Received: 11 January 2018 | Revised: 6 September 2018 | Accepted: 19 September 2018

DOI: 10.1111/cea.13282

ORIGINAL ARTICLE

Clinical Allergy

WILEY

Potential cofactors in accidental food allergic reactions are frequently present but may not influence severity and occurrence

Astrid Versluis[1] | Harmieke van Os-Medendorp[1] | W. Marty Blom[2] | Anouska D. Michelsen-Huisman[1] | Jacqueline J. M. Castenmiller[3] | Hubert P. J. M. Noteborn[3] | Geert F. Houben[2] | André C. Knulst[1]

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

[2]TNO, Netherlands Organization for Applied Scientific Research, Zeist, The Netherlands

[3]Netherlands Food and Consumer Product Safety Authority, Utrecht, The Netherlands

Correspondence
Astrid Versluis, Department of Dermatology/Allergology, University Medical Centre Utrecht, Utrecht, The Netherlands.
Email: a.versluis-7@umcutrecht.nl

Funding information
Netherlands Food and Consumer Product Safety Authority

Abstract

Background: Cofactors, such as physical exercise and alcohol intake, might be associated with the severity or occurrence of food allergic reactions.

Objective: To gain insight into the frequency of presence of potential cofactors in accidental food allergic reactions in adults and to what extent these factors influence the severity and occurrence of allergic reactions.

Methods: A prospective cohort study was conducted, with a 1-year follow-up in adult patients with a physician-diagnosed food allergy. Patients were required to fill in a questionnaire after every accidental allergic reactions to food over a 1-year period. The primary outcome measure was the frequency that potential cofactors were present in these allergic reactions.

Results: A total of 157 patients were included, of which 46% reported a total of 153 reactions during a 1-year follow-up period. In 74% of the reactions, ≥1 potential cofactor was reported to be present: tiredness (38%), alcohol intake (16%), stress (14%), symptoms of pollinosis (16%), symptoms of asthma (9%), sickness/flu (3%), physical exercise (3%) and use of analgesics (2%). More than one potential cofactor was reported in almost half of all reactions (47%). There was no significant difference in the presence of these factors between mild, moderate and severe reactions (P = 0.522). In the total study population, 9% of the patients used medication that might act as cofactor (antacids, angiotensin receptor blockers [ARBs], beta blockers and angiotensin-converting enzyme inhibitors [ACEIs]) on a daily basis, which however did not influence the occurrence of reactions. Furthermore, 38% daily used allergy-suppressing medication.

Conclusions: Although factors suggested to be cofactors were frequently present during accidental food allergic reactions, we found no evidence for an association between the potential cofactors examined and reaction severity, in a population where most reactions were of mild to moderate severity.

KEYWORDS

accidental reaction, alcohol, cofactor, exercise, food allergy

 © 2018 John Wiley & Sons Ltd

1 | INTRODUCTION

The point prevalence of food allergy is estimated to be 1%-3% of the European population, based on clinical history and IgE and/or food challenge.[1] Food allergy has a negative impact on quality of life and places a psychological burden on patients, caused by the daily requirement to avoid potentially offending foods and the risk of accidental allergic reactions.[2,3] Despite the effort of health care professionals and patients to prevent allergic reactions, many patients experience accidental allergic reactions to food.[4,5]

Literature reports that cofactors, such as infections,[6] physical exercise,[6-9] use of specific types of medication (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], antacids and beta blockers[9,10]) and alcohol intake,[6,9] might influence the occurrence and severity of food allergic reactions.[11,12] There is limited evidence about the frequency of presence of these potential cofactors in food allergic reactions in adults and to what extent cofactors influence the severity and occurrence of allergic reactions. Data from anaphylaxis registers in Europe report the presence of potential cofactors in, respectively, 25.6% and 39% of the anaphylactic reactions to food in adults.[13,14] Physical exercise, alcohol intake and use of medication were reported most often in anaphylactic reactions to food in adults.[13,14] Infection, stress and use of specific types of medicine (eg, aspirin/NSAIDs, beta blockers, angiotensin receptor blockers [ARBs] and angiotensin-converting enzyme inhibitors [ACEIs]) were present in only a few of the anaphylactic allergic reactions.[13,14] The underlying mechanisms of how these potential cofactors could influence food allergic reactions are still not fully understood. Several mechanisms are suggested, for example an increased gastrointestinal permeability and absorption of proteins after physical exercise or intake of NSAIDs.[12,15] And in case of acute infections, fever causing an elevated blood circulation and subsequent influx of food allergens is suggested.[11]

Our previous, retrospective study suggested that 13% of the food allergic adults experience more severe allergic symptoms if a cofactor (physical exercise and/or alcohol consumption and/or use of analgesics) was present. Patients with severe food allergy reported more often that the presence of cofactors caused more severe reactions, when compared with patients with mild/moderate food allergy.[16]

There are also allergic reactions to food where additional factors are crucial for the onset of the symptoms, for example, in food-dependent exercise-induced anaphylaxis (FDEIA), an accepted separate clinical entity, where physical exercise is crucial for the onset of allergic symptoms to food. The best characterized form is wheat-dependent exercise-induced anaphylaxis (WDEIA), where the measurement of specific IgE to omega-5 gliadin and HMW-glutenin is important for the diagnosis.[15,17] Further, it has been suggested that in lipid transfer protein (LTP) allergic reactions, the involvement of cofactors such as NSAIDs, alcohol and physical exercise may play an eliciting role.[18-21] Also, the influence of cofactors on severity of LTP allergic reactions was described, where patients had severe anaphylactic reactions when cofactors were present and only mild reactions when no cofactors were present.[19]

EAACI guidelines[22] define cofactors as "patient-related or external circumstances that are associated with more severe allergic reactions". In the literature, cofactors are also referred to as additional, associated or augmentation factors.[11,12,23] In this study, cofactors are defined as external circumstances and patient-related factors that have influence on the occurrence and severity of allergic symptoms.

