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Reintroduction failure after negative food challenges in adults is common and mainly due to atypical symptoms

Astrid Versluis[1] | André C. Knulst[1] | Francine C. van Erp[1] | Mark A. Blankestijn[1] | Yolanda Meijer[2] | Thuy-My Le[1] | Harmieke van Os-Medendorp[3]

[1]Department of Dermatology/Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands

[2]Department of Pediatric Pulmonology and Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands

[3]Department of Health Care, Saxion University of Applied Sciences, Enschede, The Netherlands

Correspondence
Astrid Versluis, Department of Dermatology/Allergology (D02.244), University Medical Centre Utrecht, PO Box: 85500, 3508 GA Utrecht, The Netherlands.
Email: a.versluis-7@umcutrecht.nl

Abstract

Background: Reintroduction of a food after negative food challenge (FC) faces many obstacles. There are no studies available about this subject in adults.

Objective: To investigate the frequency, reasons and risk factors of reintroduction failure in adults.

Methods: In this prospective study, adult patients received standardized follow-up care after negative FCs including a reintroduction scheme and supportive telephone consultations. Data were collected by telephone interview (2 weeks after FC) and questionnaires (at baseline and 6 months after FC(s)): food habits questionnaire, State-Trait Anxiety Inventory, Food Allergy Quality of Life Questionnaire-Adult Form and Food Allergy Independent Measure. Frequency and reasons of reintroduction failure were analysed using descriptive statistics and risk factors with univariate analyses.

Results: Eighty patients were included with, in total, 113 negative FCs. Reintroduction failed on short-term (2 weeks after FC) in 20% (95% CI: 13%-28%). Common reasons were symptoms upon ingestion during the reintroduction scheme (50%) and no need to eat the food (23%). On the long-term (5-12 months after FC(s)), reintroduction failure increased to 40% (95% CI: 28%-53%). Common reasons were atypical symptoms after eating the food (59%) and fear for an allergic reaction (24%). Five risk factors for long-term reintroduction failure were found: if culprit food was not one of the 13 EU regulated allergens, reintroduction failure at short-term, atypical symptoms during FC, a lower quality of life and a higher state anxiety.

Conclusions and clinical relevance: Reintroduction failure after negative FCs in adults is common, increases over time, and is primarily due to atypical symptoms. This stresses the need for more patient-tailored care before and after negative food challenges.

KEYWORDS

food allergy, food challenge, reintroduction

1 | INTRODUCTION

The prevalence of food allergy diagnosed by clinical history and positive serology in Europe ranges from 0.3% to 6%.[1] The prevalence of self-reported food allergy is much higher and ranges from 2% to 37%.[2] Therefore, adequate diagnostic testing is of key importance. A double-blind food challenge is the gold standard to confirm or rule out food allergy.[3,4] After a negative food challenge, patients are advised to reintroduce the food in their daily diet. This is important because it helps to reduce unnecessary restrictions in the diet. Dietary restrictions were shown to be associated with nutritional deficiencies, increased costs and a negative impact on quality of life.[5-7] Moreover, the importance of exposure in decreasing the risk of developing food allergy has been demonstrated in children.[8-10] Remarkably, patients frequently do not succeed in reintroducing the food after negative food challenge. Studies in children show that even up to 44% fail to reintroduce the food.[11-15] Reasons for reintroduction failure in children are (atypical) symptoms during reintroduction, ongoing fear for an allergic reaction, being not convinced by the challenge test result, aversion, habit of avoiding the food and having family members who also eliminate the food.[11,13-18] Several factors are associated with a higher chance of reintroduction failure in children, for example being a girl,[13,17] lower age,[17] not receiving advice about food reintroduction,[17] symptoms occurring during FC,[17] symptoms during reintroduction[17] and the type of allergen.[14]

There are no studies found about reintroduction failure after negative food challenges in adults. Therefore, we investigated the frequency, reasons and risk factors of reintroduction failure in adults after a negative food challenge.

2 | METHODS

2.1 | Study design, setting, study population and ethics

A daily practice study with a quantitative prospective design was carried out from 2014 till 2017 at the Department of Allergology/Dermatology of a tertiary referral centre for food allergy in the Netherlands.

All patients who underwent a food challenge based on a history suspected of type 1 food allergic reactions were included. Patients who had one or more negative food challenges were followed until 6 months after the last food challenge. Inclusion criteria were as follows: a negative food challenge with any type of food with exception of composite meals, ≥18 years of age and with the ability to read and write Dutch.

