

Effects of Exercise and Sleep Deprivation on Reaction Severity During Oral Peanut Challenge: A Randomized Controlled Trial



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What is already known about this topic? There are limited data on the effect of cofactors or repeat challenges on allergic reaction severity.

What does this article add to our knowledge? This is the first study showing that both sleep deprivation and repeated challenges increased the severity of peanut-allergic reaction in adults by 48% and 38%, respectively, using a weighted severity score. Exercise does not significantly increase severity.

How does this study impact current management guidelines? Knowing how these factors modulate severity can better allow health care professionals to advise patients about their future reaction risk and facilitate the avoidance of a severe reaction, for example, when advising about cofactors during immunotherapy.

BACKGROUND: The severity of allergic reactions to foods can vary markedly. Little is known of variations in reaction severity within or between individuals or the effects of cofactors.

OBJECTIVE: We examined the effects of sleep deprivation and exercise and repeat challenges on the severity and patterns of allergic reactions to peanut.

METHODS: In a randomized crossover study, adults with peanut allergy underwent 3 open peanut challenges in random order: with exercise after each dose, with sleep deprivation preceding challenge, and with no intervention. The primary outcome was eliciting dose, reported elsewhere. Reaction severity was a secondary outcome, evaluated using a weighted log-transformed numerical severity score. Analyses estimated the difference in severity between nonintervention challenge and

challenges with exercise or sleep deprivation, adjusting for challenge order and using the highest dose tolerated by each individual across all their challenges. Symptom pattern reproducibility was assessed by comparing symptom sequences using pairwise sequence alignment to obtain a percentage match in symptom pattern.

RESULTS: Eighty-one participants (mean age 25 y) completed at least 1 postbaseline challenge. Sleep deprivation, but not exercise, significantly increased severity score by 48% (95% CI 12%–84%; $P = .009$) compared with no intervention. A 38% increase in severity was observed between the first and the last postbaseline challenge (95% CI 1%–75%; $P = .044$). The average pairwise match of symptoms within individuals was 82.4% and across individuals was 78.3%.

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Conflicts of interest: P. Ewan is a director of Camallergy Ltd which develop peanut allergy treatments. R. J. Boyle has participated in an advisory board for DBV technologies and Prota therapeutics, which both develop food allergy treatments; has acted as an expert witness in legal cases related to infant formula health claims, allergy, and food anaphylaxis; receives compensation for editorial work at Cochrane and at Clinical and Experimental Allergy; and is a member of the UK Nutrition and Health Claims Committee and Scientific Advisory Committee on Nutrition Subgroup on Maternal and Child Nutrition. A. Clark is a director of Camallergy Ltd which develop peanut allergy treatments. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

DBPC- Double-blind placebo-controlled

GI- Gastrointestinal

IgE- Immunoglobulin E

IgG4- Immunoglobulin G4

IM- Intramuscular

OFC- Oral food challenge

SPT- Skin prick test

TRACE- Threshold Reactivity and Clinical Evaluation (study)

CONCLUSIONS: A novel severity score demonstrates that sleep deprivation and repeated challenges increase reaction severity. Understanding factors affecting severity is essential for effective risk management. We also show that symptom patterns in repeat peanut challenges are similar within and between individuals. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2404-13)

Key words: Peanut; Allergy; Severity; Exercise; Sleep deprivation

INTRODUCTION

The severity of allergic reactions to food is influenced by several factors that are likely to be both host- and event-specific, making allergic reactions unpredictable. This unpredictability is of concern given the propensity of food allergy to occasionally cause severe and fatal reactions.¹ Various factors are known to influence the severity of allergic reactions including cofactors such as exercise, individual factors such as comorbid allergic conditions, mastocytosis, difference in gastrointestinal (GI) absorption, or other allergen-related factors such as food matrix or allergen processing.²

A lack of stability in allergic reactions over time can add to anxiety for patients managing their own allergy and uncertainty for clinicians when advising patients. A further practical implication is that oral food challenge (OFC), the current gold standard of food allergy diagnosis, carries with it an inherent risk of provoking severe allergic reactions, with 1 study reporting that 28% of OFC resulted in systemic and potentially life-threatening reactions.³ There are limited data on the variability of reactions within individuals, particularly with regard to severity. Most information comes from patient recollection of symptoms occurring during reactions following accidental exposures, which are anxiety-provoking events and may be subject to recall bias. Little information is available on the change in severity with repeat food challenges,⁴ because normally, these are used to establish diagnosis and once an allergy is confirmed, most patients do not undergo subsequent challenges. Therefore, more granular, prospectively collected detail on the evolution of symptoms during challenge has not been reported. Such information would be useful to allergic individuals to help guide them about potential warning symptoms and the timely administration of treatment. Physicians will also find the information helpful when advising patients about the potential severity of accidental reactions and ways to reduce risk.

Furthermore, there is a lack of consensus about how to grade severity, with several different grading systems proposed. It has been reported that this is due to patients not presenting with a consistent constellation of allergic symptoms⁵ as well as debate

about how much weight to attribute to certain symptoms, for example, comparing GI to extensive cutaneous symptoms. Attempts have been made to determine clinical and laboratory predictors of severity on the basis that, if higher risk-allergic individuals could be identified, enhanced surveillance and education of this group would be possible.

We previously reported that exercise and sleep deprivation lowered the threshold of reactivity to peanut in the Threshold reactivity and clinical evaluation (TRACE) study.⁶ However, data on how severity is affected by cofactors are sparse. Christensen et al⁷ recently reported in patients with wheat-dependent exercise-induced anaphylaxis undergoing an OFC with gluten that reaction severity increased with exercise compared with rest when using the Sampson severity grading. Study safety data from immunotherapy studies have demonstrated that cofactors are often responsible for severe reactions occurring during treatment. Thus, a greater insight into how cofactors modulate allergic reaction severity and, in addition, how severe reactions may be avoided would have important implications for how immunotherapy is delivered. In general, few studies have evaluated how the severity of allergic reactions changes within individuals with repeated reaction.