Studies into the frequency of presence of potential cofactors and the influence of these factors on severity and occurrence of food allergic reactions have been predominantly conducted in children or in a mixed population consisting of children and adults, with severe food allergy, and carried out with a retrospective design. More evidence about this subject is needed for better treatment and advice to patients.[11,12]

The aim of this prospective study was to gain deeper insight into the frequency of presence of potential cofactors in accidental food allergic reactions in adults with a physician-diagnosed food allergy and to what extent these factors influence the severity and occurrence of allergic reactions.

2 | METHODS

2.1 | Study design and setting

A longitudinal prospective cohort study was conducted from 2012 to 2015 at the University Medical Centre Utrecht in the Netherlands. This study was part of a study concerning accidental allergic reactions to food in adults.[5,24] Patients had to fill in a questionnaire after every accidental allergic reactions to food over a 1-year period.

2.2 | Participants and ethics

Patients ≥18 years with physician-diagnosed food allergy, based on patient's convincing history, and positive skin prick test, IgE and/or food challenge, were included. Patients were excluded from participation if they did not have the ability to read or write the Dutch language or if they did not have computer or Internet access. Additionally, patients with established FDEIA, based on convincing history and where possible on serology, were not included, because in FDEIA, the presence of physical exercise is crucial for the onset of allergic symptoms to food.[15]

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: 11-309/C).

2.3 | Data collection

At baseline, data about history and severity of food allergy, atopic comorbidities and medication use were collected by means of a structured interview combined with information from the patients'

medical records. Additionally, an online questionnaire was completed by the patients about demographics (sex, age, education).

Further, during 1 year, patients were required to complete an online questionnaire after every accidental allergic reaction to food. This questionnaire included questions about the causes and severity of the accidental reaction and about the presence of potential cofactors: tiredness, alcohol intake, stress, symptoms of pollinosis, symptoms of asthma, sickness/flu and physical exercise. Patients were contacted for further clarification if necessary.

2.4 | Outcome measures

The primary outcome measure was the frequency that potential cofactors were present shortly prior to, during and/or shortly after an allergic reaction. Factors of interest were tiredness, alcohol intake, stress, symptoms of pollinosis, symptoms of asthma, sickness/flu, physical exercise and use of analgesics (NSAIDs or opioids). Physical exercise was considered as potential cofactor if performed within a time period of 30 minutes before till 2 hours after eating the suspected food.[15] Alcohol intake and use of analgesics were considered as potential cofactor when used within 8 hours prior the reaction, symptoms of asthma and sickness/flu when being present the day of the reaction, and tiredness, stress and symptoms of pollinosis when present directly prior to the reaction. To avoid over- or underestimation of the frequency of potential cofactors due to patients with multiple reactions, we looked into all reactions and every first reaction of patients.

Secondary outcome measures compared the severity of reactions in the presence or absence of potential cofactors and the number of these factors present and the extent to which patients reported reactions with and without presence of these factors. Also, the influence of asthma, pollinosis, age and gender was determined, on the basis of the likelihood that one or more cofactors were present in every first reaction.

Further, the frequency of daily used medication types in patients with and without reactions and in all, mild, moderate and severe reactions was determined and compared to investigate whether there were differences between these groups/reactions. Medication types suggested in the literature as potential cofactors[11,12] and that were analysed in this study were antacids, ARBs, beta blockers and ACEIs. Also included was the use of medication that could suppress allergic reactions, for example antihistamines, systemic corticosteroids/immunosuppressive drugs, inhaled corticosteroids, corticosteroids/betamimetics and tricyclic antidepressants (TCAs). Some items for this outcome measure were added at a later time in the study, resulting in missing data in n = 67 of the study population.

The patient characteristics and food allergy-related data included gender, age, atopic comorbidities and distribution and severity of food allergy. Severity of food allergy and accidental food allergic reactions was classified using an adapted version of the Mueller classification.[25,26] Reactions with local oral symptoms (Mueller 0) were classified as mild, reactions with skin-, mucosal- or gastro-intestinal symptoms (Mueller 1-2) as moderate and reactions with respiratory or cardiovascular symptoms (Mueller 3-4) as severe. Further, the Ewan and Clark grading[27,28] was used to classify severity, because there is no agreed consensus on how to measure severity of reaction in food allergy. According to this grading system, reactions with oral pruritus, skin symptoms, angio-oedema, gastrointestinal symptoms and rhinoconjunctivitis were classified as mild, laryngeal edema and mild respiratory symptoms as moderate and dyspnea and hypotension as severe.

2.5 | Data analysis

The study population consisted of 157 patients, based on the primary outcome of the other part of this study, published by Michelsen-Huisman et al[5]. Data were analysed with descriptive analyses, using IBM SPSS Statistics 21 (IBM Corporation, Armonk, NY, USA).

