had 1 FA; 24.5% had 2 FAs; and 17.4% had 3 or more FAs.

There were 1.82 ± 1.07 (mean $\pm$ SD) symptoms per subject recorded: urticaria, 57%; angioedema, 26%; gastrointestinal symptoms, 22%; eczema, 10%; headache, 10%; rhinitis, 6.5%; oral syndrome, 6.5%; asthma, 5.7%; anaphylactic shock, 2.7%; and conjunctivitis, 1.4%.

The most frequent allergens were of plant origin: Rosaceae fruit, 14%; all types of vegetables (eg, umbelliferae and leguminosae), 9%; milk, 8%; crustaceans, 8%; shellfish, 7%; fruit cross-reacting with latex (ie, avocado, kiwi, banana, and chestnut), 5%; egg, 4%; and tree nuts, 3%. Peanut alone represented 1% of FAs. Intolerance to alcohol was noted in 6% of patients.

Clinical expression of FA was dependent on the existence of a sensitization to pollens. This favored the expression of FA in the form of angioedema, asthma, and rhinitis (*P* < .01, Table II). In the same way, the nature of the allergens was dependent on pollen sensitization because allergy to Rosaceae and to the latex group fruit was correlated with allergy to pollens (*P* < .03).

Frequent contact with latex gloves was significantly related to FA. Twenty-five percent of subjects with FAs often used latex gloves (vs 10.9% in the general population). The overall prevalence of glove intolerance was at 0.7%. In subjects reporting that they used gloves, latex intolerance was found in 10.4% of subjects with FA (vs 5.6% of subjects without FA). Similarly, FA was found in

8.2% of subjects reporting that they used gloves without incident but in 15% of subjects presenting with latex glove intolerance. Intolerance to latex gloves is associated to a prevalence of FA multiplied by 4. The figures were identical for the 1268 phase 1 subjects and the 724 reactive phase 2 subjects. The subjects who were intolerant to latex gloves had more allergies to latex group fruit and to vegetables and were more likely to experience anaphylactic shock.

The natural history of the FA showed a modulation of the reported prevalence, clinical signs, and allergens according to the age. The reported prevalence of FA was estimated at 4.19% (range, 3.20% to 5.18%) in patients from 1 and 3 years of age, 2.79% (range, 2.01% to 3.57%) from 3 to 6 years, 2.80% (range, 2.34% to 3.26%) from 7 to 15 years, 3.22% (range, 2.85% to 3.59%) from 16 to 30 years, and 3.97% (range, 3.67% to 4.27%) from 31 to 60 years. Eczema was the symptom most frequently seen in children under 6 years of age. It decreased by 30% from 7 to 15 years and by 60% from 16 to 30 years and was rare in adults over 31 years of age (*P* < .0007). Children between the ages of 4 and 6 years had more asthma than did adults (*P* < .04). Ninety-seven percent of anaphylactic shocks occurred in adults, and among these subjects, adults over 30 years experienced more anaphylactic shock than adults between 16 and 30 years of age (*P* = .007, Fig 2). Anaphylactic shock, as compared with other allergic reactions (*P* < .04), was most often caused by seafood. Similarly, age influenced the relative frequency of FA, with milk and eggs being the most important in children and seafood, fruits, and vegetables gaining importance with age (Fig 3).

The subjects with FAs presented a mean of 4.7 ± 5.6 (mean $\pm$ SD) episodes, and 53% of the subjects had 2 or more reactions to the same food (Fig 4).

The duration of FA in children under the age of 15 years was greater than 4 years in 34% of patients. In adults older than 15 years, the duration was greater than 7 years in 91.2% of patients (Fig 5).

Associated factors were observed: simultaneous alcohol intake in 13% of patients, physical effort immediate-

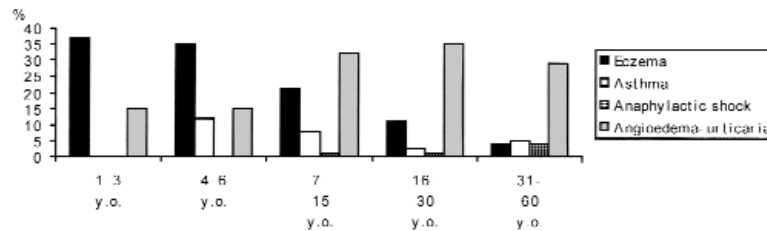


FIG 2. Evolution of frequency of FA according to age.

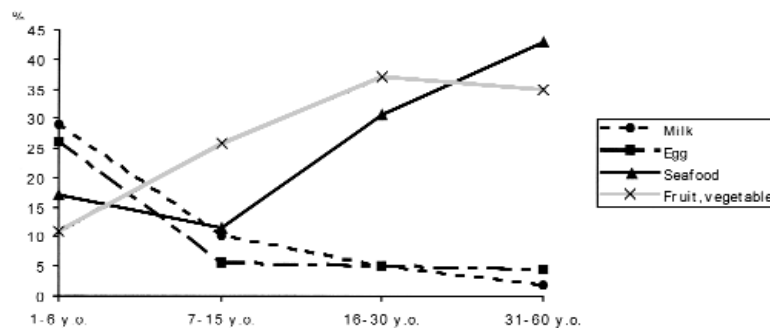


FIG 3. Relative frequency of 4 food allergens with age.