All patients gave written informed consent prior to inclusion. The local Medical Ethics Review Committee confirmed that the Medical Research Involving Human Patients Act (WMO) did not apply to the study (protocol number: 14-237/C).

2.2 | Standardized methods for food challenges and follow-up care

Food challenges were conducted and interpreted by experienced staff, consisting of a trained allergy nurse, clinical nurse specialist, dietician and dermatologist in accordance with standardized procedures.[19] The criteria for conducting a blinded food challenge were as follows: (a) the availability of good recipe, (b) risk of non-specific complaints, (c) risk of false positive or unclear result and (d) patient preferences. The food challenge protocols differed per type of food and all ended with an estimated daily normal dose of that food. For example, a blinded hazelnut challenge and blinded peanut challenge consisted of a placebo day and active day and occurred with the following incremental protein doses: for hazelnut 1.5, 10, 30, 100, 300, 1000 and 3000 mg and for peanut 1, 10, 30, 100, 300, 1000, 3000 and 5000 mg. In case of fruits an open challenge was performed with the following dose series: 1, 3, 10, 30 and 100 g.

After negative food challenges, patients received standardized follow-up care to support reintroduction in daily diet. Since there were no guidelines about follow-up care, we developed standardized follow-up care based on literature[12,13,16] and expert opinion. If no symptoms occurred during food challenge, patients received a 1-day stepwise reintroduction scheme directly after the food challenge. The reintroduction scheme differed per type of food. For example, the scheme for hazelnut and peanut was as follows: ½ nut, 1 nut, 2 nuts and 5 nuts and for fruits 1/8 portion, 2/8 portion and 5/8 portion, all with time intervals of 30 minutes, at the same day. This was followed by telephonic consultation the next day to evaluate if no late symptoms occurred after the food challenge and to give permission to start reintroduction at home. If symptoms occurred, these were first evaluated by a physician before advice was given about reintroduction. Two weeks after this advice, telephone consultation took place to evaluate reintroduction. If reintroduction was successful, patients were advised to continue eating the food in their daily diet. If reintroduction failed, a patient-tailored follow-up based on reasons of failure was provided. In case of mild to moderate (atypical) symptoms, patients were advised to repeat the reintroduction scheme. In the case of (repeated) symptoms during reintroduction, the food challenge outcome and diagnosis were re-evaluated by experienced staff. Six months after the food challenge(s), reintroduction in the daily diet was evaluated. The follow-up care was carried out by a clinical nurse specialist.

2.3 | Outcome measures

Primary outcome measures were the frequency of short-term and long-term reintroduction failure. Short-term reintroduction failure was defined as "never started with or not able to successfully complete the reintroduction scheme." Long-term reintroduction failure was defined as "not eating the food, eating only products that might

contain traces of the food or eating the food at a frequency of <1 occasion per month (in case of seasonal products: <once a month when the food was regularly available), 6 months after the last food challenge."

Secondary outcome measures were patient-reported reasons for short- and long-term reintroduction failure. Furthermore, we studied the influence of a number of potential risk factors on long-term reintroduction failure, namely consisting of patient characteristics (gender, educational level, atopic comorbidities, sensitization to negatively challenged food, sensitization to any food), duration of the pre-challenge elimination diet, patients purpose of food challenge, factors related to food challenge (food challenge method, symptoms during food challenge, if culprit food was a major allergen (ie one of the 13 EU regulated allergens: cereals contain gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, lupin, molluscs) and patients' conviction about the conclusion from food challenge), short-term reintroduction failure, if patient underwent one or more positive food challenges, food allergy-related quality of life and state and trait anxiety. Only risk factors for long-term reintroduction failure were analysed, because continued reintroduction in daily diet is the final purpose of reintroduction.