Patient characteristics, frequency of presence of potential cofactors in allergic reactions and the use of medication were analysed using frequency data (n/percentage). A 95% confidence interval of the primary outcome of this study was calculated to provide a precise estimation. Differences in severity of reactions between reactions with and without potential cofactors, in severity of reactions as a function of the number of present potential cofactors and in patients with and without allergic reactions with regard to daily medication use were analysed using the chi-square test (or the Fisher's exact test in case of small numbers).

We carried out multiple testing. Bonferroni correction was applied resulting in a P-value <0.01. Univariate logistic regression analyses were used to assess the influence of asthma, pollinosis, age and gender on the likelihood that one or more potential cofactors were present in every first allergic reaction of all patients.

Only full cases were used, and missing data were excluded from analysis.

3 | RESULTS

3.1 | Patient characteristics and frequency of allergic reactions

Of the 336 patients who were eligible for inclusion, 157 were included (Figure 1). The majority of patients were female (74%). The mean age was 35 years (range: 18-70). The frequency of atopic comorbidities was: pollinosis (76%), atopic dermatitis (59%) and asthma (54%). Most patients had a moderate (Mueller 1-2) (23%) or severe (Mueller 3-4) (73%) food allergy. The mean number of confirmed food allergies per person was 3.5 (range: 1-10). The most common allergies were fruit (61%), hazelnut (55%), other nuts (excluding hazelnut) (48%), peanut (47%) and vegetables (32%).

Of these patients, 73 (46%) patients reported a total of 153 reactions during a 1-year follow-up period; 0.97 (range: 0-11) reactions were reported per person. These reactions were caused by prepacked foods (41%), meals outside the home (24%), fresh products (20%), products or meals in a foreign country (9%) and whilst having a meal at home (7%).[5] In 19 out of 51 analysed products, the

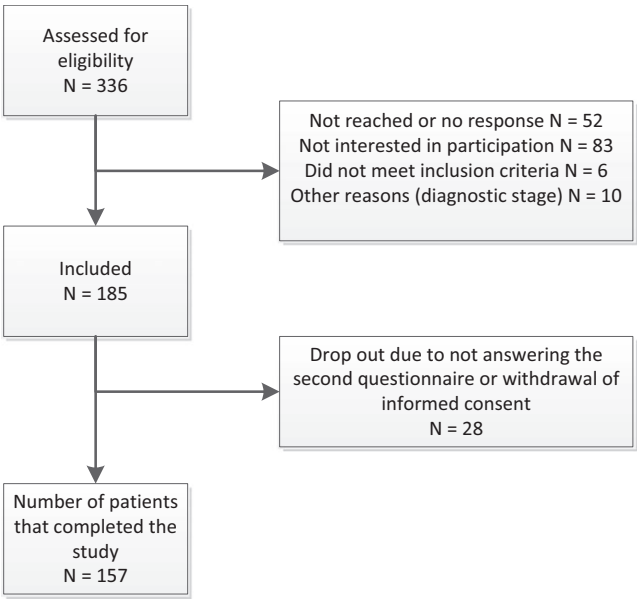

FIGURE 1 Flow chart of patient inclusion

culprit food allergen was found: cow's milk (n = 8), peanut (n = 6) and hazelnut (n = 5) were the most common (noningredient) allergens.[24]

3.2 | Frequency of presence of potential cofactors in allergic reactions

One or more potential cofactors were reported to be present in 74% (95% CI: 66%-81%) of the accidental allergic reactions to food (Figure 2). The most common potential cofactor in accidental allergic reactions was tiredness (38%), followed by alcohol intake (16%), stress (14%), symptoms of pollinosis (16%) and symptoms of asthma (9%).

More than one potential cofactor was reported to be present in almost half of all allergic reactions (47%). In these reactions, two (30%) or three (14%) of these factors were present. Less frequent were reactions in the presence of four (1%) and five (3%) factors. Of the twenty-eight patients reporting more than one allergic reaction (in four patients, data about potential cofactors were missing), 15 patients (54%) reported only reactions in the presence of potential cofactors (ranging from one up to five factors), 12 (43%) reported reactions both with and without presence of these factors and one patient (who reported four allergic reactions) only had reactions in the absence of these factors.

In every first accidental allergic reaction per patient, one or more cofactors were reported to be present in 78% of the patients.

Logistic regression analysis was performed to assess the influence of asthma, pollinosis, age and gender univariate on the likelihood that one or more potential cofactors were reported to be present in every first allergic reaction. No significant influence was found of asthma (OR: 0.61, CI: 0.17-2.20), pollinosis (OR: 1.61, CI: 0.36-7.17), age (OR: 0.97, CI: 0.92-1.01) and gender (OR: 2.34, CI: 0.58-9.43).

3.3 | Daily used medication that might act as cofactor and occurrence of allergic reactions

For 157 allergic patients, data about daily used medication that might act as cofactor were available in n = 90 patients. Daily use of these types of medication was reported by eight patients (9%): antacids (4%), ARBs (3%), beta blockers (2%) and ACEIs (1%) (Table 1). In this patient group, there was no significant difference between the number of patients that reported no or one or more allergic reactions ($P = 0.286$).

Six patients (7%) used antacids on demand, whereof two patients reported allergic reactions. None of the patients used ARBs, beta blockers and ACEIs on demand.

