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Confirmed prevalence of food allergy and non-allergic food hypersensitivity in a Mediterranean population

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Clinical and Experimental Allergy

Summary

Background Until the present, no comprehensive studies evaluating the prevalence of food allergy and non-allergic food hypersensitivity (FA/NAFH) in adults have been done in Turkey or its surrounding countries.

Objective This large population-based study was planned to identify the confirmed prevalence of adverse reactions to food in adults in Istanbul.

Methods A total of 17 064 telephone numbers were randomly selected from both the European and Asian sides of Istanbul, and the 11 816 subjects who agreed to participate in the study were addressed with a questionnaire of eight items. Those who disclosed food-related complaints in this survey were called again and a similar questionnaire was repeated. The respondents who were suspected of having food allergy or food hypersensitivity were invited for a personal clinical investigation that included double-blind, placebo-controlled food challenge tests.

Results The lifetime prevalence of self-reported FA/NAFH was found to be 9.5% [1118/11 816; 95% confidence interval (CI): 8.94–10.00%]. After the clinical investigations, the point prevalence of FA/NAFH, which also included the 'possible FA/NAFH group', was found to be as low as 0.3% (30/11 816; 95% CI: 0.17–0.36%), and the FA/NAFH rates assessed by double-blind, placebo-controlled food challenge tests were 0.1% (12/11 816; 95% CI: 0.05–0.18%) and 0.1% (11/11 816; 95% CI: 0.05–0.17%), respectively. The most significant factor influencing FA/NAFH was familial atopy (adjusted OR 4.3; 95% CI: 3.67–4.99), and the most related atopic disease was itching dermatitis/urticaria (adjusted OR: 3.9; 95% CI: 3.31–4.54). **Conclusion** We may conclude that FA/NAFH in the Turkish population seems to be low when compared with Northern and Western European countries. This may be due to genetic, cultural or dietary factors, and further studies evaluating the reasons for this low prevalence of FA/NAFH in our population are needed.

Keywords Cross-sectional study, epidemiology, food allergy, food challenge test, food hypersensitivity

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Introduction

Adverse reactions to food have become a major health concern in most countries during the last few decades [1, 2]. There are some differences between the nomenclature and the classification of adverse food reactions used in Europe and in the United States [2]. Therefore, in 2001 the European Academy of Allergology and Clinical Immunology (EAACI) and in 2003 the World Allergy Organization (WAO) produced documents on this subject [3, 4]. In both of these documents, the term food

allergy (FA) is used to define clinical symptoms, which are mediated by the immune system, and the IgE-mediated FA when IgE is involved in these reactions. Non-allergic food hypersensitivity (NAFH) is used to describe the reactions that are not mediated by the immune system. The term food hypersensitivity represents the umbrella term for both reaction patterns [3, 4]. In this study, these terms will be used to define the adverse food reactions.

Community-based studies in various countries using different methodologies have been conducted to

determine the prevalence of reported food hypersensitivity, and a wide range of results have been reached [5]. A meta-analysis of studies has found that the incidence of self-reported food allergies ranges between 3% and 35%, but is lower (2–5%) in the studies where subjects were assessed for sensitization and symptoms towards foods [6].

Today double-blind placebo-controlled food challenges (DBPCFC) remain as the 'gold standard' for the diagnosis of adverse reactions to foods and food additives [7, 8]. Skin and blood tests are additionally preferred to explain the pathogenetic mechanism that underlies the intolerance [9]. Unfortunately, there are relatively few reports that have included DBPCFC in assessing the prevalence of FA [6].

In Turkey, both the 'Mediterranean Diet' including fresh fruits and vegetables and also the 'Eastern Food Culture Diet' with red meat and various spices are evident in daily life. Until the present, no comprehensive studies evaluating the prevalence of food allergy and non-allergic food hypersensitivity (FA/NAFH) in adults have been done in Turkey or in surrounding countries. Recently, in Greece as part of a collaboration study of European Union countries, the prevalence of self-reported FA was assessed in the pediatric population, but not confirmed with diagnostic tools [10]. Therefore, this large population-based study using both DBPCFC and the other preferred diagnostic methods was planned to gather data primarily on confirmed FA/NAFH and at the same time FA/NAFH in the adult population in Istanbul, the largest city in Turkey.