2.4 | Data collection

Patients were asked to complete in four questionnaires prior to and 6 months (time that questionnaires were returned varied from 5 to 12 months) after the food challenge(s), including the food habit questionnaire, State-Trait Anxiety Inventory (STAI),[20] Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF)[21] and Food Allergy Independent Measure (FAIM).[22] The food habit questionnaire consisted of items about avoidance of the challenged food(s). The questionnaire that was filled in 6 months after the food challenge(s) included additional items about patients' conviction to the conclusion of the food challenges and reasons for avoiding the food(s). The STAI consisted of 40 items and covered aspects of state anxiety (in the specific situation of eating) and trait anxiety (feelings of stress, worry, discomfort, etc in situations that everyone experiences on a daily basis). The score varies from 20 (minimal anxiety) to 80 (maximal anxiety) in both state and trait anxiety.[20] The FAQLQ-AF consisted of four domains (Risk of accidental exposure, Emotional impact, Allergen avoidance-dietary restrictions and Food allergy-related health) including 29 items about food allergy specific quality of life. The total score ranged from 1 "no impairment'' to 7 "maximal impairment".[21] The FAIM consisted of four items about patients' perceived food allergy severity and food allergy-related risks. The total score varies from 1 (limited severity perception) to 7 (greatest severity perception).[22] The Dutch validated versions of the STAI, FAQLQ-AF and FAIM were used and the scores were calculated using standardized methods.[20-22]

Additionally, patients completed a questionnaire about atopic comorbidities (asthma, allergic rhino conjunctivitis and atopic dermatitis) and educational level.

Two weeks after the advice to reintroduce a food, data about frequency and reasons of short-term reintroduction failure were collected during telephone consultation. If patients did not answer the telephone, then an attempt was made to reach the patient in the following weeks.

Data about gender, age, sensitizations to food (skin prick tests, immunoCAP and ImmunoCAP ISAC), type/method of food challenge, patients purpose of food challenge and additional information about reintroduction were collected from patients' records.

2.5 | Sample size and statistical methods

To include a representative sample of the available population of patients undergoing one or more negative food challenges over a period of 35 months (estimated at 52 negative FCs in 42 patients per year), the required sample size of that group was calculated using the Raosoft Sample Size calculator.[23] Since there were no comparable studies to estimate the expected frequency of reintroduction failure after negative food challenges in adults, we conservatively assumed a frequency of 50%. With a margin of error of 5%, a confidence interval of 95% and assuming a response distribution of 50%, 94 patients should be included.

Outcome data regarding frequency and reasons for reintroduction failure were analysed using descriptive statistics. Based on level of measurement, we used frequencies (n/%) or mean (SD). A 95% confidence interval was calculated for the primary outcome.

Differences regarding risk factors between long-term reintroduction failure and success and between patients who did and did not respond with regard to patient characteristics and risk factors for long-term reintroduction failure were analysed by comparing the first performed food challenge of every patient using chi-square test, Fisher's exact test, Fishers-Freeman Halton test or independent-samples *t* test depending on level of measurement and data distribution. A *P*-value < .05 was considered statistically significant.

Data were analysed using IBM SPSS Statistics 25 (IBM Corporation).

3 | RESULTS

3.1 | Characteristics of patients and diets

In total 170 patients were included, of which 80 patients underwent a total of 113 negative food challenges and were followed. The 90 patients included, but not evaluated were patients with a positive outcome of the food challenge and thus considered allergic.

Patient and food challenge characteristics of the followed patients are shown in Table 1. A majority of patients were female (66%, 53/80), and the mean age was 32 years (SD: ±13). Of all patients, 82% (55/67) had one or more atopic comorbidity; 78% (56/72) had allergic rhinitis, 56% (40/72) asthma and 55% (37/67) atopic dermatitis. In 76% (61/80) patients were sensitized to any food.

TABLE 1 Patient and food challenge characteristics

	All patients N (%) N = 80[a]
Gender: female	53 (66)
Mean age in years (SD, min-max)	32 (13, 18-70)
Education level[b]	
Low/intermediate	46 (64)
High	24 (33)
Other	2 (3)
Asthma, atopic dermatitis and/or allergic rhino conjunctivitis	55 (82)
Allergic rhinitis	56 (78)
Asthma	40 (56)
Atopic dermatitis	37 (55)
Sensitization for any type of food	61 (76)
	All food challenges N (%) N = 113[c]
Food challenged	
Hazelnut	29 (26)
Nuts (excl. hazelnut)	23 (20)
Peanut	14 (12)
Fruits and vegetables (excl. celery)	13 (12)
Fish, crustaceans and/or molluscs	8 (7)
Cow's milk	8 (7)
Grains (incl. buckwheat)	7 (6)
Hen's egg	5 (4)
Seeds and kernels	3 (3)
Soy	2 (2)
Celery	1 (1)
Sensitization to the negatively challenged food	
Sensitized	63 (62)
Not sensitized	38 (38)
Duration of the pre-challenge elimination diet	
<1 y	35 (32)
1-10 y	21 (19)
>10 y or lifelong	48 (44)
Unclear	5 (5)

[a]Number of missings varied per outcome from n = 0-13.