3.4 | Daily used allergy-suppressing medication

Of all 157 patients, 38% daily used medication that could suppress allergic symptoms (Table 1). Antihistamines were most frequently used (29%). The use of medication that suppresses allergic symptoms was 10% lower in the group of patients that did not report any allergic reaction; however, this was not significantly different ($P = 0.239$).

Of the eight patients who daily used medication which is suggested as potential cofactor (antacids, ARBs, beta blockers and ACEIs), four did not use medication that could suppress allergic symptoms.

3.5 | Alcohol intake, physical exercise and analgesics use

When alcohol consumption was reported (16% of the reactions), alcohol intake was in most patients limited to 1-2 alcoholic consumptions (71%) and often the time interval between alcohol intake and the reaction was 0-2 hours (83%) (Table 2). Physical exercise was reported in five (3%) allergic reactions, varying between ½-0 hours prior eating and ½-2 hours after eating the suspected food. All three patients that used analgesics reported a reaction within 4 hours of the intake of analgesics.

3.6 | Cofactors and severity of allergic reactions

In mild, moderate and severe reactions, potential cofactors were present in 70%, 72% and 80% of the reactions, respectively, and absent in 30%, 28% and 20% of the reactions, respectively (Figure 2). There was no significant difference in the presence of these factors between mild, moderate and severe allergic reactions in all reactions ($P = 0.522$) and in every first reaction per patient ($P = 0.792$), and also, no difference was found between mild, moderate and severe reactions in the presence of individual potential cofactors: tiredness ($P = 0.977$ and 0.949), alcohol intake ($P = 0.058$ and 0.036), stress ($P = 0.396$ and 0.423) symptoms of pollinosis ($P = 0.759$ and 0.170) and symptoms of asthma ($P = 0.582$ and 0.424). Using an alternative scoring system for

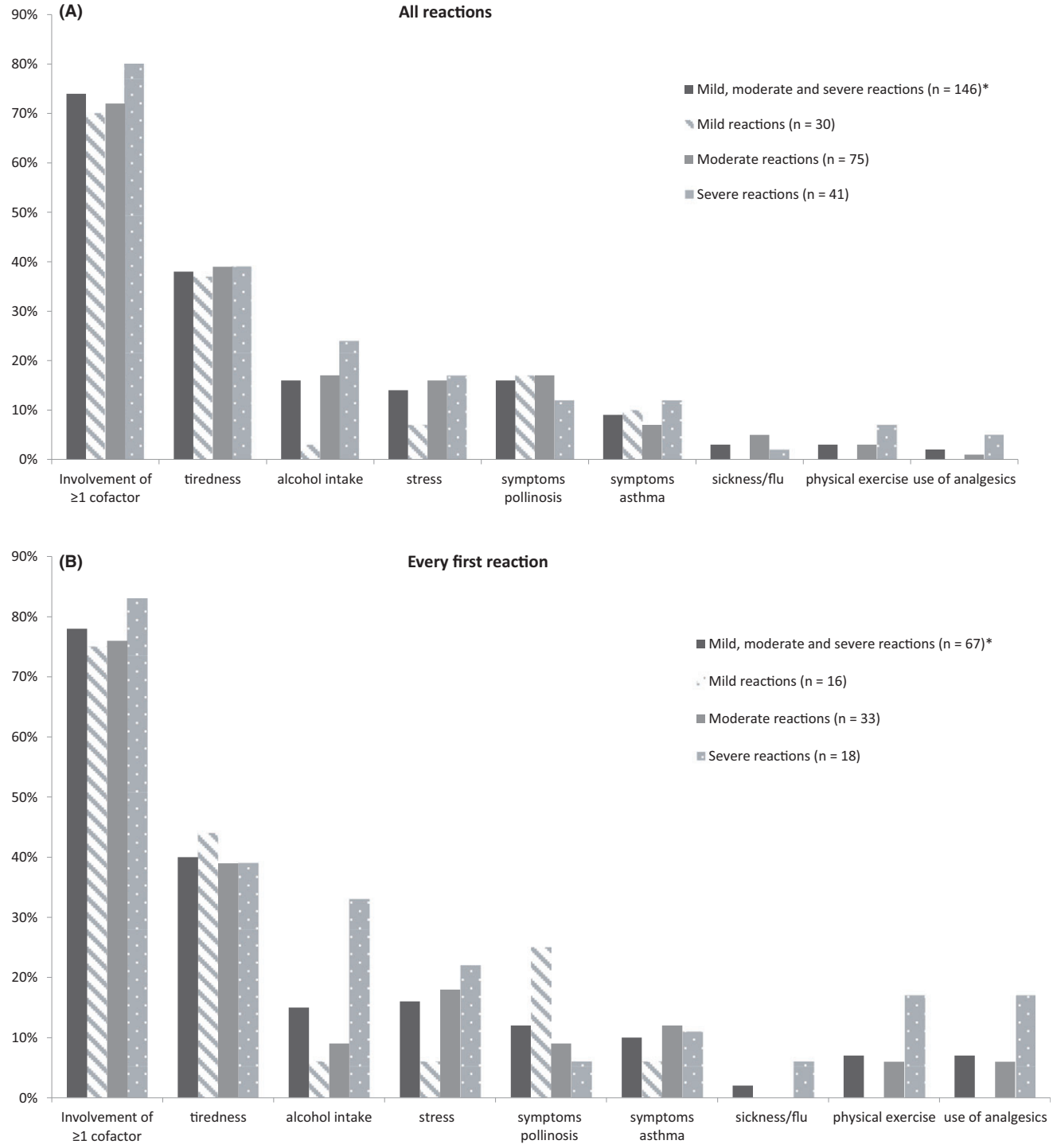

FIGURE 2 Frequency of presence of potential factors in accidental allergic reactions to food in all reactions (A) and every first reaction (B). *Reactions with local oral allergy symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe[25,26]

