

Elicitors and phenotypes of adult patients with proven IgE-mediated food allergy and non-immune-mediated food hypersensitivity to food additives

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Funding information

German Federal Ministry of
Education and Research; Deutsche
Forschungsgemeinschaft

Abstract

Background: Food allergy is a growing health concern with a prevalence of 2%–3% in the adult population in Europe. Non-immune-mediated food hypersensitivities, which include reactions after ingestion of food additives, affect 1% of adults and may resemble IgE-induced allergic reactions without identifiable immunologic sensitization. A double-blind placebo-controlled food challenge (DBPCFC) is the gold standard for the diagnosis of any food hypersensitivity.

Objective: We analysed a large group of adult patients with suspected food hypersensitivity, who had undergone DBPCFC, to better understand IgE-mediated food allergy and non-immune-dependent food hypersensitivity to food additives in adults regarding elicitors, symptoms and positivity rates of oral challenges.

Methods: Data from 541 patients with suspected food hypersensitivity were analysed, who underwent an oral food challenge between 2010 and 2019.

Results: IgE-dependent food allergy was confirmed in 114 of 329 adult patients (34.6%). The confirmation rate was lower in the group of patients with suspected non-immune-mediated reactions to food additives (65 of 286, 22.7%). Urticaria and angioedema appeared more frequently in patients with IgE-mediated food allergies. By contrast, flush and diarrhoea were the most frequent symptoms after a challenge in the group with the non-immune-mediated reactions to food additives. Wheat and celery were the most frequently identified food allergens in adults, whereas colourings and preservatives were the most frequent elicitors of non-immune-mediated food hypersensitivity.

Conclusion: The importance of oral food challenges for the diagnosis of food hypersensitivity is confirmed. IgE-dependent food allergy is more frequently proven, reaching a positivity rate of one-third and only about 20% for non-immune-mediated hypersensitivity. Future studies should elaborate on the mechanisms of non-immune-mediated food hypersensitivity and the clinical impact of cofactors in this setting.

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KEYWORDS

anaphylaxis, double-blind, food additives, food allergy, non-immune-mediated food hypersensitivity, placebo-controlled food challenges

1 | INTRODUCTION

Immunoglobulin (IgE)-mediated food allergy is a common medical condition with clinical manifestations ranging from mild skin symptoms to life-threatening impairment and in rare cases resulting in death.¹ On the other hand, it is also an overestimated medical problem, as up to 20% of the general population report hypersensitivity reactions to some kind of food.² Different studies throughout Europe indicated that the rate of proven food allergy is much lower and depends on various endogenous and exogenous factors (e.g., geographical region, age or eating habits).³

Primary food allergies occur mainly not only via gastrointestinal but also epicutaneous sensitization to thermo- and acid-stable food allergens, such as the plant-based storage proteins, e.g., peanut and tree nuts, or food allergens from animal sources, e.g., cow's milk, hen's egg or shellfish, and the panallergenic lipid transfer proteins (LTP).^{4,5} The latter ones are present in native as well as cooked or processed plant-based food.⁶⁻⁸ Secondary food allergies are induced by thermolabile allergens found in raw fruits, vegetables and some tree nuts due to cross-reactivity mainly with birch pollen allergens.⁹

Food allergy in adults is mostly caused by tree nuts, fruits and vegetables.^{10,11} Pollen-associated food allergies are more common in adulthood.¹² Recent data from EuroPrevall studies indicated a large variation in food allergy prevalence throughout Europe, being more common in central northern versus southern European countries.¹³ The prevalence of a probable food allergy in adults has been reported from 0.3% to 5.6%.¹⁴

IgE-mediated food allergy requires sometimes the presence of cofactors for elicitation.¹⁵⁻¹⁷ This phenomenon is well known not only for wheat-induced anaphylaxis¹⁸ but has also been reported for other elicitors like shellfish as well as LTP-dependent reactions.⁸ Such cofactors can either enhance the clinical severity or are even indispensable for the elicitation of a given reaction.¹⁹ In adults, in up to 30% of food hypersensitivity cases, the requirement of such cofactors for the elicitation of a given reaction has been reported.²⁰

In adults, immediate reactions may occur after the ingestion of food additives, causing non-immune-mediated food reactions which are supposed to affect up to 1% of adults.²¹ Food additives are generally categorized as natural additives and synthetic additives. Natural and synthetic food additives are further classified depending on their specific role into many functional classes, e.g., flavour enhancers, preservatives, thickeners, stabilizers, glazing agents, flavours, emulsifiers, humectants, colourants and gelling agents.²² Recent epidemiological data on the prevalence and symptoms are missing. The mechanism of how food additives induce symptoms in a given individual is poorly understood. Due to the lack of a

Key Messages

- Non-immune-mediated food hypersensitivities to food additives may resemble IgE-induced allergic reactions
- The "gold standard" for the diagnosis of food hypersensitivities remains the double-blind, placebo-controlled oral food challenge.
- Our results show not only clear differences but also overlaps of the clinical profiles in patients with proven IgE and non-immune-mediated food hypersensitivity to food additives.

standardized diagnostic workup, this patient group is often under-recognized and under-diagnosed.