Materials and methods

Study design

To evaluate the prevalence of allergies including FA/NAFH in the Turkish population, Istanbul, a metropolis with a population of nearly 10 000 000 inhabitants, many of whom have migrated from every region of the country, was thought to be an appropriate example. Therefore, randomly selected telephone numbers from both the European and Asian sides of the city were contacted. A total of 17 064 telephone numbers were called, and 11 816 (69.25%) individuals who agreed to contribute to the study were applied a questionnaire of eight items on allergies, only two focusing on food (Fig. 1). Those who disclosed food-related complaints in this survey were called once more and a similar questionnaire was repeated. Those who were suspected of having FA/NAFH were invited for a personal investigation at the clinic.

Questionnaire

A questionnaire inquiring about familial atopy, atopic diseases such as asthma, nasal allergies, itching dermati-

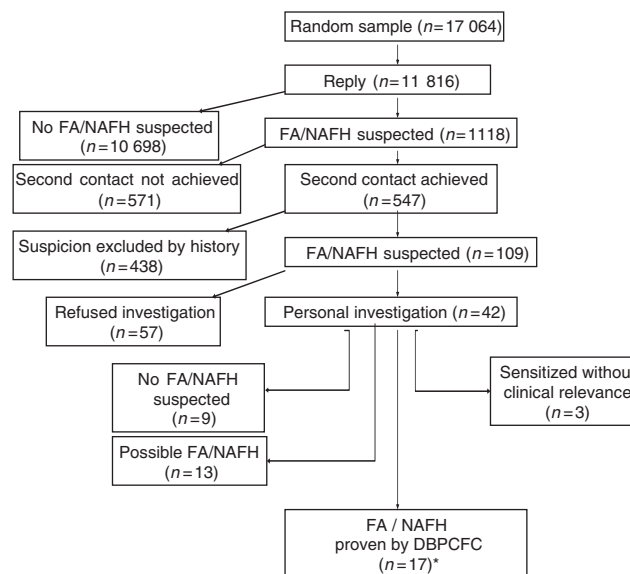


Fig. 1. Flow sheet of the study and investigations performed. *17 subjects consisted of six subjects forming the 'food allergic group', five subjects forming the 'NAFH (non-allergic food hypersensitivity) group' and six subjects forming the 'both allergic and NAFH group'.

tis/urticaria and some risk factors such as smoking habits and household pets as well as perceived connections between food ingestion and systemic symptoms was designed. The exact questions related to food hypersensitivity in the first call were 'Do you think that you are allergic to a particular food or foods?' 'Have you nearly always had the same reaction like itching, eczema, urticaria, angioedema, rhinitis, asthma, intestinal symptoms, headache or others due to repeated ingestion of the same type of food, and if so which foods?' During the application, the interviewer did not read a list of foods to the respondents or probe for additional foods. In the second application, the second question evaluating food hypersensitivity was repeated and additionally the question 'Do you want to be examined for food hypersensitivity at the clinic?' was asked. Food hypersensitivity was ruled out if the food items had given rise to symptoms only once and were afterwards again repeatedly ingested without any complications.

In order to calculate the reliability, the questionnaire was first applied to a pilot sample of 500 subjects and the reliability of the questions was analysed with Kuder Richardson formula (KR-20). The coefficient (KR) was calculated as 0.75. Additionally with this pilot study, we verified that the questions were intelligible and comprehensible.

Additionally, before the study started, the questionnaire was applied to 50 patients who had been diagnosed as food allergic in our allergy clinic and to 50 healthy subjects. The 2×2 contingency table was evaluated according to the ones who had answered 'YES' to at least

one or both of the two questions concerning food hypersensitivity and the ones who had answered 'NO'. The sensitivity of the questionnaire was 0.90 [95% confidence interval (CI): 0.78–0.96], specificity: 0.80 (95% CI: 0.66–0.89), PPV (positive predictive value): 0.81 (95% CI: 0.69–0.90), NPV (negative predictive value): 0.88 (95% CI: 0.75–0.96) and the accuracy was 0.85.