severity, namely that according to Ewan and Clark grading,[27,28] also showed no significant differences (Table S1). Furthermore, there was no significant difference in the number of present potential cofactors between mild, moderate and severe allergic reactions ($P = 0.171$).

In severe reactions, daily use of medication that might act as a cofactor (antacids, ARBs, beta blockers and ACEIs) was not more frequent compared to mild and moderate reactions.

Mild, moderate and severe reactions were reported after a low as well as high amount of alcohol consumption (Table 2).

TABLE 1 Medication use that might act as cofactor or that could suppress allergic symptoms

	Total patient group	Patients with no allergic reactions	Patients with ≥1 allergic reactions	All allergic reactions	Mild[a] allergic reaction (Mueller 0)	Moderate allergic reactions (Mueller 1-2)	Severe allergic reactions (Mueller 3-4)
	Patient level	Patient level	Patient level	Reaction level	Reaction level	Reaction level	Reaction level
Daily use of medication that could act as cofactor	**N = 90 (missing: n = 67)[b]**	**N = 51 (missing: n = 18)**	**N = 39 (missing: n = 34)**	**N = 79 (missing: n = 74)**	**N = 20 (missing: n = 13)**	**N = 38 (missing: n = 39)**	**N = 21 (missing: n = 22)**
Uses **daily** medication from ≥1 of below medication groups	8 (9%)	3 (6%)	5 (13%)	7 (9%)	3 (15%)	2 (5%)	2 (10%)
– Antacids	4 (4%)	3 (6%)	1 (3%)	1 (1%)	1 (5%)	0	0
– Angiotensin receptor blockers (ARBs)	3 (3%)	1 (2%)	2 (5%)	2 (3%)	1 (5%)	1 (3%)	0
– Beta blockers	2 (2%)	0	2 (5%)	2 (3%)	1 (5%)	1 (3%)	0
– Angiotensin-converting enzyme inhibitors (ACEIs)	1 (1%)	0	1 (3%)	3 (4%)	0	1 (3%)	2 (10%)
Medication that could suppress allergic symptoms (daily use[c])	**N = 157**	**N = 84**	**N = 73**	**N = 153**	**N = 33**	**N = 77**	**N = 43**
Uses medication from ≥1 of below medication groups	59 (38%)	28 (33%)	31 (43%)	83 (54%)	16 (49%)	45 (58%)	22 (51%)
– Antihistamines	45 (29%)	21 (25%)	24 (33%)	71 (46%)	13 (39%)	37 (48%)	21 (49%)
– Inhaled corticosteroids	13 (8%) (missing: n = 1)	4 (5%)	9 (12%)	21 (14%)	5 (15%)	12 (16%)	4 (9%)
– Combination inhalers (corticosteroids/ betamimetics)	10 (6%) (missing: n = 1)	3 (4%)	7 (10%) (missing: n = 1)	20 (13%) (missing: n = 2)	1 (3%)	14 (18%)	5 (16%) (missing: n = 2)
– Inhaled betamimetics	9 (6%)	5 (6%)	4 (6%)	11 (7%)	0	7 (9%)	4 (9%)
– Systemic corticosteroids/ immunosuppressive drugs	4 (3%)	3 (4%)	1 (1%)	4 (3%)	0	4 (5%)	0
– Tricyclic antidepressants (TCAs)	3 (3%) (missing: n = 67)	0	3 (8%) (missing: n = 34)	4 (5%) (missing: n = 74)	0 (missing: n = 13)	3 (8%) (missing: n = 39)	1 (5%) (missing: n = 22)

[a]Reactions with local oral allergy symptoms (Mueller 0) were classified as being mild, reactions with symptoms from skin and mucous membranes (Mueller 1) and/or gastro-intestinal tract (Mueller 2) were classified as moderate and reactions with respiratory symptoms (Mueller 3) and/or cardiovascular symptoms (Mueller 4) were classified as being severe.[25,26]

[b]The items for this outcome measure were added at a later moment in the study, resulting in relatively many missing data.

[c]In case of methotrexate: one dose weekly.