[b]Low: Primary school, pre-vocational Secondary Education. Intermediate: senior general secondary education, Pre-university education, secondary vocational education. High: Higher professional education, university education.

[c]Number of missing varied per outcome from n = 0-11.

The number of negative food challenges per patients ranged from 1 (69%, 55/80) to 2 (20%, 16/80) to 3-4 (11%, 9/80).

The duration of the pre-challenge elimination diet varied from: <1 year (32%, 35/109), 1-10 years (19%, 21/109) to >10 years or lifelong (44%, 48/109) and in 5% (5/109) of the food challenges this was unclear (Table 1).

3.2 | Short-term reintroduction failure occurred in 20% for various reasons

After a negative food challenge, patients were advised to reintroduce the food using a reintroduction scheme. Figure 1 shows a flow chart of the frequency of reintroduction failure. In 20% (95% CI: 13%-28%; 22/113) of the negative food challenges, patients failed to reintroduce the food using the reintroduction scheme. Of the patients who failed short-term reintroduction, 23% (5/22) failed before even to start the reintroduction scheme.

Figure 2 shows the patient-reported reasons for short-term reintroduction failure. The most common reason, reported by 50% (11/22), was having symptoms during reintroduction. In nine out of these 11, the patients had atypical symptoms, mainly atypical gastro-intestinal and skin/mucosal symptoms. In the remaining two, there were typical allergy symptoms, namely itchy mouth, mild coughing, mild rhinitis and mild hoarseness. Both patients were considered allergic after re-evaluation. Another common reason for short-term reintroduction failure was feeling no need to eat the food (23%, 5/22).

3.3 | Long-term reintroduction failure occurred in 40% partly due to similar reasons

On the long-term (data available in 67 food challenges, carried out in 47 patients) reintroduction failure increased to 40% (95% CI: 28%-53%; 27/67). The most common reason for long-term reintroduction failure (data available for 17 food challenges) was having atypical symptoms after eating the food (59%, 10/17), mainly atypical gastro-intestinal and skin/mucosal symptoms. Other reasons were fear of an allergic reaction (24%, 4/17), having other food allergies (18%, 3/17), not liking the taste of the food (12%, 2/17) and feeling no need to eat the food (6%, 1/17; Figures 1 and 2).

3.4 | Daily diet on the long-term after successful and failed reintroduction

In the 40 cases in which long-term reintroduction was successful, the frequency at which the food was consumed differed from daily (30%, 12/40) to weekly (28%, 11/40) to monthly (43%, 17/40), either as ingredient (100%, 40/40) or as pure food (70%, 28/40).

Long-term reintroduction failure was defined as "not eating the food, eating only products that might contain traces of the food or eating the food at a frequency of <1 occasion per month (in case of seasonal products: <once a month when the food was regularly available), 6 months after the last food challenge." Of the food challenges where long-term reintroduction failed (data available for 25 food challenges), in 64% (16/25) the food was not strictly avoided: in 40% (10/25) the food (pure and/or as ingredient) was used at a frequency of less than once a month and in 24% (6/25) only products with precautionary allergen labelling (PAL) were used.