In this report, we assessed the influence of exercise and sleep deprivation on the severity of reaction to oral peanut challenge in the TRACE study, while controlling for threshold dose.

METHODS

Trial design

A multicenter randomized crossover study was performed between February 2013 and June 2016 at the National Institute for Health Research (NIHR)/Wellcome Trust Cambridge Clinical Research Facility (Cambridge, U.K.) and Royal Brompton & Harefield National Health Service (NHS) Foundation Trust Clinical Research Facility (London, U.K.), supported by the University of Manchester (U.K.). Following confirmation of allergy by a double-blind placebo-controlled (DBPC) peanut challenge (baseline challenge), eligible participants underwent 3 further open peanut challenges in a randomly assigned, balanced order: 1 with exercise, 1 with sleep deprivation on the night preceding the challenge, and 1 with neither intervention (termed non intervention).

Participants

To ensure that participants represented a broad spectrum of peanut allergy severity, peanut-allergic participants were recruited from the U.K. adult general population, nationally through advertisements in the media and national patient support groups (Anaphylaxis Campaign and Allergy UK) and locally (tertiary allergy clinics specializing in severe food allergy and local media). Participants were included in the study if they gave informed consent, were aged 18 to 45 years with a history of an immediate systemic allergic reaction after peanut ingestion with evidence of sensitization to peanut and the diagnosis confirmed by positive DBPC peanut challenge. Sensitization was defined as a positive skin prick test to peanut (extract ALK-Abello, Hørsholm, Denmark), skin weal of 3 mm or larger greater than the negative control or serum-specific immunoglobulin E (IgE) to peanut greater than 0.35 kUA/L (ImmunoCAP). Volunteers were excluded if they gave a history suggestive solely of pollen-related oral allergy syndrome to peanut (a different, milder disorder). They were also excluded if they had previous life-threatening reactions to peanut, poorly controlled asthma, a significant drop in lung function with exercise, or a diagnosis of mastocytosis. A full list of inclusion and

TABLE 1. Weighted numerical severity score*

Symptom number	Symptom	Numerical score
1	Pruritus—occasional scratching (green)	1
2	Rash—few areas of faint erythema (green)	1
3	Rare bursts of sneezing, occasional sniffing (green)	1
4	Transient nausea (green)	1
5	Throat tingling/altered sensation in throat (green)	1
6	Oral itching (green)	1
7	Itching in inner ear canal (green)	1
8	Pruritus—scratching continuously for > 2 min at a time (green)	2
9	Transient abdominal pain (green)	2
10	Chest tightness without any fall in PEFR (green)	2
11	Rash—areas of erythema (yellow)	6
12	I bursts < 10, intermittent rubbing of nose and/or eyes or frequent sniffing (yellow)	6
13	Continuous rubbing of nose and/or eyes (yellow)	6
14	Hard continuous scratching > excoriations (yellow)	6
15	Persistent nausea (yellow)	10
16	Urticaria < 3 hives or mild lip edema (yellow)	12
17	>3 discrete episodes of throat clearing or cough (yellow)	12
18	Chest tightness with ≤ 10% fall in PEFR (yellow)	13
19	Persistent abdominal pain (yellow)	15
20	Emesis/diarrhea (1 episode) (yellow)	18
21	Periocular swelling and/or long bursts of sneezing (yellow)	20
22	Persistent rhinorrhea (yellow)	20
23	Urticaria < 10 or ≥ 3 hives or significant lip or face edema (red)	20
24	Altered level of consciousness (red)	20
25	Persistent throat tightness (yellow)	25
26	Weak/dizzy or tachycardia (yellow)	25
27	Emesis/diarrhea (>1 episode) (red)	25
28	Rash—generalized marked erythema > 50% (red)	30
29	Urticaria—generalized involvement (red)	30
30	Chest tightness with a 10%–20% fall in PEFR (yellow)	35
31	Hoarseness or frequent dry cough (red)	40
32	Expiratory or inspiratory wheeze (red)	50
33	Chest tightness with a > 20% fall in PEFR (red)	70
34	Use of accessory muscles (red)	70
35	Stridor (red)	100
36	Drop in BP of > 20% from baseline (red)	150
37	Cardiovascular collapse/signs of impaired circulation (red)	200

BP, Blood pressure; PEFR, peak expiratory flow rate; PRACTALL, practical allergy.

*Using a modified version of the PRACTALL criteria, symptoms were assigned a green, yellow, or red color code. Challenges were stopped when participants reached an objective threshold of 3 concurrent yellow symptoms or 1 red symptom. Symptoms across all organ systems from stopping criteria ranked from least severe to most severe and assigned a weighted numerical score.

exclusion criteria is included in the [Table E1](#) (available in this article's Online Repository at www.jaci-inpractice.org).

The study was approved by the National Research Ethics (NRES) committee East of England (12 EE02/89) and performed with each

participant's written informed consent. The UK Food Standards Agency funded the study.

The full methodology including how the peanut challenges (including dosing regimen) were performed has been previously described. The challenge meals were supplied by the University of Manchester, UK.

The exercise challenge regimen consisted of a 10-minute bout of exercise on a static bike at an intensity of 85% maximum oxygen consumption (maximum exercise capacity, determined during screening) undertaken 5 minutes after each dose. For the sleep deprivation challenge, participants were admitted to the research ward on the night preceding the challenge and permitted to sleep for a maximum of 2 hours and then kept awake until the challenge. Participants kept a sleep diary prior to challenge, and if they had experienced a disruption to their normal sleep pattern (<30% normal sleep in the 2 weeks preceding the challenge), appointments were postponed. The non intervention challenge was conducted in the same way as the baseline challenges, except that, like the interventional challenges, the challenge was open, with only 1 active challenge taking place.