Investigations at the clinic

During the first visit, a detailed personal history was taken, skin prick tests (SPTs) with standard inhalant allergens (common grass, weed, tree, and cereal pollens, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinea*, *Alternaria*, *Aspergillus fumigatus*, *Penicillium notatum*, dog, cat, bird, *Blatella germanica* and latex by ALK-Abello, Spain), food allergens (chicken meat, egg yolk, egg white, white fish mix, bluefish mix, carrot, potato, wheat flour, peanut, hazelnut, walnut, sunflower seed, banana, peach, orange, apple, strawberry, spinach, cow's milk, cacao by ALK-Abello), positive (histamine) and negative controls were applied on the volar surface of the forearm. In the second visit, according to the participants' history and prick test results, detailed prick-to-prick tests with fresh foods, *in vitro* specific IgE (sIgE) tests for special foods indicated by the history and the prick tests were done. Prick tests were regarded as positive when wheal diameter was at least 3 mm and were equal to 60% of that induced by histamine without reaction of the negative control. Subjects were advised to avoid antihistamines and topical steroids for 72 h before the test. Subjects' sera were analysed for sIgE concentrations to dietary allergens addressed by history and SPTs (hen's egg, carrot, orange, pear, banana, strawberry, peanut, hazelnut, tomato, eggplant) by FEIA (Fluoro-Enzyme Immunoassay) using the Pharmacia CAP-System (Pharmacia Diagnostics, Freiburg, Germany). The detection limit was 0.35 kU/L IgE, and subjects were regarded as sensitized if the sIgE was above the detection limit.

Afterwards, all the subjects were asked to participate in DBPCFC tests. Written informed consent was obtained from the study participants investigated in the clinic.

Before the food challenges, subjects were asked to omit suspicious food items from the diets for 3 days for typical immediate-type reactions and up to 7 days for late reactions such as eczema. For those reporting symptoms to multiple unrelated foods or for the ones who had symptoms to foods commercially prepared but not when homemade, food additives were considered as the causative agent and a diet free of food additives was applied for 2 weeks before the challenge [11]. All the subjects were also instructed not to exercise or consume alcohol or NSAID medications before the challenge tests.

After the elimination diet, DBPCFC tests were applied. Nutritionists used peppermint oil, pure cacao powder,

cereal flakes, wheat flour, lemon juice, honey, sugar, mashed potato, milkshake, rice pudding, carob, cinnamon and various vegetables for blinding of food items.

Frequently used food additives were given altogether in gelatine capsules to persons likely to show adverse reactions to food additives. Placebo capsules filled with mannitol and silicon dioxide were given on separate days as well [12].

All provocation tests were performed at the clinic with subsequent surveillance of 2–12 h depending on the patient's history. Each day, a maximum of two food items were challenged and subsequent visits were individually arranged for the subjects. All the negative DBPCFC tests were continued with an open meal to exclude FA/NAFH.

In addition, 50 healthy volunteers with a negative history for FA/NAFH and negative prick tests underwent DBPCFC tests after a 3-day diet free of typical food allergens and pseudoallergens. The same blinded food items and capsules of food additives given to the other participants were also given to these 50 subjects, and the blinding procedures were confirmed by tasting panels.

Study population

It was calculated that a sample size of 5000 persons would be sufficient to report an expected prevalence of 2% with a 95% confidence interval less than 1.63–2.43. Further calculating a reply rate of 30–40%, a random sample of 15 000 persons of all districts was drawn from the Istanbul telephone directory. The respondents had to be 18 years of age or older to be eligible to participate in the study, and only one household member qualified on the basis of age from each contacted telephone number was selected for the questionnaire.

Approval for all stages of the study was obtained from our Institutional Ethics Committee.

Statistical analyses

Univariate analyses of categorical variables (ages, familial atopy, household pets, nasal allergy, itching dermatitis/urticaria, doctor-diagnosed asthma, smoking habits) were made using Pearson's χ^2 test. Multivariate logistic regression (forward LR) models were performed to examine the association between the suspicion of FA/NAFH and the categorical variables found significant in the univariate analyses. These included age, familial atopy, household pets, symptoms of nasal allergy, itching dermatitis/urticaria and doctor-diagnosed asthma. The two-tailed *P*-value of < 0.05 was considered significant.