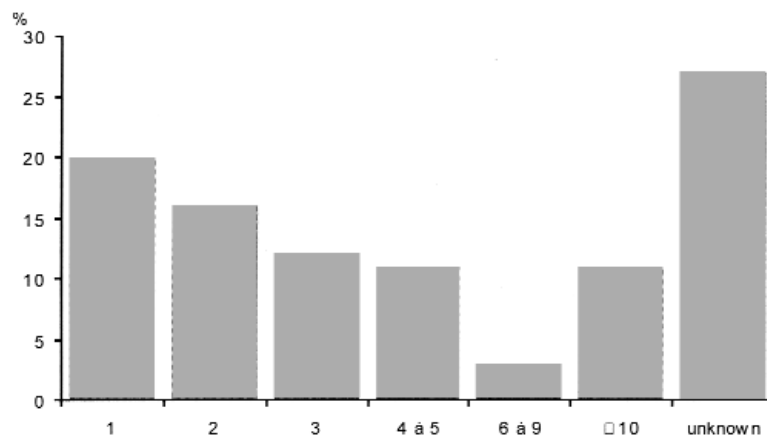


FIG 4. Recurrence of food-allergic reactions (724 subjects).

ly before the clinical reaction in 3% of patients, and concomitant intake of a drug in 30% of patients. Alcohol and NSAID intake were significantly more frequent in the cases of anaphylactic shocks than in other milder reactions ($P < .01$ and $P < .04$, respectively).

Medical care in the case of FA included emergency hospitalization in 5% of patients, a doctor's home visit within 24 hours in 17% of patients, and a later visit to a doctor in 32% of patients. Fifty percent of the patients

underwent a complementary allergy evaluation, which confirmed FA in 56% of patients. Confirmed FA corresponded mainly to asthma ($P < .0004$), eczema ($P < .0001$), shock ($P < .07$), angioedema ($P < .02$), and rhinitis ($P < .01$). A negative correlation existed with headache ($P < .0004$). A positive correlation existed between the confirmation of FA and the vegetable allergens ($P < .002$) and egg ($P < .01$), and a negative correlation existed with delicatessen foods ($P < .005$).

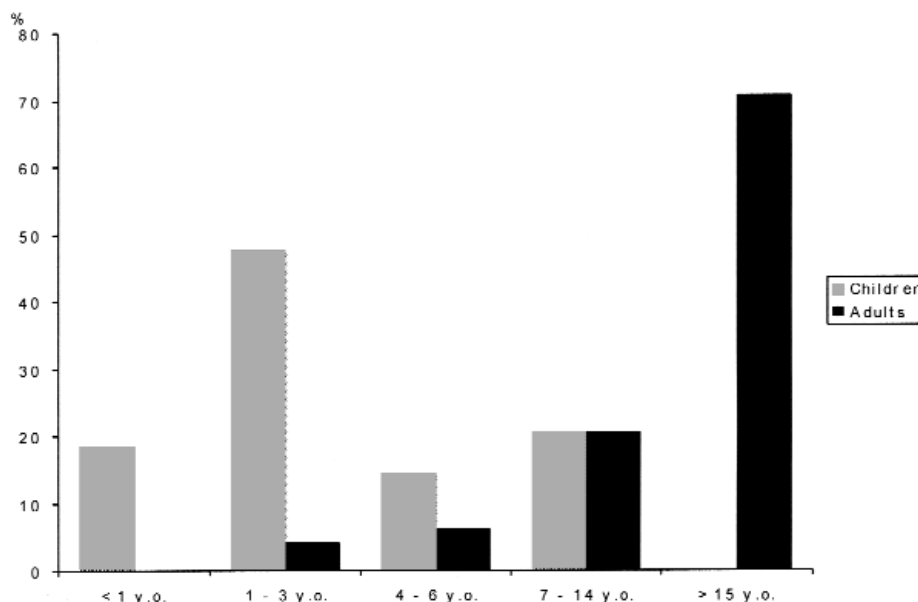


FIG 5. Duration of FA in children younger than 15 years (194 FAs) and in adults from 16 to 60 years of age (897 FAs).

DISCUSSION

Because the study was performed solely by questionnaire, a certain number of elements were considered to validate the responses as true FAs. A high rate of positive responses concerning adverse food reactions are observed in the literature when the question is asked directly without specifying the expected symptoms. That is why the questions concerning FA were deliberately placed in the seventh, eighth, and ninth positions after focusing on atopic disease (question 2).

The questionnaire was designed so that reactions could only be noted for an identified food and not for the general diet. The incriminated foods were limited to 3 because we know that it is rare to observe more than 3 FAs in the same subject.