For safety, asthma control was assessed prior to each challenge using the Asthma Control Questionnaire and spirometry, and if these parameters were abnormal, the challenge was postponed. Other potential cofactors were carefully controlled, for example, atopic conditions were controlled, nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol were avoided prior to challenge, and challenges were postponed if a participant had evidence of infection.

Criteria for scoring symptoms and stopping food challenge

Using a modified version of the practical allergy (PRACTALL) criteria,⁸ symptoms were assigned a green, yellow, or red color code. Challenges were stopped when participants reached an objective threshold of 3 concurrent yellow symptoms or 1 red symptom. The threshold was called by the study investigator; the same investigator conducted all challenges at each study site for consistency. After piloting the established PRACTALL challenge criteria on 6 participants (data not shown), it was decided by Trial Steering Committee consensus that further refinement of the criteria was needed to enhance safety. Greater discrimination was added to lower respiratory symptoms defining milder airway symptoms, and peak flow was incorporated as a functional measurement to detect rapid progression to severe symptoms. Gastrointestinal symptoms were also further defined in terms of their persistence (≥30 min). Detail on the modification of the criteria has been discussed previously.⁶ Participants who developed symptoms were given treatment as appropriate. If participants suffered severe reactions at baseline DBPC peanut challenge, it was deemed unsafe for them to continue, and they were excluded from the study.

If 2 or more doses of intramuscular (IM) adrenaline were given to a single participant owing to inadequate response to the first dose on 2 separate occasions, they were excluded from further challenges, but their data were included in analyses up to the point of withdrawal.

Grading severity of reactions

Various grading systems are used to report systemic reactions but none are globally accepted. These proposed systems typically present 4 or 5 different grades of severity and are limited in discriminating reactions of varying severities especially toward the moderate and moderate-severe end of the spectrum. Therefore, in this study, a

TABLE II. Method for determining comparable dose in 2 example participants

	Challenge type	Threshold dose reached	Dose chosen for Comparison
Example participant 1*	Baseline	6 (100 mg)	5 (30 mg)
	Exercise	5 (30 mg)	
	No intervention	6 (100 mg)	
	Sleep	5 (30 mg)	
Example participant 2*	Baseline	8 (1,000 mg)	6 (100 mg)
	Exercise	6 (100 mg)	
	No intervention	7 (300 mg)	
	Sleep	6 (100 mg)	

*In Example participant 1, the highest common dose reached across all challenges was dose 5; thus, this dose was chosen for comparison for this participant. In Example participant 2, dose 6 was the highest common dose reached across all challenges; thus, this was the dose chosen for comparison for this participant.

weighted numerical score, based on the stopping criteria, was prospectively devised to capture shifts in severity between challenges.

Development of the severity score

A severity classification was developed based on 2 principles: (1) as the severity increases, the number of involved organ systems usually increases and (2) cardiovascular, neurological, bronchial, and laryngeal involvement are potentially life-threatening and therefore signify more severe reactions.⁹ Numerical weighting was assigned by a consensus panel comprising a committee of experts. All symptoms across all organ systems in the stopping criteria were ranked from least severe to most severe. Each symptom was assigned a weight. In previous studies of fatal food anaphylaxis, acute dyspnea is a prominent feature and the mode of death has been reported to be respiratory arrest.¹⁰ This differs from anaphylaxis caused by venom or parenteral drugs in which cardiovascular symptoms predominate. Cardiovascular and respiratory symptoms have previously been considered by consensus to be life-threatening features of anaphylaxis.¹¹ Therefore, severe cardiovascular and respiratory symptoms were deemed potentially life-threatening red symptoms and were assigned a considerably higher weight than all other symptoms to reflect their importance. The score was tested on example cases in pilot TRACE participants to ensure that there was adequate discrimination to capture shifts in severity particularly at the mild-moderate end of the spectrum where shifts may be smaller. The score is shown in [Table I](#).

Statistical analysis

A threshold was called at the development of objective symptoms by the investigator, and therefore, participants' reactions were unable to evolve fully. As a result of this, there is an unavoidable relationship between threshold dose and severity in this study. To address this issue, we controlled for dose by examining severity at a consistent dose that was reached across all challenges within an individual. The chosen dose was the highest common dose that the participant reached across all challenges as demonstrated in [Table II](#).

The primary outcome of threshold dose for the study has been reported elsewhere. Reaction severity was a secondary outcome and was reported as the challenge mean severity score. Analysis estimated the difference in log-severity between the nonintervention challenge and each intervention challenge (exercise and sleep deprivation) using a linear mixed-effects model along with 95% confidence interval and *P* value for whether the difference in log-severity was significant. Changes in severity were expressed as percentage change. Controls included fixed effects for challenge type (exercise, sleep deprivation, with nonintervention as reference), order of challenge

and baseline log-severity score, and participant-level random intercepts.

Frequency of symptoms

The frequency of each symptom across all challenges was reported.

To identify at an organ system level whether there was a change in symptom severity, symptoms were grouped into organ systems and a system severity score was calculated. The effect of sleep deprivation and exercise on individual organ systems was examined using the same linear mixed-effects model as the main analysis.

Reproducibility of symptom patterns within and across individuals

Participants' symptom patterns during each challenge were compared. A comparison of symptom patterns across participants was also examined using a bioinformatics technique called pairwise sequence alignment that has previously been used to align 2 query sequences of amino acids to find similarities in 2 proteins.¹²

Using the same method as described previously, for each individual, the highest dose causing objective symptoms common to all challenges was taken and all symptoms up until that point in each reaction were observed. If a symptom occurred twice, it was counted once only.