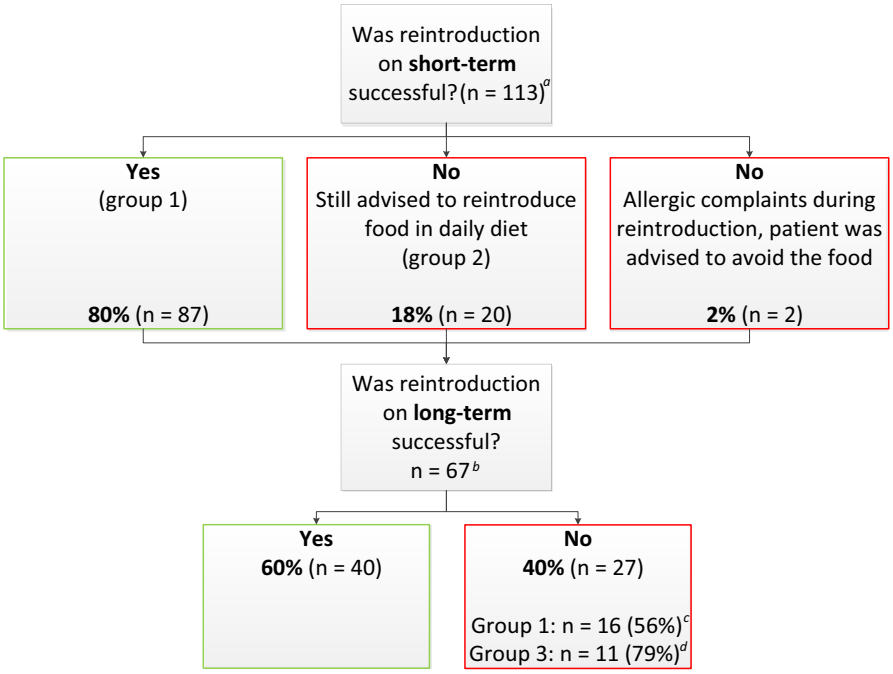

FIGURE 1 Flow chart of the frequency of short- and long-term reintroduction failure

[a]*N = 4 short term success unknown, not reached by telephone to evaluate reintroduction*
[b]*Loss to follow up: n = 46*
[c]*Loss to follow up: n = 34*
[d]*Loss to follow up: n = 6*

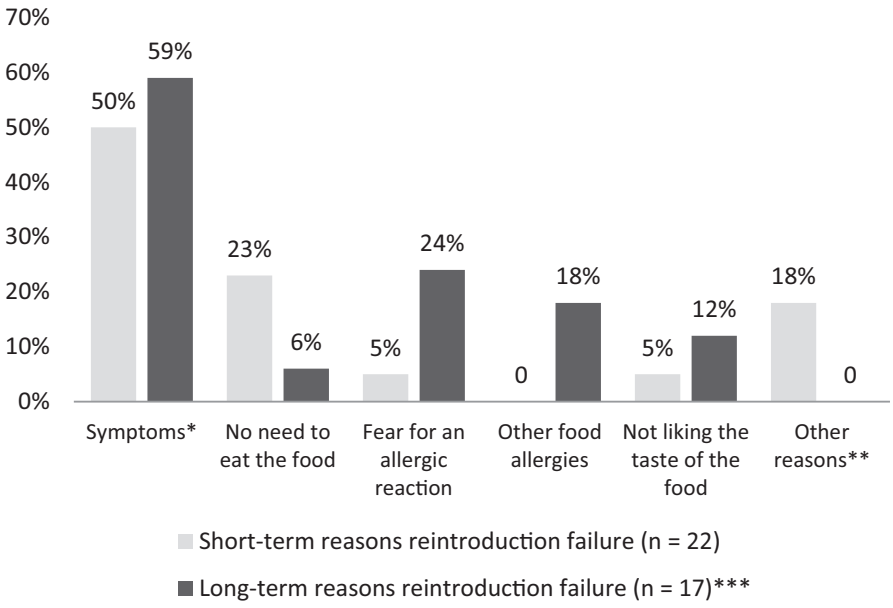

FIGURE 2 Patient-reported reasons for reintroduction failure. Short-term: 82% atypical symptoms, 18% typical allergy symptoms. Long-term: 100% atypical symptoms. **Other reasons were (n = 4) as follows: (a) abdominal problems cause other than food allergy, (b) first wanted advice about other non-allergic symptoms to the food, (c) seasonal food product, not available anymore when patient had to repeat the reintroduction scheme and (d) wanted to reintroduce but it just did not happen. ***More than one answer possible

3.5 | Risk factors for long-term reintroduction failure

Comparing successful and failed long-term reintroduction, five possible risk factors for long-term reintroduction failure were found, namely: if culprit food was not a major allergen (7% vs 42%, *P* = .01), a higher mean baseline score of FAQLQ-AF domain Risk of accidental exposure (mean score 4.0 (SD: 1.1) vs 5.0 (SD: 1.1), *P* = .01), a higher mean baseline score of state anxiety (mean score 27.9 (SD: 7.4) vs 35.6 (SD: 10.5), *P* = .01), short-term reintroduction failure (11% vs 42%, *P* = .03) and atypical symptoms during food challenge (48% vs 79%, *P* = .04; Table 2 and Suplemmentary Table 1).

If patients did underwent one or more positive food challenge was not a risk factors for negative food challenges (successful reintroduction 23% vs failed reintroduction 29%, *P* = .642).