TABLE 2 The amount/intensity of potential cofactors and the time interval between these factors and allergic reactions: alcohol intake, physical exercise and use of analgesics

Alcohol	**Allergic reactions with the presence of alcohol. n = 24**
Total alcoholic consumptions:	
– 1-2	17 (71%) (Mueller[a]: 0 (n = 1), 1 (n = 2), 2 (n = 8), 3 (n = 5), 4 (n = 1))
– 3-4	4 (17%) (Mueller: 2 (n = 2), 3 (n = 1) 4 (n = 1))
– ≥5	3 (12%) (Mueller: 1 (n = 1), 3 (n = 1), 4 (n = 1))
Time interval between alcohol intake and reaction:	
– 0-2 h prior reaction	20 (83%) (Mueller: 0 (n = 1), 1 (n = 2), 2 (n = 9), 3 (n = 6), 4 (n = 2))
– 2-4 h prior reaction	3 (13%) (Mueller: 1 (n = 1), 2 (n = 1), 3 (n = 1))
– 4-8 h prior reaction	1 (4%) (Mueller: 4 (n-1))
Physical exercise	**Allergic reactions with the presence of physical exercise. n = 5**
Time interval between physical exercise and eating:	
– ½-0 h prior eating	2 (Mueller: 2 (n = 1), 3 (n = 1))
– 0-½ h after eating	2 (Mueller: 3 (n = 1), 4(n = 1))
– ½-2 h after eating	1 (Mueller: 2 (n = 1))
Use of analgesics (including NSAIDs and opioids)	**Allergic reaction with the presence of analgesics use. n = 3**
Type of analgesic:	
– NSAIDs	1 (Mueller: 1 (n = 1))
– Tramadol	2 (Mueller: 3 (n = 2))
Time interval between intake of analgesic and reaction:	
– 0-2 h prior reaction	2 (Mueller: 3 (n = 2))
– 2-4 h prior reaction	1 (Mueller: 1 (n = 1))
– 4-8 h prior reaction	0

[a]Mueller classification for severity: Mueller 0: Reactions with local oral allergy symptoms; Mueller 1: reactions with symptoms from skin and mucous membranes; Mueller 2: symptoms from gastro-intestinal tract; Mueller 3: reactions with respiratory symptoms and Mueller 4 reactions with cardiovascular symptoms.[25,26]

4 | DISCUSSION

This study is to date the only prospective study on this subject. It showed that in 74% of the accidental allergic reactions to food, one or more potential cofactors were reportedly present. The most common potential cofactor was tiredness, followed by alcohol intake, stress, symptoms of pollinosis and symptoms of asthma. However, there were no differences in severity of reactions with and without these factors. Daily use of medication that might act as cofactor was also found not to influence the occurrence either.

We found that in most allergic reactions (74%), one or more potential cofactors were present, with differences in frequency per specific factor, ranging from 2% to 38%. Retrospective data from anaphylaxis registers[13,14] reported the presence of these factors in 25.6% and 39% of the anaphylactic reactions to food in adults, with differences in frequency per specific factor ranging from 1.3% to 15.9%. We found that tiredness (38%), alcohol intake (16%), stress (14%) and symptoms of pollinosis (16%) were the most frequently present potential cofactors. Less frequently present potential cofactors were sickness/flu (3%), physical exercise (3%) and use of analgesics (2%). Remarkably, in the anaphylaxis registers, exercise was the most frequently present factor (9.6% and 15.9%).[13,14] However, the anaphylaxis registers made no distinction between physical exercise as potential cofactor influencing severity of reactions and FDEIA in which physical exercise is crucial for the onset of allergic symptoms. In our study, patients with FDEIA were excluded, which could partly explain the lower frequency of physical exercise reported. Other potential cofactors that were reported in the anaphylaxis registers were alcohol intake in, respectively, 3.7%[14] and 9.6%[13] of anaphylactic reactions, stress (4.5%),[13] NSAIDs (4.7%),[14] (other) drugs (3.7%[14] and 21.2%[13]) and infection (1.3%).[13] Remarkably, tiredness (the 1st most frequent potential cofactor in our study) was not reported in the anaphylaxis registers.[13,14] No other studies have been published about the frequency of tiredness in food allergic reactions. The differences in frequency that potential cofactors are present in allergic reactions between our study and the anaphylaxis register studies could be explained by differences in study design. The prospective design of our study with a 1-year follow-up period likely resulted in less recall and information bias than studies based on an online registry with questionnaires filled in by many different physicians. Besides, in our study, patients with mild, moderate and severe reactions were included, probably resulting in other outcomes compared with the anaphylaxis registries in which only patients with anaphylactic reactions (severe reactions involving respirator and/or cardiovascular tract) were included.[13,14]

We found no differences in severity of reactions between those with and without potential cofactors. Also, when using the Ewan and Clark grading,[27,28] which resulted in a higher number of mild reactions as compared with the Mueller classification,[25,26] no differences were found in severity of reactions between those with and without potential cofactors. Further, the daily use of medication that might act as cofactor was found not to influence the occurrence either. This seems to be in contrast with the literature. Wölbing et al[12] carried out a review about cofactors in anaphylactic reactions and concluded these factors seem to have an important role in elicitation and severity of anaphylactic reactions, however that underlying mechanisms are still not fully understood and further research is needed. One study following twenty-two children during peanut oral immunotherapy reported that more than half of them (12/22) often developed unexpected allergic reactions after ingestion of a previously tolerated dose when a potential cofactor was present, including exercise, excessive tiredness, exposure to inhalant allergens, infection and menstruation.[29] However, the small sample size in this study limits the generalizability from patient level to population level. A database study with 382 cases of anaphylaxis showed that severe and uncontrolled asthma is a risk factor for severe anaphylactic reactions.[30] In our previous retrospective study, 13% of the food allergic

patients reported experiencing more severe reactions after physical exercise (10%), alcohol intake (5%) and/or use of analgesics (0.6%).[16] Further, patients with severe food allergy reported significantly more often that the presence of cofactors caused more severe reactions, when compared with patients with mild/moderate food allergy.[16] The prospective design of the current study with data collected by questionnaires filled in per accidental allergic reactions, likely resulted in better recall and more precise data than our previous retrospective study with data collected with a questionnaire administered at one point in time.