To compare sequences, a 37-digit (all possible symptoms) binary code was produced for each reaction based on the presence (1) or absence (0) of each symptom ([Figure 1](#)). The percentage match for pairs of reactions was calculated based on the coincident presence or absence of each symptom. Percentage match was identified by calculating the number of matches in the pair divided by the length of sequence (ie, 37 symptoms) and multiplying by 100. Random mixed pairs of challenges were compared in this analysis, for example, baseline with exercise or sleep with nonintervention.

In order to assess across-participant symptom patterns, 1,000 randomly selected pairs of reactions across-participants were selected and analyzed for pairwise matches.

Predictors of severity

Severity of reaction was regressed on clinical characteristics including presence of asthma, presence of eczema, age of onset of peanut allergy, severity of worst historical reaction, number of previous adverse reactions, and the timing of last community reaction. Severity was also correlated to markers of sensitisation including skin prick test (SPT) wheal to peanut (mm), specific IgE peanut, and specific IgE to Ara h2.

Symptom	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Participant A	1	1	0	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	1	0	0	1	0	0	1	1	0	1	1	1	0	0	1	
Challenge 1	1	1	0	0	1	0	1	0	0	0	1	0	0	1	0	0	0	0	1	0	0	0	1	0	0	1	0	0	1	1	0	1	1	1	0	0	1	
Participant A	1	0	1	0	1	1	0	0	1	0	1	0	1	1	0	1	1	0	1	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	1	0	1	0
Challenge 2	1	0	1	0	1	1	0	0	1	0	1	0	1	1	0	1	1	0	1	1	0	0	1	1	0	0	0	1	0	0	0	1	0	0	1	0	1	0
Match?					Y	Y			Y		Y	Y	Y		Y	Y		Y		Y	Y	Y		Y	Y	Y			Y	Y		Y			Y	Y		

Symptom	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	
Participant A	1	1	0	0	1	1	1	0	0	0	0	0	0	1	0	1	0	0	0	1	0	0	0	0	0	1	1	1	0	1	1	1	1	1	0	0	1	
Participant B	0	0	1	1	1	1	0	0	1	0	1	0	1	1	0	1	1	0	1	0	1	1	0	1	1	0	0	1	1	0	0	1	0	0	1	0	0	0
Match?					Y	Y		Y		Y		Y		Y	Y		Y	Y				Y									Y				Y			

FIGURE 1. Method of determining a pairwise sequence percentage match using example participants. Each symptom was assigned a number as shown in Table I. A 37-digit (all possible symptoms) binary code was produced for each reaction based on the presence (1) or absence (0) of each symptom. The percentage match for pairs of reactions was calculated based on the coincident presence or absence of each symptom. The number of matches in the pair was then divided by the length of sequence (ie, 37 symptoms) and multiplied by 100. Y, Yes.

Definition of anaphylaxis

Participants who suffered from anaphylaxis during any of their challenges were identified as a distinct group for analysis.

For the purposes of this study, anaphylaxis was defined as 2 or more of the following rapidly occurring symptoms (minutes to up to 2 h) following exposure to peanut: generalized involvement of the skin-mucosal tissue, respiratory compromise (pronounced dyspnea, wheeze, bronchospasm), reduced blood pressure or associated symptoms, severe and persistent abdominal symptoms (cramping abdominal pain and vomiting) using the NIAID/FAAN (National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network) criteria.¹³

To compare whether the underlying characteristics were more predictive of developing anaphylaxis compared with not developing anaphylaxis, univariate linear regressions of the presence of anaphylaxis on the underlying characteristics (linear probability model) were used.

Adrenaline use

The frequency of IM and nebulized adrenaline use was reported using descriptive statistics.

Serum-specific IgE and IgG4 levels to peanut component Ara h2

Serum specific IgE and IgG4 to peanut component Ara h2 was quantified using ImmunoCAP. Samples obtained for each individual at baseline, exercise, nonintervention, and sleep challenge were assayed. A linear mixed-effects model was used to examine the percentage change in these parameters for each visit compared with the baseline visit.

RESULTS

Participants

One hundred and twenty-three participants with a mean age of 24.3 years completed a baseline challenge. This included participants with a history of reactions involving adrenaline use (37%) and reactions involving wheeze (47%) representing participants with more severe peanut allergy. One hundred were randomized to undergo further intervention challenges and 81 completed at least 1 further challenge (exercise, sleep deprivation, or non intervention; n = 73, 71, and 71, respectively). Three

hundred and forty-two challenges were completed in total. Reasons for nonrandomization of participants postbaseline included tolerance of all challenge doses and, hence, inability to identify a threshold, an extremely severe reaction, noncompliance, and quota of randomized participants already being complete.

A distribution of the overall challenge severity score across all challenges (n = 342) is shown in Figure 2. As a comparison, the distribution of severity grades according to Sampson's criteria is shown (Tables III and IV). Fifty-six reactions were categorized as anaphylaxis using the NIAID/FAAN criteria, 35% occurred in baseline challenge, 20% in exercise, 20% in sleep deprivation, and 25% in nonintervention. No symptoms experienced during the placebo challenges met the stopping criteria (ie, 3 concurrent yellow symptoms or 1 red symptom).

Adrenaline use

Intramuscular adrenaline was delivered in 52 of 342 challenges (15%). Adrenaline was administered in 17% baseline challenges, 11% sleep deprivation challenges, 15% exercise challenges, and 14% no-intervention challenges. Two doses of IM adrenaline were delivered to stabilize the participants in 6 of 342 challenges (2%). Nebulized adrenaline was administered in 3 of 342 challenges (1%).

The effect of exercise and sleep deprivation on severity

Using the highest common dose within individuals to examine the effect of exercise and sleep deprivation, sleep deprivation was associated with a 48% increase in severity (95% CI 12%–84%; $P = .009$) compared with the no-intervention challenge. Exercise was associated with a 28% increase in severity, although this was not significant at a 5% level (95% CI –9% to 66%; $P = .143$; Figure 3).