In this study, we investigated a large cohort of adult patients with suspected food hypersensitivity. The patients underwent controlled food challenges to food allergens and/or food additives to exclude or confirm the diagnosis. The data reveal positivity rates and clinical profiles of adult patients with food allergy or non-immune-mediated reactions to food additives including demographic features, elicitors and symptoms.

2 | MATERIAL AND METHODS

We assessed data of patients with suspected food hypersensitivity who presented for an allergy workup because of suspected food hypersensitivity excluding FPIES, lactose and fructose intolerance in the Division of Allergy and Immunology at the Charité – Universitätsmedizin Berlin, Germany, between 2010 and 2019. The patients included in this analysis had immediate symptoms after food ingestions in their medical history and underwent at least one food and/or food allergen challenge. The food challenges were carried out in an inpatient setting and were conducted as double-blind, placebo-controlled food challenges (DBPCFC). In a few cases, open food challenges were performed when the blinding of the suspected allergen was impossible. The assessment of the clinical data for the research purposes was approved by the ethics committee at the Charité (EA2/301/21).

2.1 | Assignment to an oral food challenge

All subjects reported here received an oral food challenge. The decision to proceed with an oral food challenge was based on the patient's medical history (previous reactions, atopic history and

comorbidities) and allergy workup including skin-prick test (SPT) and/or serum IgE testing.⁵ Important decision-making factors for conducting an oral food challenge included: the importance of the food in the individual's diet, the expansion of the diet in patients with multiple dietary restrictions, the evaluation of the status of tolerance to cross-reactive food and, in a few cases, the re-assessment of an existing allergy. The decision to challenge with food additives was based on the patient's medical history, negative sensitization tests (sIgEs and SPTs) and as a mandatory criterium on the improvement of symptoms during a protocol of a food additive-free diet over 3 weeks.²¹ Patients with suspected non-IgE-mediated hypersensitivities such as food protein-induced enterocolitis syndrome (FPIES), food protein enteropathy (FPE), food protein-induced allergic proctocolitis (FPIAP) and eosinophilic gastrointestinal disorders (EGIDs) such as eosinophilic oesophagitis (EoE) were not included in our analysis.

2.2 | Food allergen challenges

DBPCFC was performed with five increasing dose steps. The food challenge started with 0.1 g of the suspected food allergen up to a cumulative dose that corresponded to an average daily consumption (Table S1). The daily consumption doses differed for each food and were based and calculated according to an average amount for consumption (for examples see Table S1). The time interval between the first and second dose was 15 and 30 min between the following steps. There was a minimum interval of 2 h between verum and placebo if multiple allergens were tested in a single hospital visit. For some allergens such as mammalian meats and wheat, the intervals were longer; in these cases, the allergens were tested on different days. In the cases of exclusion of food allergy in patients with no history of anaphylaxis, the challenges were conducted with one dose of a daily consumption amount and no titration. The food allergens used in the challenges were blinded and mixed into defined provocation meals (porridges). A hypoallergenic infant formula (Nestlé BEBA SINLAC) was the basic ingredient. Cacao and beta-carotene were used for colour blinding. To blind the flavour, sugar and different flavoured syrups (peppermint, lemon, pear and raspberry) were used as described previously.²³ Rice flakes were used as consistency blinders.

2.3 | Food additive challenges

The challenges for food additives following an elimination diet, excluding colourants, preservatives and antioxidants, were conducted as capsule challenges as previously described.²⁴ The food additive challenges were conducted only if the symptoms improved during a food additive-free diet. The food additives were blinded in capsules. The capsules were ingested at least 2 h away from meals and the number of capsules ingested differed according to the food additives tested. The patients underwent

the challenge with a mixture of the food additives, with all capsules given at once. The tested food additives included the following: colouring agents (E110, 122, 124, 151, 104, 127, 131, 132, 172 and 120; 5 mg each, and E102; 50 mg), preservatives (E200, 211 and 214; 1000 mg each, E223 and 251; 100 mg each), antioxidants (E320, 321, 310 and 306–309; 50 mg each), taste enhancer (E621; 500 mg) and naturally occurring substances (salicylic acid, 100 mg). The placebo capsules were filled with mannitol and silicon dioxide or glucose. The capsules are manufactured from the pharmacy in-house.

2.4 | Consideration of cofactors

If the patient's history indicated a possible relevance of a cofactor, we integrated the cofactor during the food challenge. Cofactors were applied separately before the addition of the suspected food allergen. In detail, acetyl-salicylic acid (ASA) was applied 60 min before food intake, and doses were given according to the patient's history, ranging from 100 to 500 mg. Alcohol (15 ml ethanol 96%, mixed with 200 ml water and aroma) has to be ingested 10 min before the challenge. The exercise was applied 60 min after the food intake.²⁵ The length and intensity of physical activity were based on the patient's performance status on a bicycle ergometer (and reached up to 60 min).