TABLE 2 Potential risk factors of long-term reintroduction failure on long-term of the first performed food challenge of every patient

Factors	Success N (%)	Failure N (%)	*P*-value
Food challenge and reintroduction			
Food challenge method (n = 46)			.58
Open	12 (44)	10 (53)	
Blind	15 (56)	9 (47)	
If culprit food was a major allergen[a] (n = 46):			**.01**
Yes	25 (93)	11 (58)	
No	2 (7)	8 (42)	
Non-specific symptoms during food challenge (n = 46)			**.04**
Yes	13 (48)	15 (79)	
No	14 (52)	4 (21)	
Patients conviction about the conclusion from food challenge (n = 45)			**.01**
Very convinced	19 (70)	5 (28)	
Pretty, little or not convinced	8 (30)	13 (72)	
Short-term reintroduction (n = 46)			**.03**
Successful	24 (89)	11 (58)	
Failure	3 (11)	8 (42)	
Underwent one or more positive food challenges			.642
Yes	6 (23)	5 (29)	
No	20 (77)	12 (71)	
Factors	**Success Mean (SD)**	**Failure Mean (SD)**	***P*-value**
FAQLQ-AF, FAIM and STAI			
Food allergy-related quality of life, before food challenge (n = 43)			
Total score	4.1 (1.1)	4.8 (0.9)	.05
Domain Risk of accidental exposure	4.0 (1.1)	5.0 (1.1)	**.01**
Domain Emotional impact	4.3 (1.4)	4.8 (1.1)	.20
Domain Allergen avoidance-dietary restrictions	4.0 (1.3)	4.6 (1.1)	.14
Domain Food allergy-related health	4.3 (1.4)	4.7 (1.6)	.35
FAIM before food challenge (n = 43)	3.5 (1.0)	4.0 (0.9)	.10
STAI: state-anxiety, before first food challenge (n = 43)	27.9 (7.4)	35.6 (10.5)	**.01**
STAI: trait-anxiety before food challenge (n = 43)	31.3 (7.6)	34.9 (8.1)	.14

[a]The 13 EU regulated allergens includes: cereals contain gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, lupin, molluscs.

The bold values are significant values.

4 | DISCUSSION

This is the first study addressing frequency and reasons for reintroduction failure in adults after a negative food challenge. Reintroduction failed on short-term in 20% (95% CI: 13%-28%) and on long-term in even 40% (95% CI: 28%-53%). Common reasons were atypical symptoms (both on short- and long-term), no need to eat the food (short-term) and fear of an allergic reaction (long-term). Five risk factors for long-term reintroduction failure were found: a culprit food other than the major food allergens, short-term reintroduction failure, atypical symptoms during FC, a lower quality of life and a higher state anxiety.

Reintroduction failure rate in adults appeared to be in the same range as in children: 8%-44%.[11-15,17] We based the definition of long-term reintroduction failure on the assumption that the foods that are challenged were eaten at least once a month in the general Dutch population,[24] which was the case for almost all negatively challenged foods (data not shown). In literature, the definition for successful reintroduction varied from eating the food regularly,[11,14] to at least once a month[25] to occasionally.[13,17] This makes comparison of the studies difficult. If we would adapt our definition for long-term failure, and consider the 10 patients who used the food at a frequency of less than once a month as successful, then the result would be that 50 patients (77%) would be successful and 15 (23%) failed introduction. The high frequency of reintroduction failure and the increase over time stresses the need for improved and more patient-tailored care after negative food challenges, not only in the first weeks after negative challenge but also thereafter. This should lead to less elimination diets, reduced social impairment,[26] decreased fear of accidental reactions,[27] decreased nutritional deficiencies[28] and improved quality of life.[29,30]

The most common reason for reintroduction failure both on short- and long-term was having atypical symptoms. In children this was reported in 7%.[16] This difference between adults and children might be caused by the fact that young children are less capable of reporting (subjective) symptoms. It is important that professionals give specific attention to such symptoms by explaining that such symptoms are not due to food allergy and therefore are not a reason to stop reintroduction or avoid the food and to discuss other potential explanations for these symptoms.

Another common reason for reintroduction failure was that patients felt no need to eat the food. Two studies in children showed that this was a reason for reintroduction failure in 3%-13% of children.[11,17] Recent literature indicates the importance of (early) introduction of food and continued exposure in preventing food allergy in children.[8-10] We saw that patients who failed reintroduction more often reported "expansion of diet and to experience fewer limitation in daily life" as purpose of the food challenge compared with patient who successfully reintroduced; however, this was not a significant difference. If patients purpose of a food challenge is not to reintroduce the food after a negative food challenge it is still important to discuss the benefits from a food challenge. An important reason for a food challenge is to better estimate the

chance of severe allergic reactions to a food and the need for an adrenalin auto injector. Professionals should discuss the purpose of the challenge from patients and professionals perspective before proceeding to food challenges, to assess the added value of carrying out a food challenge.