The effect of visit number on severity

Using the highest common dose within individuals to examine the effect of visit number on severity, there was an increase in severity with each successive postbaseline visit. Severity for visit 3 versus visit 1 postbaseline was 38% higher (95% CI 1%–75%; $P = .044$). Alternatively repeating the model with a linear trend

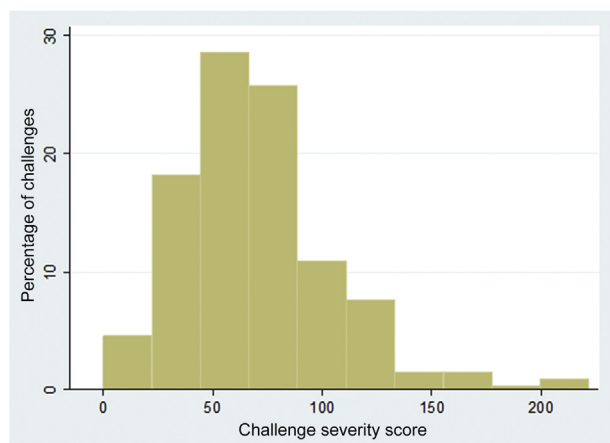


FIGURE 2. Distribution of overall challenge severity score across all challenges including baseline, exercise, sleep, and nonintervention.

TABLE III. Severity of reactions according to Sampson's grading

Grade	Percentage (%) of reactions
1	0
2	33
3	47
4	20
5	0

for visit resulted in a 19% rise (95% CI 1%–38%) for each visit (Figure 3).

Symptom frequency and severity

The frequency of the 37 symptoms during all challenges is displayed in Figure 4.

Symptoms were also grouped into physiological systems. With regard to changes in severity score at a system level, exercise caused an increase in respiratory system severity by 63% (95% CI 25%–100%; $P = .001$). Significant effects were observed in sleep deprivation challenges for 3 systems. The severity of cutaneous, throat, and GI symptoms increased under sleep deprivation conditions by 41% (95% CI 8%–74%; $P = .016$), 53% (95% CI 17%–88%; $P = .004$), 46% (95% CI 8%–84%; $P = .017$). There were no significant effects for other organ systems (data not shown).

Symptom patterns within and across individuals

There were 462 possible within-participant pairs of reactions. The average pairwise percentage match in symptom code was 82.4%. When examining symptom pattern across individuals, 1,000 random across-participant pairs of reactions were selected, ensuring that reactions were compared with like-for-like doses, for example, symptom pattern at dose 7 in 1 individual was compared with symptom pattern at dose 7 in a different individual. The average pairwise percentage match across participants was 78.3%.

Correlation of reaction severity score and anaphylaxis with participant characteristics

Using linear regression analyses, SPT wheal to peanut, peanut specific IgE, Ara h2 specific IgE, presence of asthma, presence of eczema, timing of last reaction, previous anaphylaxis, number of adverse reactions, and age of onset of peanut allergy were not significantly associated with challenge severity score. However, when examining the severity score of respiratory symptoms only, the presence of asthma was associated with a higher severity of respiratory symptoms ($P = .011$). In participants who had anaphylaxis during a challenge, there was a positive correlation with a history of anaphylaxis ($R^2 0.14$; $P = .035$).

Serum-specific IgE and IgG4 levels to peanut component Ara h2

Data were available for 30 participants. The reasons for missing data were random, including random sampler error or insufficient serum to run the test. The level of Ara h2-IgE was unaffected by challenges over time. Conversely, there was a significant increase in Ara h2-IgG4 in successive visits, there was an increase of 29% at visit 2 (95% CI 6%–51%; $P = .014$), 30% at visit 3 (95% CI 8%–51%; $P = .007$), and 49% at visit 4 (95% CI 15%–84%; $P = .005$) compared with the baseline (Figure 5). The median time between visit 1 and visit 4 was 358 days.

Post hoc analysis

A *post hoc* analysis was carried out using a count of organ systems involved in each challenge reaction as an outcome measure. Although there was a positive correlation between the number (count) of organ symptoms involved outcome measure with the mean challenge severity score (coefficient 0.5), substituting this measure into the model resulted in statistically insignificant results.

DISCUSSION

These are the first data obtained prospectively through repeat peanut challenges on individuals to show that allergic reaction severity increases with a cofactor such as sleep deprivation and also with repeat challenges within individuals. An increase in reaction severity with exercise was also observed, although this was not significant at the 5% level. Patient characteristics could not be correlated with overall reaction severity, but the presence of asthma was associated with an increase in the severity of respiratory symptoms at a system level. For the first time, we demonstrate that symptom patterns during repeated peanut allergic reactions are generally the same within individuals and a similar level of commonality exists in symptom patterns across participants in our sample also.

In this study, there was an increase in challenge severity score with successive visits. There was a significant increase in severity score of 38% at visit 3 postbaseline compared with visit 1. There are limited data on how reaction severity changes over time within an individual with most information coming from patients' accounts of reaction potentially subject to recall bias. Van der Leek et al¹⁴ followed up children with peanut allergy and compared index reactions with subsequent reactions following accidental exposure and found that 44% patients who had suffered a non-life-threatening reaction initially would subsequently suffer from life-threatening symptoms. However, there were no challenge data in this study and community reactions