2.5 | Data processing and analysis

Statistical analysis was performed using R version 4.0.0 (2020-04-24) and the R package gtsummary.²⁶ A simple comparison of categorical variables was performed using either the Chi² test or Fisher's exact test (where the number of observations in a bin was less than 10). Continuous variables were analysed using the Wilcoxon rank-sum test. We defined statistical significance as $\alpha = 0.05$.

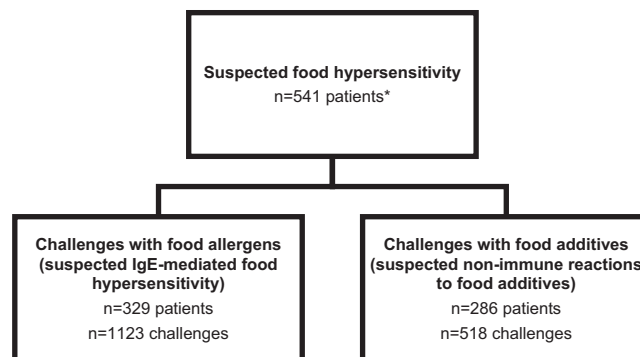


FIGURE 1 Patients included in the analysis. Patients included in this analysis were divided into two groups: patients who underwent challenges with food allergens and food additives. *A total of 74 individuals underwent challenges with food allergens and food additives and were included in both groups.

3 | RESULTS

3.1 | Patient population

A total of 541 patients were included in this analysis. Based on their history and their clinical assessment including SPT, in vitro diagnostics and dietary measures, 329 patients were challenged with food allergens, 286 patients with food additives and 74 patients with both (Figure 1). Patients from the food allergen challenge group had a median age of 39 years and the majority were females (72%). The median total IgE was 122 kU/L and the median tryptase was not elevated (median value 3.83 µg/L). Patients in the food additive challenge group had a higher median age (45 years), lower total IgE (51 kU/L) and the median tryptase was within normal limits (median

value 3.78 µg/L). In this group, 81% were female and the medical history of previous anaphylaxis and/or atopic diseases was lower than in the food allergy group, 16% versus 52% for anaphylaxis and 50% versus 86% for atopic diseases (Table 1).

The symptom profile of previous reactions differed significantly between the groups. Patients with suspected IgE-mediated food allergy suffered predominantly from skin symptoms including angioedema (53%) and urticaria (43%), whereas diarrhoea and vomiting were less frequent (24% and 12%). In contrast, patients with suspected non-immune-mediated reactions to food additives reported most frequently diarrhoea (39%). Skin symptoms were also present, but to a lesser extent than in the IgE food allergy group (angioedema 31%, urticaria 27% and flushing 15%) (Table 1, Figure 2).

TABLE 1 Patient characteristics (entire cohort)

Characteristics of the patients ^a	Entire cohort			Patients with positive OFC						
	Suspected IgE-mediated food hypersensitivity (n = 329)	Suspected non-immune-mediated reactions to food additives (n = 286)	p-Value ^b	Confirmed IgE-mediated food hypersensitivity (n = 114) ^c	Confirmed non-immune-mediated reactions to food additives (n = 65)	p-Value ^b				
Median age at challenge (years)	39 (13–81)	45 (15–81)	.005	36 (20–75)	41 (19–71)	.6				
Median levels of total IgEs (kU/L)	122	51	<.001	136	54	<.001				
Median levels of tryptase (µg/L)	3.83	3.78	.2	3.83	3.33	.054				
	n	%		n	%					
Gender (female)	236	72%	232	81%	.006	84	74%	55	85%	.091
Medical history of anaphylaxis	170	52%	45	16%	<.001	63	55%	8	12%	<.001
Coexisting atopic diseases	282	85%	143	50%	<.001	102	89%	35	54%	<.001
Coexisting gastrointestinal diseases	43	13%	65	23%	.002	22	19%	13	20%	>.9
Other coexisting diseases	73	22%	83	29%	.052	21	18%	17	26%	.2
Symptoms of previous reactions	n	%	n	%		n	%	n	%	
Angioedema	173	53%	89	31%	<.001	57	50%	21	32%	.022
Flushing	25	8%	43	15%	.003	6	5%	11	17%	.011
Urticaria	140	43%	76	27%	<.001	43	38%	14	22%	.025
Generalized erythema	28	9%	23	8%	.8	12	11%	6	9%	.8
Diarrhoea	80	24%	112	39%	<.001	35	31%	30	46%	.039
Vomiting	39	12%	27	9%	.3	16	14%	7	11%	.5
Loss of consciousness	28	9%	12	4%	.03	14	12%	3	5%	.093

Note: The basic demographics and patient characteristics of the entire cohort and patients with confirmed IgE-mediated and non-immune-mediated reactions to food additives. Patients included in this analysis were divided into two groups, patients who underwent challenges with food allergens (suspected IgE-mediated food hypersensitivity) and with food additives (suspected non-immune-mediated reactions to food additives).

^aA total of 74 individuals underwent challenges with food allergens and food additives and were included in both groups.