Fear of allergic reactions was another common reason, as was previously shown in children.[11,14,17] This was illustrated by the relatively higher score on state anxiety (anxiety in the specific situation of eating) before food challenge in the group who failed reintroduction. Adequately addressing anxiety appears another important issue to be integrated in the follow-up care, for example by identifying the presence, discussing the impact and considering counselling by a psychologist.

Typical allergic symptoms during reintroduction were also reported, but only in two patients. Symptoms were never severe, confirming the strong diagnostic value of the food challenge procedure.[3] Literature in children shows a somewhat higher frequency of typical allergic symptoms upon reintroduction, namely in 3%-12%, but in line with our data, the reported symptoms are not severe.[12,13] Dambacher et al [12] suggested that the explanation for this false-negative result of the food challenge is that the threshold dose for the allergic reaction is higher than the dose reached at the food challenge. This was, however, not the cause in our study, where typical allergic symptoms occurred during following the reintroduction schema which did not exceed the highest dose of the food challenge. Another explanation might be the influence of the matrix of the food challenge on the threshold dose[31] or the presence of cofactors during reintroduction in daily life.[32] In these (rare) cases, it is important to reconsider the challenge result and adjust the dietary advice. Since no severe allergic symptoms were reported, we feel that the reintroduction procedure can be performed at home.

Three of the risk factors for long-term reintroduction failure are measured before food challenge, namely if culprit food was no major allergen, a higher mean baseline score of FAQLQ-AF domain risk of accidental exposure and a higher mean baseline score of state anxiety. In daily practice, measuring these risk factors will give insight in the chance of reintroduction failure and might be helpful for tailoring follow-up care to the patients' needs.

A limitation of this study was that part of the results on the long-term were missing because of non-response to the questionnaires. Comparing completers versus non-responders with regard to patient characteristics and risk factors for long-term reintroduction failure, the only difference was that in patients who did respond, the culprit food was significantly more frequently not a major allergen (data not shown), which was a risk factor for reintroduction failure. This might lead to overestimation of the frequency of long-term reintroduction failure. The strength of this study was the prospective design, which minimizes the risk of recall bias.

In conclusion, this study shows that despite careful standardized follow-up care, reintroduction failure after a negative food challenge in adults is common and increases over time, with a major impact of atypical symptoms. This stresses the need for more patient-tailored care before and after negative food challenges.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

A. Versluis, A. C. Knulst, F. C. van Erp, Y. Meijer and H. van Os-Medendorp designed the study. A. Versluis and M. A Blankestijn collected the data. A. Versluis, H. van Os-Medendorp and A. C. Knulst analysed the data and wrote the manuscript. All authors contributed to interpretation of results and manuscript revision. The final version of the manuscript was approved by all authors.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

ORCID

Astrid Versluis https://orcid.org/0000-0003-3235-7648

REFERENCES

1. 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 Pract*. 2019;7(6):1920-1928.
2. Burney PG, Potts J, Kummeling I, et al. The prevalence and distribution of food sensitization in European adults. *Allergy*. 2014;69(3):365-371.
3. 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.
4. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, et al. Standardization of food challenges in patients with immediate reactions to foods–position paper from the European Academy of Allergology and Clinical Immunology. *Allergy*. 2004;59(7):690-697.
5. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. *Allergy*. 2010;65(2):238-244.
6. Muraro A, Agache I, Clark A, et al. EAACI food allergy and anaphylaxis guidelines: managing patients with food allergy in the community. *Allergy*. 2014;69(8):1046-1057.
7. Zurzolo GA, Mathai ML, Koplin JJ, Allen KJ. Hidden allergens in foods and implications for labelling and clinical care of food allergic patients. *Curr Allergy Asthma Rep*. 2012;12(4):292-296.
8. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med*. 2015;372(9):803-813.
9. Fleischer DM, Conover-Walker MK, Christie L, Burks AW, Wood RA. Peanut allergy: recurrence and its management. *J Allergy Clin Immunol*. 2004;114(5):1195-1201.
10. Busse PJ, Nowak-Wegrzyn AH, Noone SA, Sampson HA, Sicherer SH. Recurrent peanut allergy. *N Engl J Med*. 2002;347(19):1535-1536.
11. van Erp FC, Boot J, Knulst AC, Pasmans SG, van der Ent CK, Meijer Y. Reintroduction failure after negative peanut challenges in children. *Pediatr Allergy Immunol*. 2014;25(6):580-585.