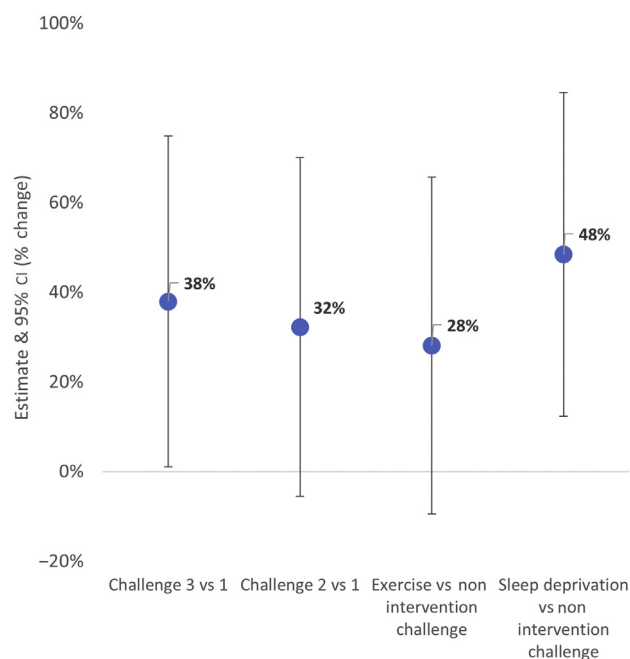
TABLE IV. Severity of reactions according to Sampson's grading divided by challenge type

Challenge type	Grade	Percentage (%) of reactions
Baseline	1	0
	2	29
	3	50
	4	21
	5	0
Exercise	1	0
	2	30
	3	48
	4	22
	5	0
Sleep deprivation	1	0
	2	40
	3	41
	4	19
	5	0
No intervention	1	0
	2	34
	3	46
	4	20
	5	0

will inevitably differ in dose exposure, matrix, and cofactors that potentially influence severity. Glaumann et al¹⁵ found no association between severity scores following 2 consecutive challenges in 14 peanut-allergic patients. This may be explained by the fact that the study population consisted of children rather than adults as in our study and peanut allergy is expected to resolve in 20% of children over time.¹⁶ This was also a small study of 14 children receiving only 2 successive peanut challenges and, therefore, lacking statistical power. Our study compared like-for-like challenges, that is, the exercise and sleep deprivation challenges were compared with the nonintervention challenge. These challenges were all open challenges. In the Glaumann et al study,¹⁵ the baseline challenge was double-blind and compared with a subsequent open challenge; therefore, like-for-like challenges were not being compared.

Purinton et al¹⁷ compared symptom severity rank in patients who had 2 repeat challenges with the same food and found that patients had more severe symptoms during the second challenge. However, the dose was not controlled, the sample size was small, and they did not adjust the analyses for allergen administered. In our study, even when controlling for dose, an effect of increasing severity was still observed. Three-month challenge intervals were planned in the study to guard against the possibility of a desensitization effect. However, our severity analysis has shown that the opposite effect may be happening, that patients may develop increased reactivity at each subsequent exposure. We have previously shown a reduction in threshold dose of peanut protein with successive visits, which we postulated may be due to a participant and investigator learning effect. However, the present data suggest that this may be a true immunological effect of repeated challenges.

Sleep deprivation increased overall reaction severity in our cohort. It has been observed in animal studies conducted with an

**FIGURE 3.** Percentage change in severity (logged) for each covariate. Visits (vs) 1–3 refer to the chronological order of post-baseline challenge days.

acute stressor, such as sleep loss, that corticotropin-releasing factor is released. This hormone has potent effects on the gut via modulation of inflammation, increase in gut permeability and modulation of gut motility and it may be hypothesized that this leads to increased permeability of the GI tract to allergen.¹⁸ Indeed, the results of this study indicate that the severity of GI symptoms significantly increases during sleep deprivation, which supports this hypothesis. Brown¹⁹ demonstrated a correlation between GI manifestations and the severity of anaphylaxis. Furthermore, the presence of chronic and relapsing GI symptoms and the degree of GI permeability has been positively correlated with the severity of anaphylaxis in humans.²⁰ Exercise did result in an overall increase in severity score, although this did not reach statistical significance. However, at a system level, exercise increased the severity of respiratory symptoms by 63%.

A *post hoc* analysis showed that using a score based on a count of the number of organ systems involved rather than the mean challenge severity score produced statistically insignificant results. The likely explanation is that this outcome measure was not discriminatory or sensitive enough to capture shifts in severity. It was based on a 7-point scale (1 for each organ system) and over 60% of the challenges actually involved either 4 or 5 organ systems. Often these challenges represented only mild reactions. This arguably provides further justification for using our 37-point challenge severity score based on a range of mild to severe symptoms for each system and, therefore, more sensitive to shifts in severity. Indeed, another study that attempted to measure severity differences between 2 successive challenges using only a 5-point severity scale failed to detect any difference in severity.¹⁵

Throat and cutaneous symptoms most frequently occurred during baseline and no-intervention challenges (82.7% and