^bWilcoxon rank-sum test; Pearson's Chi-squared test.

^cPositive sensitization tests in 106/162 cases (n = 74 SPT positive, n = 32 negative SPT but positive sIgE and n = 56 no sensitization tests available or possible).

3.2 | Confirmation rates of IgE-dependent and non-immune-dependent food allergies differ significantly and display distinct clinical profiles

IgE-dependent food allergy was confirmed in 114 of 329 adult patients (34.6%) (Table 1). The confirmation rate was lower in patients with suspected non-immune-mediated reactions to food additives (65 of 286, 22.7%). Comparing the confirmed cases of food allergy and non-immune-mediated reactions to food additives, in the latter group, the median ages (36 vs. 41 years) and the proportion of females (74 vs. 85%) were higher. By contrast, in the IgE-dependent hypersensitivity group (Table 1), the medical history of anaphylaxis and the co-existence of atopic diseases were significantly more frequent and median tryptase levels and total IgE were higher.

The symptoms as depicted in Figure 2 show a dominance of angioedema and urticaria in patients with IgE-mediated food allergy while flush and diarrhoea were the most prevalent symptoms in the group with non-immune-mediated reactions to food additives. Similar symptom profiles were seen during food challenges (Table S2, Figure 3).

3.3 | Celery and wheat were the most frequently identified food allergens in adults

The most frequently identified food allergens in the adult cohort of patients with suspected IgE-dependent food allergies were celery,

wheat, soy and hazelnut (Table 2). However, when the positivity ratio of the challenges was considered, hazelnut, almond but also hen's egg ranged among the elicitors with the highest positivity ratio. In contrast, wheat provocations had the lowest positivity ratio. A total of 25/162 (15%) food challenges were only positive if a cofactor was considered. Table 3(a,b) shows the data regarding the requirement of a cofactor for the elicitation of a reaction. In particular, wheat and celery were among the allergens most frequently requiring a cofactor for the elicitation of a reaction (12 and 5 cases). Exercise ($n = 11$), food additives ($n = 10$) and acetylsalicylic acid ($n = 8$) were the most frequently included cofactors during positive oral food challenges.

3.4 | Colourings and preservatives are among the most frequent elicitors of non-immune-mediated food hypersensitivity

The overall positivity ratio for the food additive challenges given as a mixture was 15% (44/292). Colourings and preservatives, as well as stabilizers, reached higher positivity ratios, with 18% for preservatives and colourings and 25% for stabilizers (Table 4), in those who reacted to the mixture or had a highly suspicious history of non-immune hypersensitivity.

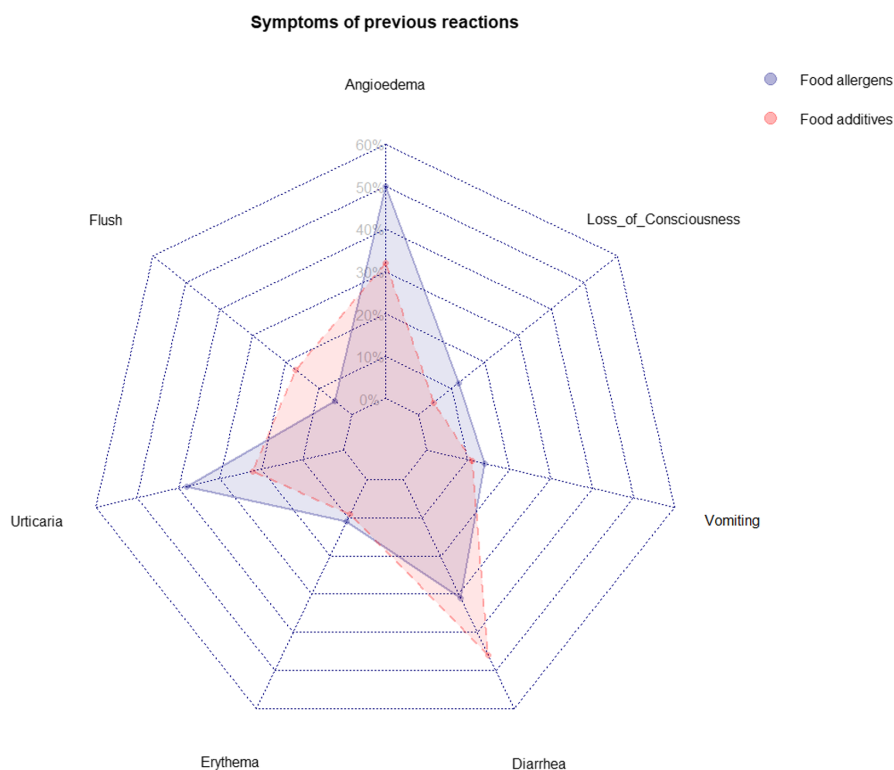


FIGURE 2 Symptoms of previous reactions (data are shown in descriptive Table 1). The symptoms observed during previous reactions. The colour blue is used for patients with suspected IgE-mediated food allergy and the colour red is used for patients with suspected non-immune-mediated reactions to food additives.