In phase 2 the symptoms proposed were the classic symptoms of IgE-mediated FA.^{4,5,23-25} Other symptoms could be noted: they only affected 3% of the positive responses and occurred in association with one of the first symptoms. This corresponded with the data in the data bank of the Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire.

The analysis of the characteristics of the 1268 phase 1 and the 724 phase 2 questionnaires enabled us to consider the latter as representative of the 1268. It was confirmed that the prevalence of atopic diseases detected by means of skin prick tests or RASTs (ie, sensitization, clinical signs, incriminated allergens, or use of latex gloves), whether well tolerated or not, was similar. Consequently, corrections were made in the phase 1 sample in accordance with the results of the follow-up telephone

calls resulting in a reported prevalence of present FA of 3.24%, which fits with the prevalence reported in other European studies.^{14-16,20,21}

However, some bias has to be taken into account: answers associating migraine and delicatessen foods were probably false allergies because of intolerance to biogenic amines.²⁶ These represent only a small number of subjects. In the same way, the comparison of the frequencies in the group confirmed by evaluation and the unconfirmed group showed that certain immediate reactions to fish or crustaceans were due to nonspecific histamine effects. Inversely, diagnosis could be insufficient: a prevalence of 3% of anaphylactic shock reflects only diagnosed cases, whereas cases of idiopathic shock are not collected by this type of survey. Moreover, pathologies caused by masked food allergens are not yet currently identified.^{27,28}

Peanut allergy is severe and long lasting.^{29,30} It only represented 1% of the FAs in this study. It represents 25.7% of FAs in children under the age of 15 years in the Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire data bank.³⁰

Fifty percent of the younger children with food reactions had not undergone allergy evaluation. When allergy evaluation was performed, an FA was detected in 85% of patients. Thus FA in the pediatric population may be underestimated. In adults results of the investigations were positive in only 56% of patients. Milk, egg, and peanut are the main allergens in childhood, and commercial extracts (or native milk) have a good sensitivity. Vegetal allergens mainly involve adults, and the allergenic extracts have a low sensitivity. This fact could explain the discrepancy between the results obtained according to the age.³¹

The overall rate of 3.24% could then be close to reality. The rate of FA in the pediatric population is lower than previous estimations, which have been as high as 8%.¹⁻³ The rate of 3.97% for the adults reflects the persistence of FAs, some of which are asymptomatic through eviction diets and thus no longer require medical follow-up. Some FAs are benign, such as the oral syndrome caused by fruit and vegetables that is observed in subjects allergic to pollens. Nonetheless, anaphylactic shock is recorded in 3% of patients, occurring mainly in adults.⁹

FAs are the earliest atopic disease.³² This study confirms the present state of knowledge: they characterize the most atopic fraction of the population because 57% of the subjects with FA present with annual or seasonal allergic rhinitis, asthma, or eczema (vs 17% in the non-symptomatic population).^{33,34}

Caution is required with regard to drugs that worsen or induce FAs. The concomitant intake of β -blockers, angiotensin-converting enzyme inhibitors, NSAIDs, and alcohol in the course of anaphylactic reactions is stressed once again.^{9,35} Lacking references to the surveyed population, it was not possible to consider as abnormally frequent the intake of these drugs associated with the FA. Nonetheless, it is rather unlikely that 8.2% of French persons begin their meals with aspirin. The comparison of anaphylactic shock with other allergic reactions confirms that anaphylactic shock is significantly associated with the intake of alcohol and NSAIDs.

Data on deaths caused by acute asthma induced by food in allergic patients have been published.³⁶ No near-fatal reactions during the 9-month period of observation were reported.

Pollen sensitization played an important role in the onset of FAs to fruit and vegetables: they appear to be related and to progress with age, starting in prepuberty. There was no correlation of this kind with FAs caused by animal allergens.³⁷ This study confirmed the association of pollen allergy with Rosaceae and the latex group fruit and with the most frequently observed manifestations, respiratory signs, and facial or laryngeal angioedema. The tissues could be more sensitized to pollens, thus being the most reactive to cross-reacting food allergens. The pollen season, creating a state of hyperreactivity of the respiratory mucosa in subjects allergic to pollen, could precipitate serious acute asthma caused by cross-reacting food allergens.³⁸

Latex allergy induces cross-reacting FAs. A large number of major latex allergens present homologies with plant allergens, particularly hevein and a profilin.³⁹⁻⁴¹ The importance of latex allergy is underlined by the overrepresentation of health care personnel in the population of subjects with FAs. Cross-reacting food allergens could be considered a part of the occupational allergy and not taken into consideration in the tables defining compensation rights.

This study presents a landscape of FAs. It is situated in a wider context: a general increase in pollen sensitization; new risks in professional environments (health care personnel); profound changes in industrial processes for preparing food; and increased risk of allergy in

older subjects linked to interference with drugs. At the present time, FA give rise to multiple issues in the industrialized countries.

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