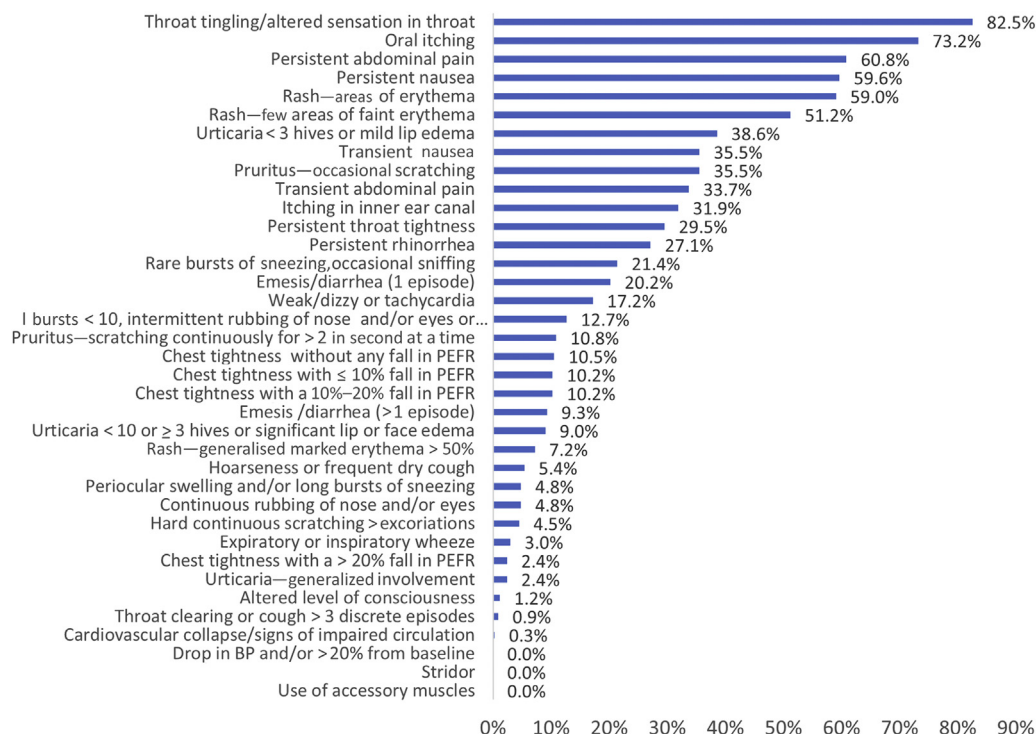


FIGURE 4. Frequency of symptoms during all challenges, $n = 342$. BP, Blood pressure; PEFR, peak expiratory flow rate.

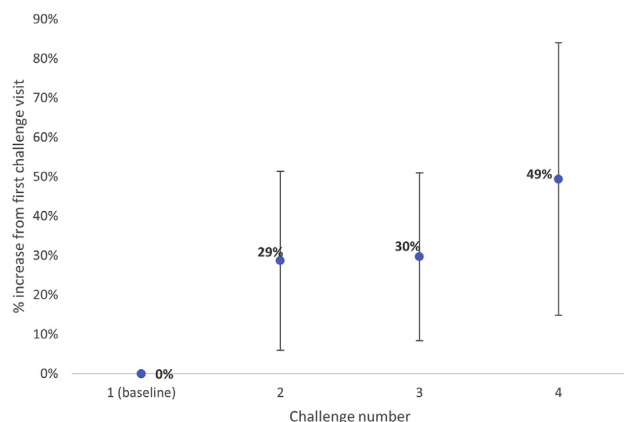


FIGURE 5. Within-patient increase in Ara h2 IgG4 mg/L from first visit (with 95% CIs).

80.5%, respectively). Reassuringly, severe throat symptoms during challenge, such as stridor or dysphagia, were rare and the majority of throat symptoms were due to an altered sensation in the throat or persistent throat tightness. Our ranking of system involvement is similar to other studies. An early study on a series of nut-allergy patients identified that respiratory symptoms were dominant and that hypotension was unusual.²¹ However, Beyer et al²² observed that 86.1% of anaphylactic reactions in the community, in which food was the most common elicitor, involved cardiovascular symptoms. In our study, although overt cardiovascular symptoms were rare, more detailed cardiovascular

assessment on participants at 1 of our study sites identified subtle changes in cardiovascular parameters.²³

Few data exist on the pattern of symptoms and the sequence of symptom progression both within and across allergic individuals. Using a sequence alignment technique, similarity of symptom patterns within an individual from one challenge reaction to another could be demonstrated. However, reaction patterns across individuals in our sample were also similar (78.3% across vs 82.4% within), suggesting that reaction conditions are almost as important as individual susceptibility in determining peanut-allergy reaction phenotype. This analysis looked at absolute numbers of all symptoms that appeared over the course of a reaction, although further work is needed on the combinations of symptoms that appear during a reaction and whether there are tendencies for certain symptoms to coappear. However, the information presented here will allow clinicians to better inform patients about the likely nature of further reactions in terms of organ systems involved.

We found that no participant characteristics including SPT weal to peanut, peanut-specific IgE, Ara h2—specific IgE, presence of asthma, presence of eczema, timing of last reaction, previous anaphylaxis, number of adverse reactions, and age of onset of peanut allergy could be correlated with challenge severity score. Previous studies have failed to find any consistent link between these factors and reaction severity.^{24–27}

Previous studies have identified asthma as a risk factor in fatal and nonfatal anaphylaxis. Although the presence of asthma could not be correlated with the overall challenge severity score, when examining the relationship at a respiratory system level, we did find that the presence of asthma was associated with a higher severity of respiratory symptoms. It is possible that this occurs as

a result of active inflammatory processes within the airways and reduced physiological reserve in patients with asthma who develop respiratory symptoms during reaction.¹⁹ Less physiological reserve may mean that people with asthma progress to a severe state more quickly, particularly when the asthma is poorly controlled. These findings contrast with Van Erp's group²⁸ who found that, in children with a positive food challenge, those with asthma were not more likely to report a severe respiratory reaction (29% vs 22%; $P = .50$) or have more frequent reactions involving the lower airways. However, other studies support the importance of asthma as a risk factor, with 1 study reporting that, in patients with severe asthma, the risk of life-threatening bronchospasm during nut-associated anaphylaxis was increased 6.8-fold, although this relative risk was only 2.7 times higher for the patients with mild asthma.²⁹ Thus, when managing patients with food allergy, the role of asthma in increasing the severity of respiratory symptoms, if they are present, should not be underplayed and patients should be well versed on optimization of their general asthma control.

We observed a significant rise in the level of Ara h2 IgG4 on visit 4 compared to visit 1 (baseline) but no change in Ara h2 IgE. Previous peanut oral immunotherapy studies have noted a rise in total peanut IgG4 early in desensitization.^{30,31} However, these studies have also noted a reduction in IgE, although this was measured at a much later timepoint (24 months) in both studies compared with 12 months in ours. It may be postulated in our study that the exposure to peanut protein, which occurred once every 3 months in this study, was not sufficiently frequent to induce desensitization of the participants but was sufficient to induce immunological changes associated with an increase in severity.