Insight into the underlying mechanisms of the different potential cofactors would help to understand the relevance of these potential cofactors in food allergic reactions. Several mechanisms are suggested, for example increased blood circulation after physical exercise leading to increased influx of allergen in the gut, and relaxation of the tight junction of the gut epithelium after alcohol intake leading to increased gastro-intestinal absorption of protein. However, the amount of evidence differs per cofactor and the significance of these suggestions is still not clear.[11,12,31]

This study further showed that about one-third of the food allergic patients used medication (such as antihistamines and corticosteroids) that likely suppresses allergic symptoms. Patients used these types of medication regularly for other atopic comorbidities such as asthma and pollinosis. Although it is suggested in the literature that unstable asthma and active pollinosis can act as potential cofactors in food allergy, adequate treatment might result in suppression of severity of reactions.[32-34] We found no significant difference in use of allergic symptoms suppressing medication comparing patients who did or did not report any allergic reaction.

A limitation of this study was that the accidental allergic reactions were reported by the patient, which could lead to information bias and response bias, possibly resulting in over- or underestimation of the presence of potential cofactors in reactions and of severity of reactions. In addition, the experience of symptoms of an allergic reaction might differ per person, which could lead to bias in data when it is self-reported. However, a study in young children showed that self-reported data about severity of allergic reactions were not biased,[35] suggesting that the role of bias in self-reported data might be limited. Besides, all reported reactions were reviewed by the research team within 1 week and if necessary the patient was called by phone for further clarification.

Tiredness and stress were often present during the reported allergic reactions. We did not measure the degree of tiredness and stress, so we could not make a differentiation between, for example, mild and severe tiredness and stress. This limits the strengths of our conclusion.

We did not study hormonal changes during the premenstrual and ovulatory phase as a potential cofactor, which has been suggested by others,[36,37] However, we did not find any evidence for the influence of gender on the likelihood that one or more cofactors were present in allergic reactions.

Alcohol consumption was considered to be a potential cofactor when used within 8 hours prior the reaction. Literature describes several factors that influence the time interval by which alcohol is eliminated from the body, for example the amount of alcohol, gender, age, food and biological rhythms.[38] This makes it impossible to determine whether alcohol was actually present during the accidental allergic reaction. In our study, in most reactions, alcohol was consumed within 2 hours prior the reaction (83%). This suggests that alcohol had influence on the occurrence of the reaction.

Further, it needs to be mentioned that use of medication that could act as cofactor was only questioned in part of the study population which limits the generalizability.

In conclusion, although factors suggested to be cofactors were frequently present during accidental food allergic reactions, we found no evidence for an association between the potential cofactors examined and reaction severity, in a population where most reactions were of mild to moderate severity.

ACKNOWLEDGEMENTS

This study was financially supported by the Netherlands Food and Consumer Product Safety Authority, Utrecht, the Netherlands.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

H. van Os-Medendorp, A. D. Michelsen-Huisman, J. J. M. Castenmiller, G. F. Houben and A. C. Knulst designed the study. A. Versluis, H. van Os-Medendorp and A. Michelsen-Huisman 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.

ORCID

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

REFERENCES

1. Nwaru BI, Hickstein L, Panesar SS, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69(1):62-75.
2. 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.
3. Lange L. Quality of life in the setting of anaphylaxis and food allergy. *Allergo J Int*. 2014;23(7):252-260.
4. Versluis A, Knulst AC, Kruizinga AG, et al. Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review. *Clin Exp Allergy*. 2015;45(2):347-367.
5. Michelsen-Huisman AD, van Os-Medendorp H, Blom WM, et al. Accidental allergic reactions in food allergy: causes related to products and patient's management. *Allergy*. 2018;Jul 13:1-5.