FIGURE 3 Symptoms at challenges. The symptoms observed during the oral food challenges. The colour blue is used for patients with confirmed IgE-mediated food allergy and the colour red is used for patients with confirmed non-immune-mediated reactions to food additives.

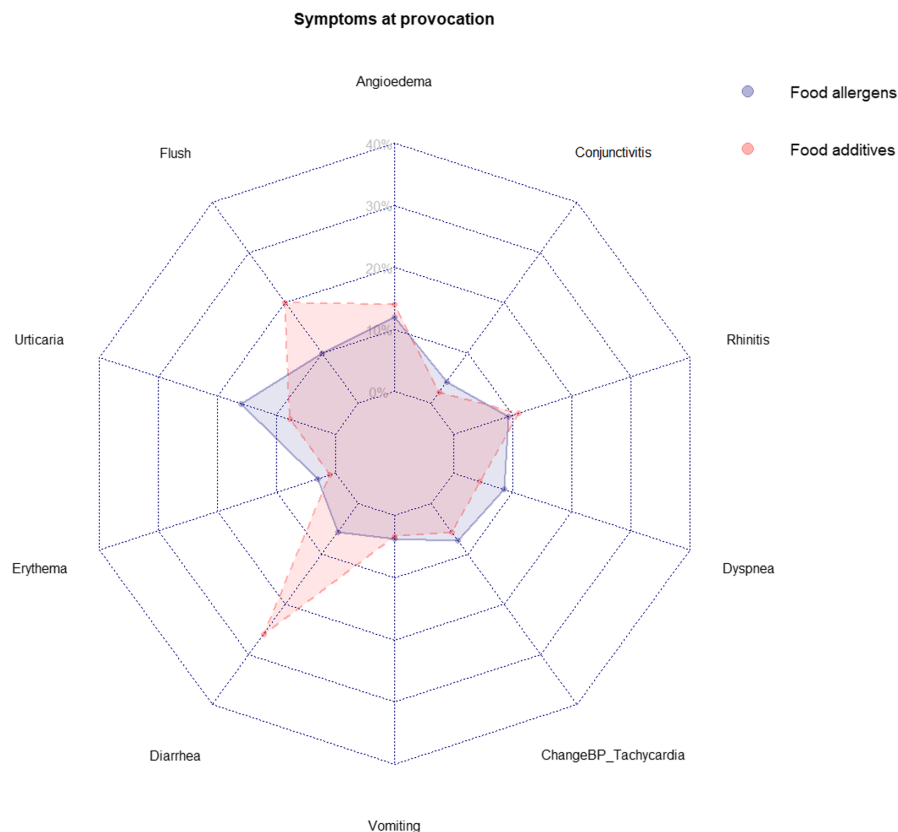


TABLE 2 Most frequently confirmed food allergens, $n = 162$

	<i>n</i>	Positive OFC	Positivity ratio (%)
Positive oral food challenges: most common, proven food allergens			
Wheat	272	20	7%
Celery	135	27	20%
Soy	68	15	22%
Shrimps	45	6	13%
Rye	43	6	14%
Hazelnut	33	11	33%
Peanut	30	6	20%
Cow's milk	28	5	18%
Hen's egg	23	6	26%
Almond	15	4	27%

4 | DISCUSSION

The “gold standard” for the diagnosis of food allergy remains the double-blind, placebo-controlled oral food challenge.⁵ This procedure allows to confirm or exclude the clinical relevance of existing sensitizations, or supposedly observed symptoms, independent of subjective factors. The value of performing an oral food challenge should be determined while taking into consideration the risks and benefits for a patient undergoing the oral food challenge. In patients with anaphylactic reactions that are clearly attributable to certain foods, challenges are usually not required. However, it may

be useful to determine the allergen amount necessary to trigger a reaction (threshold level) and/or to investigate the impact of cofactors on the outcome of a reaction. The use of recombinant single allergens (e.g., Ara h 2)^{11,12} and/or a strong skin-prick test (SPT) result (e.g., $>8\text{mm}$)¹³ allows for an improved assessment of the risk of severe reactions in clinical practice. However, the sensitivity of the SPT and sIgE values varies among different food allergens and is sometimes not sufficient for making a diagnosis (e.g., celery and wheat). On the other hand, several publications suggest a value of recombinant sIgE detection to predict a reaction. Most studies, however, have been performed in paediatric cohorts and their role in adulthood has not been completely established. For example, Tri a 19 has been suggested for wheat allergy,^{27,28} whereas for other allergens, like celery, the availability of recombinant allergen diagnostics is still limited.

In this analysis, IgE-dependent food allergy was confirmed in 34.6% of patients with suspected food allergy. We emphasize that these data represent a patient population who were seen in specialized allergy practice. In Germany, such challenge tests in adults are only performed in a few specialized centres. The oral food challenges were performed to confirm or to exclude the suspected new-onset food allergies and in a few cases to re-assess the clinical relevance of an existing allergy.