Results

The demographic data of the study participants who responded to the questionnaire concerning age, sex and

Table 1. Demographic data (questionnaires responded, $n = 11\,816$)

Variables	% (n)
Sex	
Female	72.9 (8614)
Male	27.1 (3202)
Age	
18–39	55.3 (6534)
40–59	33.4 (3947)
60–79	10.3 (1217)
80 years and above	1 (118)
Occupation	
Housewives	55.1 (6511)
White collar workers	18.8 (2221)
Unemployed, retired	7.6 (898)
Tradesmen	5.0 (591)
Students	4.9 (579)
Blue collar workers	4.2 (496)
Teachers	1.7 (201)
Health care personnel	1.0 (118)
Others	1.6 (189)

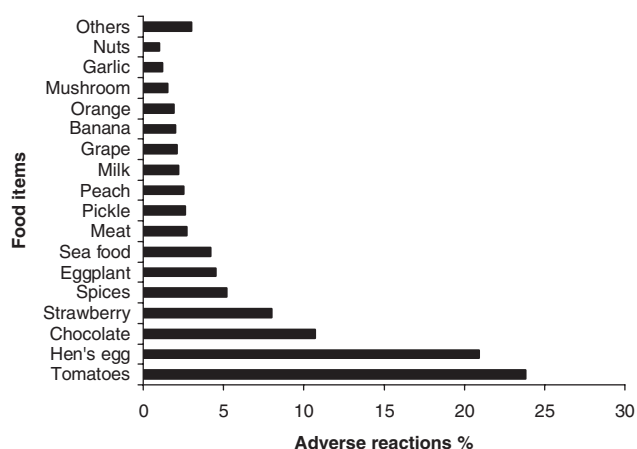


Fig. 2. Distribution of self-reported suspected foods in 1118 study participants.

occupation was as shown in Table 1. The distribution of the age groups in this study was representative of the Istanbul population according to the data obtained from the last census of the Istanbul population performed in 2000 [13]. Unfortunately, because the questionnaires were applied over the telephone, the majority of the people contacted were women, mostly housewives. This may cause a limitation in the study. However, similar to this study population, in the last census 55.3% of the population of Istanbul was housewives [13].

From the first contact, a total of 1118 study participants (9.5%; 95% CI: 8.94–10.00%) were suspected of having FA/NAFH (Fig. 1). This conclusion was made according to the number of participants who answered 'YES' to at least one of the two questions mentioned earlier. The distribution of the suspected foods mentioned by these subjects

Table 2. Calculated self-reported prevalence of food hypersensitivity (FH) according to age and gender

	Prevalence [% (n)]	Confidence interval (95%)
Female	9.7 (833/8614)	9.05–10.31%
Male	8.9 (285/3202)	7.94–9.94%
18–39 years	9.9 (652/6534)	9.26–10.73%
40–59 years	9 (358/3947)	8.19–10.01%
60–79 years	8 (98/1217)	6.59–9.73%
≥ 80 years	8.5 (10/118)	4.14–15.03%

was as shown in Fig. 2. Additives were mentioned very rarely by the subjects, and are therefore grouped in the 'others' column.

The self-reported lifetime prevalence of FA/NAFH (9.5%) was calculated for all age groups and gender (Table 2). It was found to be 9.7% for women and 8.9% for men ($P = 0.20$). The prevalence of FA/NAFH for the most relevant food items depending on sex is shown in Table 3. The lifetime prevalence rates of potential risk factors for atopic diseases such as familial atopy, exposure to cigarette smoke and household pets were 18.9% (2234/11 816), 59.1% (6986/11 816) and 8.7% (1031/11 816), respectively, and lifetime prevalence rates of atopic diseases such as rhinitis, itching dermatitis/urticaria and doctor-diagnosed asthma were 18.9% (2230/11 816), 11.3% (1331/11 816) and 10.6% (1254/11 816), respectively. The most significant factor influencing FA/NAFH was familial atopy, and the most related atopic disease was itching dermatitis/urticaria. Gender and smoking habits did not seem to have an effect on FA/NAFH, but the younger age group (< 40 years old) seemed to be more affected (Tables 4 and 5).