6. Uguz A, Lack G, Pumphrey R, et al. Allergic reactions in the community: a questionnaire survey of members of the anaphylaxis campaign. *Clin Exp Allergy*. 2005;35(6):746-750.
7. Hompes S, Kohli A, Nemat K, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents–data from the anaphylaxis registry of German-speaking countries. *Pediatr Allergy Immunol*. 2011;22(6):568-574.
8. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy*. 2003;33(8):1033-1040.
9. Fischer J, Hebsaker J, Caponetto P, Platts-Mills TA, Biedermann T. Galactose-alpha-1,3-galactose sensitization is a prerequisite for pork-kidney allergy and cofactor-related mammalian meat anaphylaxis. *J Allergy Clin Immunol*. 2014;134(3):755-759.e1.
10. Pfeffer I, Fischer J, Biedermann T. Acetylsalicylic acid dependent anaphylaxis to carrots in a patient with mastocytosis. *J Dtsch Dermatol Ges*. 2011;9(3):230-231.
11. Niggemann B, Beyer K. Factors augmenting allergic reactions. *Allergy*. 2014;69(12):1582-1587.
12. 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.
13. Worm M, Scherer K, Köhli-Wiesner A, et al. Nahrungsmittelanaphylaxie und kofaktoren – daten aus dem anaphylaxie-register. *Allergologie*. 2011;34(7):329-337.
14. Cercle d'Investigations Cliniques et Biologiques en Allergologie Alimentaire. Présentation du Réseau d'Allergo-Vigilance (dates de 2002). 2009. http://www.cicbaa.org/pages_fr/allergovigilance/allergovigilance_01-04_fr.pdf. Accessed August 20, 2015.
15. Ansley L, Bonini M, Delgado L, et al. Pathophysiological mechanisms of exercise-induced anaphylaxis: an EAACI position statement. *Allergy*. 2015;70(10):1212-1221.
16. Versluis A, van Os-Medendorp H, Kruizinga AG, Blom WM, Houben GF, Knulst AC. Cofactors in allergic reactions to food: physical exercise and alcohol are the most important. *Immun Inflamm Dis*. 2016;4(4):392-400.
17. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlstrom J, Tanaka A. Food-dependent exercise-induced anaphylaxis -importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis-. *Allergol Int*. 2009;58(4):493-498.
18. Asero R, Piantanida M, Pinter E, Pravettoni V. The clinical relevance of lipid transfer protein. *Clin Exp Allergy*. 2018;48(1):6-12.
19. Pascal M, Munoz-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.
20. Romano A, Scala E, Rumi G, et al. Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2012;42(11):1643-1653.
21. Cardona V, Luengo O, Garriga T, et al. Co-factor-enhanced food allergy. *Allergy*. 2012;67(10):1316-1318.
22. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2014;69(8):1026-1045.
23. Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol*. 2001;108(1):133-140.
24. Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, et al. Accidental food allergy reactions: products and undeclared ingredients. *J Allergy Clin Immunol*. 2018;142:865-875.
25. Peeters KA, Koppelman SJ, van Hoffen E, et al. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? *Clin Exp Allergy*. 2007;37(1):108-115.
26. Mueller HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res*. 1966;3(4):331-333.
27. Ewan PW, Clark AT. Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. *Clin Exp Allergy*. 2005;35(6):751-756.
28. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. *Lancet*. 2001;357(9250):111-115.
29. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy*. 2011;41(9):1273-1281.
30. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LAG. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol*. 2010;125:1098-1104.
31. Wolbing F, Biedermann T. Anaphylaxis: opportunities of stratified medicine for diagnosis and risk assessment. *Allergy*. 2013;68(12):1499-1508.
32. Panesar SS, Javad S, de Silva D, et al. The epidemiology of anaphylaxis in Europe: a systematic review. *Allergy*. 2013;68(11):1353-1361.
33. Gonzalez-Perez A, Aponte Z, Vidaurre CF, Rodriguez LA. Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review. *J Allergy Clin Immunol*. 2010;125(5):1098-1104.e1.
34. Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. *J Allergy Clin Immunol*. 2008;121(3):632-638.e2.
35. Chan JC, Peters RL, Koplin JJ, et al. Food challenge and community-reported reaction profiles in food-allergic children aged 1 and 4 years: a population-based study. *J Allergy Clin Immunol Pract*. 2017;5(2):398-409.e3.
36. Bito T, Kanda E, Tanaka M, Fukunaga A, Horikawa T, Nishigori C. Cows milk-dependent exercise-induced anaphylaxis under the condition of a premenstrual or ovulatory phase following skin sensitization. *Allergol Int*. 2008;57(4):437-439.
37. Fischer J, Schuck E, Biedermann T. Wheat-dependent exercise-induced anaphylaxis exclusively during menstruation. *Allergy*. 2010;65(10):1347-1348.
38. Cederbaum AI. Alcohol metabolism. *Clin Liver Dis*. 2012;16(4):667-685.

SUPPORTING INFORMATION

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

How to cite this article: Versluis A, van Os-Medendorp H, Blom WM, et al. Potential cofactors in accidental food allergic reactions are frequently present but may not influence severity and occurrence. *Clin Exp Allergy*. 2019;49:207–215. https://doi.org/10.1111/cea.13282

Online supplement Table 1. Frequency of presence of potential factors in accidental allergic reactions to food – Ewan and Clark grading

Cofactors	Mild reactions (Ewan and Clark grading 1-3)*	Moderate reactions (Ewan and Clark grading 4)	Severe reactions (Ewan and Clark grading 5)	P-value mild, moderate and severe reactions vs. whether or no presence of cofactor(s)
	n =71 (missing: n = 4)	n = 40 (missing: n = 1)	n = 35 (missing: n = 2)	n = 146
Involvement of ≥1 of the cofactors below	51 (72%)	28 (70%)	29 (83%)	0.381
Tiredness	27 (38%)	15 (38%)	14 (40%)	0.973
Alcohol intake	9 (13%)	6 (15%)	9 (26%)	0.225
Stress	9 (13%)	5 (13%)	7 (20%)	0.554
Symptoms of pollinosis	12 (17%)	8 (20%)	3 (9%)	0.373
Symptoms of asthma	6 (9%)	3 (8%)	4 (11%)	0.856
Sickness/flu	1 (1%)	3 (8%)	1 (3%)	NA
Physical exercise	0	2 (1%)	3 (1%)	NA
Use of analgesics (NSAIDs or opioids)	0	1 (3%)	2 (6%)	NA

*Oral pruritus/erythema/urticaria/angio-oedema/gastrointestinal symptoms/rhino conjunctivitis = mild; laryngeal edema/mild respiratory symptoms = moderate; dyspnea/hypotension = severe (27, 28)