The challenge protocol used in our clinic differs from other standardized published protocols in terms of starting dose and number of dosing steps. This protocol is suitable to increase time and cost-effectiveness without endangering the patients at least with regard to the allergens tested and the patients challenged in our cohort.

TABLE 3 (a) Oral food challenges with cofactor inclusion, $n = 25$; (b) Most frequent allergens requiring a cofactor, $n = 25$

(a)	<i>n</i>	%
Positive oral food challenges ($n = 162$): cofactors		
With inclusion of cofactors	25	15%
With inclusion of 1 cofactor	15	9%
With inclusion of 2 cofactors	7	4%
With inclusion of 3 cofactors	1	1%
With inclusion of 4 cofactors	2	1%
Without cofactor inclusion	137	85%
(b)	<i>n</i>	
Positive oral food challenges with the inclusion of cofactors ($n = 25$)		
Wheat	12	
Celery	5	
Prawn	3	
Hazelnut	1	
Soy	1	
Fish	1	
Other original products	2	

TABLE 4 Most frequently identified food additives in groups

	<i>n</i>	Positive	Positivity ratio (%)
Challenges with food additives ($n = 519$)			
Colourings	61	11	18%
Preservatives	87	16	18%
Antioxidants	56	7	13%
Glutamate	11	1	9%
Stabilizer	4	1	25%
Others (i.e., sweeteners and salicylic acid)	6	2	33%

We identified celery, wheat, soy and hazelnut as the most frequently confirmed triggers of food allergy in our adult patient cohort. Due to the history (onset of symptoms in adulthood), we suspect the new-onset allergy in this age group^{29,30}. Celery, hazelnut and soy are also common pollen-associated food allergens in adults³¹ and whether the clinical reaction is induced via PR10 sensitization can only be determined via sIgE profiling including the PR10 storage protein and LTP subfamilies. A previous study from our group in patients suffering from food-induced anaphylaxis revealed a high-frequency PR10 sensitization.³² Another study from the USA has shown that the five most prevalent adult-onset food allergies were shellfish (13.3%), milk (6.0%), wheat (5.6%), tree nut (4.8%) and soy (3.9%).³³ Although we suspect that the prevalence numbers are estimated too high (data based on patient-based questionnaires, not provocation), the elicitors are overlapping. Interestingly, the challenges with

peanuts were positive in 20% of the suspected cases. This rather low provocation ratio may be explained by the fact that most clinically relevant cases of peanut allergy are already diagnosed in early childhood³⁴ and persist throughout adulthood.^{35,36} In addition, in patients with anaphylactic reactions to peanuts, the sensitization via SPT and/or sIgE can be identified with a certain prognostic value, which means in clinical practice with an undoubted positive medical history a challenge is not required.

Interestingly, 25 challenges were only positive after the implementation of a cofactor. Moreover, 13 of 25 patients reacted only when multiple cofactors were considered during the oral provocation. This phenomenon has been described previously,^{15,17,37} although the underlying mechanisms have not been unravelled yet. In our analysed cohort, wheat, celery and crustaceans were the most frequently proven food allergens in combination with cofactors. Exercise, NSAIDs and food additives were the most frequently involved cofactors in our cohort. This finding is in line with the literature^{15,19,38} and supports that in such patients, cofactors should be considered more routinely if a given challenge with the according food allergen was negative.

Challenges in using food additives are of scientific interest due to their largely unknown mechanism.^{39,40} However, for colourings, an IgE-dependent mechanism has been proposed in some patients.^{41,42} We suspect that confirmed food hypersensitivity to food additives is not only rare but also likely to be medically underdiagnosed, partly due to a lack of controlled challenges. Reactions to food additives should be suspected in patients who report symptoms to multiple unrelated foods or a certain food when commercially prepared (not homemade), and the allergy assessment rules out a type 1 sensitization to food proteins.⁴³ On the other hand, many adult patients presenting with various and also often non-immediate symptoms are suspected to suffer from food hypersensitivity and need to be distinguished. Currently, the placebo-controlled challenges with food additives are performed in specialized centres only. Our data indicate that most patients react only when multiple food additives (mixtures) are given. In those patients, the management should consider an incremental build-up diet. Only rarely (38/519) patients react to the fractionated challenge as well. Once the specific eliciting additive has been identified, the key therapeutic management of a non-immune-mediated food hypersensitivity is avoidance. Interestingly, preservatives and colouring agents were the most frequently identified food additives that result in a positive reaction. This observation is in line with our previous data, where we have shown that these additives may trigger a worsening of atopic dermatitis.²⁴

Given the dominance of gastrointestinal symptoms in patients with non-immune-mediated food hypersensitivity, it is important to consider a broad differential diagnosis covering gastrointestinal disorders. Recent publications discuss the potential impact of food additives on the gut microbiota composition potentially involved in the development of irritable bowel syndrome.^{44,45}