Afterwards, all 1118 participants with suspected FA/NAFH were called again and 48.9% ($n = 547$) answered the second questionnaire. This second contact was performed after a year of collecting and evaluating the received data and unfortunately reduced the answer rate. This second questionnaire was applied by two allergy specialists, thereby increasing the quality of the interviews. Almost 20% ($n = 109$) out of these were still suspected of having FA/NAFH and, therefore, were invited for investigation at the clinic. Sixty-seven subjects did not consent to participate in the study after learning the details of the investigations. Detailed histories were taken and SPTs with standard allergens were applied to 42 participants who agreed to be investigated. They were asked to come to the clinic for further investigation that included SPTs with fresh foods, food challenge tests and *in vitro* sIgE tests for individually selected special foods. Thirteen participants did not consent to food challenging and therefore remained as the 'possible FA/NAFH group' (Fig. 1). In this group, one person was afraid of a possible severe reaction due to the responsible food that had caused severe anaphylaxis in previous accidental ingestions and so did

Table 3. Prevalence of food allergy and non-allergic food hypersensitivity (FA/NAFH) for most relevant food items according to gender

	Female		Male		<i>P</i> -value
	%/ <i>n</i>	Confidence interval (95%)	%/ <i>n</i>	Confidence interval (95%)	
Tomato	2.4/(203/8614)	2.05–2.79	2.0/(63/3202)	1.52–2.51	NS
Hen's egg	2.0/(169/8614)	1.68–2.28	2.0/(66/3202)	1.60–2.61	NS
Cacao	1.2/(102/8614)	0.97–1.44	0.6/(19/3202)	0.36–0.93	0.006

NS, not significant.

Table 4. Comparisons between food allergy and non-allergic food hypersensitivity (FA/NAFH) suspected and not-suspected patients in terms of various independent variables

Independent variables	FH/NAFH suspected		FH/NAFH not suspected		Odds ratio	Confidence interval (95%)	<i>P</i> -value
	<i>n</i>	%	<i>n</i>	%			
Age							
< 40	466	41.7	4816	45.1	1.14	1.01–1.29	0.03
≥ 40	652	58.3	5882	54.9			
Familial atopy							
Yes	617	55.2	1617	15.1	6.90	6.07–7.87	< 0.001
No	501	44.8	9078	84.9			
Household pets							
Yes	119	10.7	912	8.5	1.30	1.04–1.56	0.01
No	998	89.3	9780	91.5			
Nasal allergy							
Yes	459	41.1	1771	16.6	3.50	3.08–3.99	< 0.001
No	659	58.9	8927	83.4			
Itching dermatitis/urticaria							
Yes	457	40.9	874	8.2	7.80	6.77–8.92	< 0.001
No	661	59.1	9824	91.8			
Doctor-diagnosed asthma							
Yes	230	20.6	1024	9.6	2.50	2.08–2.86	< 0.001
No	888	79.4	9670	90.4			
Smoking habits							
Yes	6316	59.1	670	59.9	1.03	0.91–1.17	0.33
No	4382	40.9	448	40.1			

not consent to be challenged. Another subject could not be challenged because she was unable to discontinue antihistaminic and steroid medication because of her severe asthma.

Sensitizations evaluated by skin prick test and in vitro specific immunoglobulin E results

SPTs with inhalant allergens revealed that the most frequent allergen was grass pollens, followed by cereal and weed pollens. The most frequent food allergens determined with SPTs and *in vitro* sIgE tests were hen's egg and also tomato, which are known to display cross-reactivity with grass and birch pollens. In addition, other grass-related fruits such as oranges and *Artemisia vulgaris*-related vegetables such as carrots were also detected in some subjects (Table 6). None of the subjects showed

Table 5. Effects of age, familial atopy, household pets and atopic diseases on self-reported food hypersensitivity (FH)

Independent variable	Adjusted odds ratio	Confidence interval (95%)	
		Lower	Upper
Suspected FA/NAFH			
Ages < 40 years	1.32	1.19	1.49
Familial atopy	4.28	3.58	4.88
Household pets	1.33	1.09	1.58
Nasal allergy	1.56	1.27	1.78
Itching dermatitis/urticaria	3.88	3.29	4.48
Doctor-diagnosed asthma	1.45	1.18	1.78

sensitivity to latex (Table 6). Additionally, none of the study participants who had reported symptoms with spices displayed positive SPTs or *in vitro* sIgE results.