12. Dambacher WM, de Kort EH, Blom WM, Houben GF, de Vries E. Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses. *Nutr J*. 2013;12(1):12-22.
13. Eigenmann PA, Caubet JC, Zamora SA. Continuing food-avoidance diets after negative food challenges. *Pediatr Allergy Immunol*. 2006;17(8):601-605.
14. Miceli Sopo S, Monaco S, Greco M, Onesimo R. Prevalence of adverse reactions following a passed oral food challenge and factors affecting successful re-introduction of foods. A retrospective study of a cohort of 199 children. *Allergol Immunopathol (Madr)*. 2016;44(1):54-58.
15. van der Valk JPM, Gerth van Wijk R, Dubois A, de Groot H, de Jong NW. Failure of introduction of cashew nut after a negative oral food challenge test in children. *Pediatr Allergy Immunol*. 2016;27(6):654-658.
16. Oole-Groen CJ, Brand PL. Double-blind food challenges in children in general paediatric practice: useful and safe, but not without pitfalls. *Allergol Immunopathol (Madr)*. 2013;42(4):269-274.
17. van der Valk JPM, van Wijk RG, Vergouwe Y, de Jong NW. Failure of introduction of food allergens after negative oral food challenge tests in children. *Eur J Pediatr*. 2015;174(8):1093-1099.
18. Strinnholm A, Winberg A, Hedman L, Ronmark E, Lindh V. Reintroduction failure is common among adolescents after double-blind placebo-controlled food challenges. *Acta Paediatr*. 2017;106(2):282-287.
19. Grabenhenrich LB, Reich A, Bellach J, et al. A new framework for the documentation and interpretation of oral food challenges in population-based and clinical research. *Allergy*. 2017;72(3):453-461.
20. Van der Ploeg HM. *Handleiding bij de Zelf-Beoordelings Vragenlijst*. 2nd ed. Liss, the Netherlands: Sweets Test Publishers; 2000.
21. The EuroPrevall Project. FAQLQ. Available at: http://faqlq.com/?page_xml:id=15. Accessed 09/24, 2018.
22. van der Velde JL, Flokstra-de Blok BM, Vlieg-Boerstra BJ, et al. Development, validity and reliability of the food allergy independent measure (FAIM). *Allergy*. 2010;65(5):630-635.
23. Raosoft. Inc.Sample size calculator. 2004; Available at: http://www.raosoft.com/samplesize.html. Accessed 09/15, 2014.
24. National Institute for Public Health and the Environment. Dutch National Food Consumption Survey 2007–2010 I Part 2 total foods, Versions 2, based on dataset FCS_2010_core20111125 Available at: https://www.rivm.nl/sites/default/files/2018-11/Part2%20Foods%20%28NEVO%29_v2.pdf. Accessed 02/15, 2019.
25. Flammarion S, Santos C, Romero D, Thumerelle C, Deschildre A. Changes in diet and life of children with food allergies after a negative food challenge. *Allergy*. 2010;65(6):797-798.
26. Muraro A, Roberts G, Clark A, et al. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy*. 2007;62(8):857-871.
27. Marklund B, Ahlstedt S, Nordstrom G. Food hypersensitivity and quality of life. *Curr Opin Allergy Clin Immunol*. 2007;7(3):279-287.
28. Sova C, Feuling MB, Baumler M, et al. Systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies. *Nutr Clin Pract*. 2013;28(6):669-675.
29. Flokstra-de Blok BM, van der Meulen GN, DunnGalvin A, et al. Development and validation of the food allergy quality of life questionnaire - adult form. *Allergy*. 2009;64(8):1209-1217.
30. Lange L. Quality of life in the setting of anaphylaxis and food allergy. *Allergo J Int*. 2014;23(7):252-260.
31. Grimshaw KE, King RM, Nordlee JA, Hefle SL, Warner JO, Hourihane JO. Presentation of allergen in different food preparations affects the nature of the allergic reaction–a case series. *Clin Exp Allergy*. 2003;33(11):1581-1585.
32. Wolbing F, Fischer J, Koberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy*. 2013;68(9):1085-1092.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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