In conclusion, we investigated a large cohort of adult patients with suspected food hypersensitivity. To our knowledge, this is the first

larger cohort demonstrating clinical profiles of adults with proven IgE-mediated food hypersensitivity and non-immune-mediated reactions to food additives. Other than a large number of patients, an advantage of our study is that a confirmation of the diagnosis was achieved with DBPCFC. However, although the DBPCFC is the gold standard for the diagnosis of food allergy, oral food challenges may not accurately reflect reactions outside of the challenge setting for the individuals because of the gradual administration of the tested food, the controlled environment, the accurate implementation of cofactors and the challenge discontinuation when objective symptoms occur. Our results show not only clear differences but also overlaps of the clinical profiles in patients with proven IgE-mediated food allergies and non-immune-mediated reactions to food additives. The underlying mechanisms of non-immune-mediated food hypersensitivity remain elusive and should be investigated in more detail in future studies.

AUTHOR CONTRIBUTIONS

AA performed a literature search, performed the statistical analysis, data interpretation and wrote the manuscript. VH and SDB contributed to the statistical analysis. MW, TZ, SDB and JG were involved in patients' workup and care. SDB and JG performed data collection. MW, TZ, SDB and JG contributed to data interpretation. MW and SDB conceived the study design. MW coordinated the manuscript and the data analysis. All authors received and approved the final manuscript.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

FUNDING INFORMATION

This work was partially funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) as part of the clinical research unit (CRU339): Food allergy and tolerance (FOOD@) – 428447634; and by the German Federal Ministry of Education and Research (BMBF; 01KU2005 and 01EA2107B).

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

1. Bock SA, Muñoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. *J Allergy Clin Immunol.* 2007;119(4):1016-1018.
2. Nwaru BI, Hickstein L, Panesar SS, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy.* 2014;69(8):992-1007.
3. Nurmatov U, Dhimi S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy.* 2017;72(8):1133-1147.
4. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy.* 2014;69(8):1008-1025.
5. Worm M, Reese I, Ballmer-Weber B, et al. Update of the S2k guideline on the management of IgE-mediated food allergies. *Allergol Select.* 2021;5:195-243.
6. Pascal M, Muñoz-Cano R, Reina Z, et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. *Clin Exp Allergy.* 2012;42(10):1529-1539.
7. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J.* 2016;9(1):32.
8. Skypala IJ, Asero R, Barber D, et al. Non-specific lipid-transfer proteins: allergen structure and function, cross-reactivity, sensitization, and epidemiology. *Clinical and Translational Allergy.* 2021;11(3):e12010.
9. Worm M, Jappe U, Kleine-Tebbe J, et al. Food allergies resulting from immunological cross-reactivity with inhalant allergens: guidelines from the German Society for Allergy and Clinical Immunology (DGAKI), the German Dermatology Society (DDG), the Association of German Allergologists (AeDA) and the Society for Pediatric Allergy and Environmental Medicine (GPA). *Allergo J Int.* 2014;23(1):1-16.
10. Worm M, Eckermann O, Dölle S, et al. Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria and Switzerland. *Dtsch Arztebl Int.* 2014;111(21):367-375.
11. Baseggio Conrado A et al. Food anaphylaxis in the United Kingdom: analysis of national data, 1998-2018. *BMJ.* 2021;372:n251.
12. Savage J, Johns CB. Food allergy: epidemiology and natural history. *Immunol Allergy Clin North Am.* 2015;35(1):45-59.
13. Popov TA, Mustakov TB, Kralimarkova TZ. Food allergy in adults in Europe: what can we learn from geographical differences? *Curr Opin Allergy Clin Immunol.* 2020;20(2):215-220.
14. Lyons SA, Burney PGJ, Ballmer-Weber BK, et al. Food allergy in adults: substantial variation in prevalence and causative foods across Europe. *J Allergy Clin Immunol.* 2019;7(6):1920-1928.e11.
15. Hompes S, Dölle S, Grünhagen J, Grabenhenrich L, Worm M. Elicitors and co-factors in food-induced anaphylaxis in adults. *Clin Transl Allergy.* 2013;3(1):38.
16. Kraft M, Dölle-Bierke S, Renaudin JM, et al. Wheat anaphylaxis in adults differs from reactions to other types of food. *J Allergy Clin Immunol Pract.* 2021;9(7):2844-2852.e5.
17. Muñoz-Cano R et al. Immune-mediated mechanisms in cofactor-dependent food allergy and anaphylaxis: effect of cofactors in basophils and mast cells. *Front Immunol.* 2020;11:623071.
18. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Wheat-dependent cofactor-augmented anaphylaxis: a prospective study of exercise, aspirin, and alcohol efficacy as cofactors. *J Allergy Clin Immunol Pract.* 2019;7(1):114-121.
19. Worm M, Scherer K, Köhli-Wiesner A, et al. Food-induced anaphylaxis and cofactors - data from the anaphylaxis registry. *Allergol Select.* 2017;1(1):21-27.
20. Worm M, Moneret-Vautrin A, Scherer K, et al. First European data from the network of severe allergic reactions (NORA). *Allergy.* 2014;69(10):1397-1404.
21. Reese I, Zuberbier T, Bunselmeyer B, et al. Diagnostic approach for suspected pseudoallergic reaction to food ingredients. *J Dtsch Dermatol Ges.* 2009;7(1):70-77.