Table 6. Sensitivities evaluated by skin prick tests

Positive skin prick test results	<i>n</i>
Grass pollens	13
Cereal pollens	13
Weed pollens	8
Tomatoes	6
Hen's egg	6
Orange	3
Eggplant	3
Peanut	3
Tree pollens	3
Artemisia	3
Strawberry	2
Carrot	2
Banana	2
Hazelnut	1
Pear	1
Spinach	1

Table 7. *In vitro* sIgE results for some food items

Positive <i>in vitro</i> sIgE results	<i>n</i>
Tomatoes	4
Hen's egg	6
Orange	2
Eggplant	1
Peanut	2
Strawberry	2
Carrot	1
Banana	2
Hazelnut	0
Pear	1
Spinach	0

The SPT and *in vitro* sIgE test results of food items were compatible and are shown separately in Tables 6 and 7.

Food challenge test results

A total of 96 challenge tests (30 for spices, seven for food additives and 59 for foods) were applied to 29 people. Fifteen people were challenged with red chili and black pepper as used in traditional foods. The blinding procedures failed in spices. So as not to miss out on reactions such as oral allergy syndrome, gelatine capsules were not preferred and instead open challenge tests were applied. The rest of the 66 challenge procedures were applied as DBPCFC tests (Table 8).

During the challenge tests, food anaphylaxis arose in two patients, one due to orange and the other due to banana. One patient with a history of anaphylaxis to strawberries did not consent to challenging. The symptoms seen after provocations are shown in Table 8. The most frequent symptoms were related to skin including pruritus, urticaria and delayed reactions such as eczema.

Table 8. Food challenge test results including tested food items and symptoms

Challenged food items	No. of subjects challenged	No. of subjects reacted	Symptoms occurred
Hen's egg	15	8	OAS and pruritus (1 subject) Angioedema and urticaria (1 subject) Pruritus (3 subjects) Urticaria (3 subjects)
Tomato	13	7	OAS and pruritus (1 subject) Pruritus (3 subjects) Urticaria (3 subjects)
Red chili	15	5	OAS (1 subject) OAS and urticaria (1 subject) Pruritus (3 subjects)
Black pepper	15	2	Pruritus (2 subjects)
Food additives	7	5	Delayed skin reactions (5 subjects)
Chocolate	7	3	Urticaria (3 subjects)
Hazelnut	4	1	Pruritus (1 subject)
Orange	3	2	Food anaphylaxis (1 subject) Asthma, rhinitis (1 subject)
Carrot	3	1	Urticaria
Walnut	3	1	Urticaria
Eggplant	2	1	Pruritus
Peanut	3	0	–
Potato	1	1	Asthma, rhinitis and pruritus (1 subject)
Strawberry	1	1	Urticaria
Fish	1	1	OAS and urticaria (1 subject)
Spinach	1	1	Pruritus
Banana	1	1	Food anaphylaxis (1 subject)
Pear	1	1	Urticaria

OAS, oral allergy syndrome.

On the other hand, none of the 50 healthy subjects displayed any adverse reaction to the blinded food items and food additives.

At the challenge tests, no FA/NAFH was assessed in nine participants. Three subjects who had positive skin tests did not react on challenge and formed the 'sensitized group' (Fig. 1). In five participants with negative prick tests, challenge tests with foods and food additives were positive and they formed the 'NAFH group'. Six participants displayed positive prick tests and challenge tests to suspected foods and formed the 'food allergic group'. The remaining six participants displayed both allergic and pseudoallergic reactions to different foods and formed the 'both allergic and NAFH group'.

After all these investigations at the clinic, the point prevalence of FA/NAFH was 0.3% (30/11 816; 95% CI: 0.17–0.36%), while the FA and NAFH rates proven by DBPCFC tests were 0.1% (12/11 816; 95% CI: 0.05–0.18%) and 0.1% (11/11 816; 95% CI: 0.05–0.17%), respectively.

Six subjects who showed both FA and NAFH caused overlapping in the calculation of the confirmed prevalence. The above-mentioned 13 participants who did not consent to challenging formed the possible FA/NAFH group and were also included in the calculation of point prevalence of FA/NAFH, because they could not be excluded as not having FA/NAFH, but were not included in the confirmed prevalence estimation. This caused discordance so that the total of the confirmed prevalence of FA and NAFH was not found to be equal to the point prevalence of FA/NAFH.