A limitation of this study is that allergen dosing was stopped when a certain number of objective symptoms appeared. Symptoms could, therefore, not evolve, and reactions could not progress to their full potential had treatment intervention not occurred making threshold dose and reaction severity inextricably linked. Therefore, it was necessary to restrict analyses to the highest comparable dose across all challenges within individuals to circumvent this issue. However, an overall perspective on reaction severity incorporates threshold dose of peanut protein.⁶ Another limitation is that both investigators and participants may have learned their reactions over time, which may have influenced the reporting and management of symptoms. In addition, the open challenge design could be associated with potential observer bias. However, the study was designed to minimize this bias by ensuring that a participant's reaction threshold was only called by the investigator when prespecified objective symptoms appeared. As mentioned, all interventional and the nonintervention challenge were conducted as open challenges rather than double-blinded. We initially conducted a significant portion of the intervention and nonintervention challenges double-blinded but owing to site and staff logistical issues, it was necessary to alter the study design early in the process. As a result, we performed a sensitivity analysis examining data from 29 baseline challenge pairs (placebo and active day) and 9 interventional challenge pairs (placebo and active) and found that there was no difference in threshold with the challenge method applied. The prediction of the researcher as to whether each day was placebo or active, based on the symptoms encountered, was correct in every case. We also examined the symptoms and signs that occurred on placebo days. In every case, these were minor and

would not have triggered the challenge to be stopped or scored positive. We, therefore, found no evidence of a placebo effect.

Although for ethical and safety reasons we had to exclude participants with the most severe previous reactions (ie, life-threatening reactions), this amounted to a tiny minority of the hundreds screened. The severity of reactions seen during repeated challenge in our study (16% anaphylaxis) reassures us that we had not chosen patients with only mild reactivity.

Lastly, our proposed severity scale is one of the first continuous scoring scales for food-allergy reaction severity. Applying a numerical value to a qualitative entity is inevitably subjective. To ensure that the score provides accurate assessment of severity in different populations at different time points, validation is required in other patient cohorts.

In conclusion, using a novel severity score, we show that sleep deprivation and repeat challenges increase the severity of allergic reactions, which could have important implications for advising patients about future and frequent accidental exposures. We also provide novel data showing that there is a high degree of similarity in symptom pattern within individuals in this population, better allowing clinicians to advise adults with peanut allergy about future reactions and, most importantly, to enable patients to better understand their reactions so that they may remain vigilant for warning symptoms and initiate treatment early.

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TABLE E1. Study inclusion and exclusion criteria

Inclusion criteria

- Male and female subjects who are 18–45 y of age at the time of study entry (visit 1) who have a diagnosis of acute peanut allergy as manifested by urticaria, angioedema, or respiratory/GI tract symptoms, with acute onset of symptoms after ingestion (up to 2 h).
- A positive peanut DBPC food challenge at baseline (visit 1). This outcome is defined as the onset of objective or significant subjective allergic events after ingestion of peanut protein but not to the placebo. Eligibility to the DBPC food challenge requires fulfilment of all other eligibility criteria at visit 1.
- Subjects must be able to comply with the study procedures.
- Sensitization to peanut demonstrated by SPT or serum-specific IgE.

Exclusion criteria

- Oral allergy syndrome to peanut (defined as a clinical history of only oral allergy symptoms on exposure to peanut and principal sensitization to only pr-10 homologs of peanut (Ara h 8), and low-level serum IgE to Ara h 1, 2, 3).
- Monosensitization to Ara h 9.
- Use of investigational drugs at the time of enrollment, or within 30 d or 5 half-lives of enrollment, whichever is longer.
- History of hypersensitivity to any of the matrix components used within the material for the OFC.
- Poorly controlled asthma. Asthma control will be assessed by the ACQ. Patients with a score < 20 or higher will not be eligible for the study. Also, patients should have FEV₁ > 80% of their predicted value.
- History of significant and repeated exercise-induced asthma attacks requiring treatment, independent of food ingestion or a drop in FEV₁ > 15% during screening VO_{2max} exercise session.
- Musculoskeletal disease that, in the opinion of the investigator, could impair the participant's ability to perform the exercise challenge.
- A sleep or psychiatric disorder that, in the opinion of the investigator, could impair the participant's ability to perform the study procedures.
- Pregnancy.
- Alcohol or drug misuse.
- Night-shift worker.
- Concomitant use of
 - Systemic immunosuppressant.
 - Beta blocker use.
 - ACE inhibitor or other hypertensive drug use.
 - Sedative drugs.
 - Antacid medication (either proton pump inhibitors or H2 antagonists).
- History of any of the following:
 - Severe anaphylaxis to peanut as defined by hypoxia (SpO₂ < 92%) or hypotension (>30% drop in systolic blood pressure), with or without neurological compromise.
 - A previous reaction to peanut that, in the opinion of the investigator (or trial management group), was life-threatening.
 - Mastocytosis.
 - Coronary artery disease.
 - Eosinophilic esophagitis.
 - Gastric or duodenal ulcer.
- A past medical history of clinically significant ECG abnormalities or identified during study (visit 1).
- Recent (within the last 3 y) and/or recurrent history of autonomic dysfunction (eg, recurrent episodes of fainting, palpitations).
- Hematological parameters (total WBC count or Hb level, platelet counts) that fall outside the normal reference range of the laboratory at screening and are clinically significant.

ACE, Angiotensin-converting enzyme; ACQ, Asthma Control Questionnaire; DBPC, double-blind placebo-controlled; ECG, electrocardiogram; FEV₁, forced expiratory volume in 1 second; GI, gastrointestinal; Hb, hemoglobin; IgE, immunoglobulin E; OFC, oral food challenge; pr-10, pathogenesis related protein family 10; SpO₂, pulse oximetry; VO_{2max}, maximum oxygen consumption; WBC, white blood cell.