22. Blekas GA. Food additives: Classification, uses and regulation. In: Caballero B, Finglas PM, Toldrá F, eds. *Encyclopedia of Food and Health*. Academic Press; 2016:731-736.
23. Worm M, Hompes S, Fiedler EM, Illner AK, Zuberbier T, Vieths S. Impact of native, heat-processed and encapsulated hazelnuts on the allergic response in hazelnut-allergic patients. *Clin Exp Allergy*. 2009;39(1):159-166.
24. Worm M, Ehlers I, Sterry W, Zuberbier T. Clinical relevance of food additives in adult patients with atopic dermatitis. *Clin Exp Allergy*. 2000;30(3):407-414.
25. Scherf KA, Brockow K, Biedermann T, Koehler P, Wieser H. Wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2016;46(1):10-20.
26. Daniel D. Sjoberg, M.C. Margie Hannum, Joseph Larmarange, Karissa Whiting and Emily C.. gtsummary: presentation-ready data summary and analytic result tables. R package version 1.4.1. Zabor 2021. R package version 141.
27. Pastorello EA, Toscano A, Scibilia G, et al. Clinical features of wheat allergy are significantly different between Tri a 14 sensitized patients and Tri a 19 sensitized ones. *Int Arch Allergy Immunol*. 2022;183(6):591-599.
28. Piboonpocanun S, Thongngarm T, Wongsang C, Pacharn P, Reamtong O, Sompornrattanaphan M. Omega-5 and gamma gliadin are the major allergens in adult-onset IgE-mediated wheat allergy: results from Thai cohort with oral food challenge. *J Asthma Allergy*. 2021;14:907-917.
29. Kivity S. Adult-onset food allergy. *Isr Med Assoc J*. 2012;14(1):70-72.
30. Ramesh M, Lieberman JA. Adult-onset food allergies. *Ann Allergy Asthma Immunol*. 2017;119(2):111-119.
31. Skypala IJ, Bull S, Deegan K, et al. The prevalence of PFS and prevalence and characteristics of reported food allergy; a survey of UK adults aged 18-75 incorporating a validated PFS diagnostic questionnaire. *Clin Exp Allergy*. 2013;43(8):928-940.
32. Dubiela P, Dölle-Bierke S, Aurich S, Worm M, Hoffmann-Sommergruber K. Component-resolved diagnosis in adult patients with food-dependent anaphylaxis. *World Allergy Organ J*. 2021;14(3):100530.
33. Warren C, Stankey C, Jiang J, Blumenstock J, Smith B, Gupta R. Prevalence, severity, and distribution of adult-onset food allergy. *Ann Allergy Asthma Immunol*. 2018;121(5):S14.
34. Lack G. Update on risk factors for food allergy. *J Allergy Clin Immunol*. 2012;129(5):1187-1197.
35. Peters RL, Allen KJ, Dharmage SC, et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol*. 2015;135(5):1257.e1-1266.e2.
36. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107(2):367-374.
37. Wölbling F, Fischer J, Köberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy*. 2013;68(9):1085-1092.
38. Worm M, Francuzik W, Renaudin JM, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from The European Anaphylaxis Registry. *Allergy*. 2018;73(6):1322-1330.
39. Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. *Clin Transl Allergy*. 2015;5:34.
40. Andreozzi L, Giannetti A, Cipriani F, Caffarelli C, Mastrorilli C, Ricci G. Hypersensitivity reactions to food and drug additives: problem or myth? *Acta Biomed*. 2019;90(3-s):80-90.
41. Liippo J, Lammintausta K. An oral challenge test with carmine red (E120) in skin prick test positive patients. *Eur Ann Allergy Clin Immunol*. 2015;47(6):206-210.
42. De Pasquale T et al. Recurrent anaphylaxis: a case of IgE-mediated allergy to carmine red (E120). *J Investig Allergol Clin Immunol*. 2015;25(6):440-441.
43. Bahna SL, Burkhardt JG. The dilemma of allergy to food additives. *Allergy Asthma Proc*. 2018;39(1):3-8.
44. Rinninella E, Cintoni M, Raoul P, Gasbarrini A, Mele MC. Food additives, gut microbiota, and irritable bowel syndrome: a hidden track. *Int J Environ Res Public Health*. 2020;17(23):8816.
45. Gultekin F, Oner ME, Savas HB, Dogan B. Food additives and microbiota. *North Clin Istanbul*. 2020;7(2):192-200.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Alexiou A, Höfer V, Dölle-Bierke S, Grünhagen J, Zuberbier T, Worm M. Elicitors and phenotypes of adult patients with proven IgE-mediated food allergy and non-immune-mediated food hypersensitivity to food additives. *Clin Exp Allergy*. 2022;52:1302-1310. doi: [10.1111/cea.14203](https://doi.org/10.1111/cea.14203)