Discussion

To our knowledge, this cross-sectional study is the first representative study evaluating FA/NAFH in adults in our geographical region. Its large sample size originating from an unselected population and its method involving all available diagnostic tools to evaluate FA/NAFH to a wide range of food items including food additives strengthen the reliability of the data obtained in this study. However, despite all efforts, the number of non-responders during telephone contacts and dropouts at the phase of clinical settings were above our expectations and may cause concerns about underestimation of the real FA/NAFH rates. After considering similar studies, it was obvious that such failures are unavoidable, and accordingly, comparing the results with the previous investigations seems not to cause a great bias.

The self-reported FA/NAFH was found to be 9.5% in this study, which was relatively low when compared with some of the previous studies. This prevalence was calculated according to the answers given to the first application of the questionnaire, because the validation of this questionnaire had been done before and the second application was applied only to half of the population. Some 10 years ago, different researchers in the UK, Holland and the USA reported self-reported FA/NAFH prevalence as 14.7%, 12% and 16%, respectively [14–16]. Woods et al. compared the reported prevalence of FA and food intolerance in different countries depending on the dietary information collected as part of the ERCHS (European Respiratory Community Health Survey), and they demonstrated significantly different results from multiple countries [5]. The lowest rates were found in Spain as approximately 4.6% and the highest in Australia as 19.1%. The authors could not explore the reason for the difference, but tried to use cultural differences to explain it. Also a meta-analysis that was published very recently stated that the prevalence of self-reported FA is significantly different between countries ranging from 3% to 35% [6]. In France, the self-reported FA was estimated as 3.24% [17]. As the low prevalence of self-reported FA/NAFH in Spain, France and Turkey is all noticeable, we here can speculate that people in these countries, may in

some way, with the consumption of the 'Mediterranean Diet' develop protection against FA/NAFH.

In this study, the prevalence of FA/NAFH which was calculated by also including the 'possible FA/NAFH group' was found as low as 0.3%, and the FA and NAFH assessed by DBPCFC were 0.1% and 0.1%, respectively, which were extremely lower than the reported prevalence in previous studies which also had used DBPCFC [12, 14, 15, 18]. Young et al. reported the prevalence of FA proven with diagnostic measures as 1.4–1.8% in English households, but they tested a limited range of food items and did not include pollen-associated FA and NAFH [14]. Jansen et al. reported the prevalence of FA/NAFH in the Netherlands with DBPCFC as 2.4%, whereas Zuberbier et al. reported the confirmed prevalence of FA/NAFH in the adult population in Berlin as 3.7% [12, 15]. Roehr et al. as part of the same study presented the proven prevalence in the pediatric population as 4.2% [18]. As reported in some previous studies, the self-reported prevalence of FA/NAFH is frequently reported higher than the prevalence depending on objective measures [6, 19]. This may relate to the fact that in most of the studies, the question related to FA/NAFH is asked directly without specifying the expected symptoms. Additionally, the questionnaires usually evaluate lifetime prevalence, whereas diagnostic procedures try to explore the point prevalence. As in our study, questions dealing with food hypersensitivity were asked at the end of the questionnaire after focusing on atopic diseases, the self-reported FA/NAFH is nearly 40 times higher than the proven rate but rather lower than that of the mentioned studies.

We may speculate that the reasons for the very low prevalence of FA and NAFH in the present study may be related to some cultural, genetic and nutritional factors in the Turkish population. As mentioned previously, the 'Mediterranean Diet' may offer protection against FA/intolerance [5], although the nutrition habits in the big cities are not fully 'Mediterranean' any more and have been changing in recent years. Another possibility is that homemade yoghurt, a widely used dietary item started in infancy and frequently consumed lifelong, may function as a protecting factor against FA/NAFH. The low consumption of processed foods and the habit of prolonged slow stovetop cooking may also contribute to this low rate. Additionally, the general tendency of the population towards breastfeeding may also be a factor.

Heredity is a major predisposing factor in allergic diseases. Previously, parental history of atopy was represented as a significant causal factor for FA [20]. Sarafino investigated parent-child connections for atopic illnesses including FA in a sample of 325 families. He concluded that children are more likely to develop asthma, eczema, food allergies or hayfever if their parents are afflicted with the specific illness than if their parents are not [21]. Similarly, in the present study, the most significant factor

influencing FA/NAFH was found to be familial atopy and the most related atopic disease was itching dermatitis/urticaria. In previous studies, FA/NAFH in adults has frequently been reported and associated with other manifestations of atopy [17, 22]. In our study, nasal allergy and doctor-diagnosed asthma were also significantly associated with FA/NAFH.

In our study, gender does not seem to have an effect on FA/NAFH, although in most of the previous studies, women were found to be more affected [12, 14, 15, 17, 22]. Because the vast majority of the respondents were women, the results may be considered to be rather representative for women. However, there was not a significant difference between genders in the self-reported prevalence of FA/NAFH. In the present study, smoking habits do not seem to have an effect on FA/NAFH as again presented in previous studies, but on the contrary to the previous data, doctor-diagnosed asthma is found to be associated with FA/NAFH [5]. Additionally, the younger age group (< 40 years old) seems to be more affected.

Kanny *et al.* found that 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 [17]. In our study, the most important foods causing FA/NAFH are found to be hen's egg, fruits and vegetables such as tomatoes and strawberries. Chocolate was also frequently suspected by the subjects. The subjects who revealed positive SPT results to peanuts responded negatively on challenge. As expected in the adult population, true allergy to milk was inconsiderable [5]. Because the peanut is not consumed very much in Turkey, it was not found among the major food allergens, as opposed to many other European countries with the exception of France and the UK [2, 18]. Interestingly, our findings show us that although the hazelnut is frequently consumed, it is also not a major allergen.

Although the tomato is at the top of the list of food items causing self-reported FA/NAFH and the most important food item according to SPT results, half of the subjects did not show positive reactions to the prick tests. This may be explained by the fact that one-half of the reactions are due to type I allergy and the other half due to natural ingredients reacting as pseudoallergens. Zuberbier *et al.* have suggested that aromatic volatile ingredients in foods such as tomato are novel agents eliciting pseudoallergic reactions especially in chronic urticaria patients, and natural pseudoallergens are more important than artificial additives at least in urticaria [23, 24]. When we reconsider our patients' reactions to tomatoes from this point of view, we saw that subjects who have showed positive results to SPTs complain mostly of oral allergy syndrome and the ones that display negative SPT and *in vitro* sIgE results complain of symptoms mostly related to skin. Similarly, five out of seven participants challenged with artificial pseudoallergens showed itching dermatitis, urticaria or delayed skin rash. Wilson and Bahna suggested

that food additives are more likely to cause skin irritation in patients with underlying skin disorders [11].

Additionally, 5 of 15 participants challenged with spices displayed mostly skin lesions, but sIgE sensitivities were not shown in skin and *in vitro* tests. This may be due to the fact that although these spices may react with sIgE, the drying procedure used in the processing of these spices may have destroyed profilins and major allergen homologues [25]. Interestingly, in the present study, the most frequent symptoms due to other food items such as pruritus, urticaria and delayed reactions such as eczema were also found to be related to skin. Similarly, Vierk *et al.* reported that the most frequent reaction in adult population due to FA in the USA is usually a skin reaction, such as hives, itching or redness of the skin [26].

Only a few studies have investigated the prevalence of adverse reactions to food additives, and most of the population-based studies estimate the prevalence of reactions to food additives at < 1% in adults [23]. Similarly, Zuberbier *et al.* found the prevalence of pseudoallergic reactions as 1.1% [12]. In our study, this rate was found as 0.04% (5/11 816). This may be attributed to the dietary habits in Turkey, where most of the population consume homemade meals rather than commercially prepared foods such as western-type fast foods and thus experience fewer reactions to additives.

We conclude that FA/NAFH in Turkey is rather low compared with Northern and Western European countries. This situation may be due to genetic, cultural or dietary factors. Familial atopy was found as the most significant risk factor, while itching dermatitis/urticaria was the most frequent symptom related to FA/NAFH. The mostly suspected as well as proven to be causative food items were tomatoes and hen's eggs. Although, we think that our results may be associated with the geographic characteristic of our country, comparable data in adults from Mediterranean countries other than France and Spain are lacking. Further studies may clarify the reason of this very low prevalence of FA/NAFH.

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