

# The effect of extrinsic factors on food allergy

Area of research interest: [Food hypersensitivity](#)

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Conducted by: Cambridge University Hospital NHS Trust - Sub-contractor Organisations:  
University of Manchester and Imperial College, London

## Background

It is widely observed that there is significant intra-individual variation in the severity of food allergic reactions following exposure to the same amount of allergen on different occasions. This is thought to be, in part, the result of the influence of certain extrinsic factors such as alcohol, exercise, asthma and stress. It is understood that these and/or other factors may increase the sensitivity of allergic individuals to set amount of food to which they are allergic, resulting in more severe reactions.

Alternatively, these factors may influence the lowest dose that an individual may react to. Little is known about the scale or mechanism of these factors which makes it difficult to take them into account when undertaking risk assessments of food allergens. There is therefore a need to better understand the effect of these factors on the severity and threshold dose of reactions (i.e. the highest level of an allergen that does not cause a reaction in the food allergic population), in order to ensure that risk assessments of food allergens are accurate and meaningful.

This study helps to inform work the Agency is undertaking to develop management threshold levels (or 'action levels') for the unintentional presence of allergens in food to inform labelling and risk management/communication decisions.

## Research approach

This was a randomised cross-over clinical trial which was conducted by a UK consortium comprising four organisations, including three clinical sites. Cambridge University Hospital Trust was the coordinating centre for the study collaborating with Imperial College London and The University of Manchester. Peanut allergic individuals were recruited from clinical centres located in Cambridge (Addenbrookes Hospital) and London (Royal Brompton and St Mary's Hospital).

One-hundred twenty six adults with a diagnosed peanut allergy were recruited to undergo a total of four food (peanut) challenges at 12 week intervals – a baseline peanut double blind placebo controlled food challenge (DBPCFC) followed by three further challenges in a random order, comprising one repeat baseline challenge (non-intervention), and two further challenges with different extrinsic factors thought to have a possible influence on the thresholds and/or severity of reaction. The extrinsic factors under investigation were exercise (physical activity) and stress (via sleep restriction).

Each clinical centre performed both baseline and interventional challenges, and both extrinsic factors were also investigated at each centre, to ensure diversity of sampling. Pilot work was conducted to determine the feasibility of studying extrinsic factors using healthy volunteers to study exercise and sleep restriction. The primary measurement for each participant was to

identify the amount of peanut that causes an allergic reaction during each challenge. This is known as the participant's baseline challenge threshold (mg peanut protein) and the same oral food challenge methodology was used to record the responses for all four challenges. The challenge data was primarily used to model the variability of challenge thresholds over time within individuals, as a result of repeat challenges, and to examine how the extrinsic factors shift the dose response curve.

The University of Manchester manufactured and distributed the standardised peanut challenge meals to each clinical centre. An online database was developed to provide a secure environment for real-time in-clinic collection of patient data (i.e. clinical history, test results, challenge outcomes). The database also facilitated retrospective analysis with relevant EuroPrevall data sets, in particular the further development and application of a numeric severity score.

The University of Cambridge (Centre for Applied Medical Statistics) developed a detailed statistical analysis plan to undertake the main and final analysis.

## Results

### Thresholds of reactivity

TRACE is a ground-breaking study and the first to demonstrate that exercise and sleep-deprivation can significantly reduce the amount of peanut required to cause an allergic reaction in a UK adult peanut-allergic population.

All participants (n=126) underwent a baseline challenge to confirm their peanut allergy and to gauge how much peanut triggered an allergic reaction at baseline. Of these participants, 100 were randomised and underwent oral food challenges to establish how much peanut elicited an allergic reaction under different scenarios. Threshold doses that elicited allergic reactions were estimated for 1%, 5% and 10 %, 50%, 80% and 95% of the allergic population.

The main findings of the study were:

- The average (mean) reactivity threshold of this participants when exercise and sleep deprivation were not applied was 214mg of peanut protein which equates to roughly one peanut (330mg)
- Exercise and sleep deprivation each individually lowered the average amount of peanut required to elicit an allergic reaction by approximately half
- Mean estimated eliciting doses (ED) for 1% of the population were 1.5mg (0.8,2.5) during non-intervention challenge (n=81), 0.5mg (0.2,0.8) following sleep and 0.3mg (0.1,0.6) following exercise.
- The results show that as little as 1/30th of a peanut can cause a reaction in the most sensitive people which was 1 in 20 individuals with a peanut allergy

[TRACE study: The effect of extrinsic factors on food allergy - the full study](#)

### Further detail

The main findings for the minimum eliciting doses (MED) of peanut protein at ED01, ED05 and ED10 for UK allergic population, respectively, were:

- Baseline challenges (n=81) estimated MED as 3 mg (1.7, 4.8), 7.6 mg (4.7, 12) and 12.8 mg (8.2, 19.8).

- Non-Intervention challenges (n=71) were conducted as a reference for intervention challenges. Estimated MED values for peanut protein were 1.5mg (0.8, 2.5), 4 mg (2.4, 6.4) and 6.7 mg (4.1, 10.5).
- Exercise intervention challenges (n=73) estimated MED values 0.5 mg (0.2,0.8), 1.3 mg (0.7,2.2) and 2.4 mg (1.4,3.8).
- Sleep deprivation intervention challenges (n=71) estimated MED values 0.3 mg (0.1, 0.6), 1.1 mg (0.5, 1.7) and 1.9 mg (1.1, 3.1).

Dose-response curves for both intervention challenges (i.e. sleep and exercise) were significantly different than non-intervention challenge and shifted to the left. This shift towards the left indicates that participants reacted to lower amounts of peanut than when no intervention was applied.

No significant effects on threshold were observed for other variables, including the presence of asthma, sex, age, or IgE against Ara h 2 levels.

## Conclusion

Exercise and sleep deprivation each significantly reduce the threshold of reactivity in people with peanut allergy, putting them at greater risk of a reaction if exposed to low levels of peanut. This effect is important to help determine the unsafe levels of an allergen in a food and whether a suitable margin of safety has been applied when deriving a reference doses for the allergic population. Incorporating these data into allergen risk management through accurate food labelling is critical for optimal protection of peanut-allergic consumers.

Results on the severity of reactions observed at different threshold levels and when extrinsic factors are applied is currently being worked on for future publication.

## Publication

Dua S, Ruiz-Garcia M, Bond S, Durham SR, Kimber I, Mills C, Roberts G, Skypala, Wason J, Ewan P, Boyle R, Clark A. [Effect of sleep deprivation and exercise on reaction threshold in adults with peanut allergy: A randomized controlled study](#). *Journal of Allergy and Clinical Immunology*. 2019 July. 144(6): 1584 – 1594

Dua, S., Ruiz-Garcia, M., Bond, S., Dowey, J., Durham, S.R., Kimber, I., Mills, C., Roberts, G., Skypala, I., Wason, J. and Ewan, P., 2022. [Effects of exercise and sleep deprivation on reaction severity during oral peanut challenge: a randomised controlled trial](#). *The Journal of Allergy and Clinical Immunology: In Practice*.

## TRACE Dataset

[TRACE dataset](#)

Research report  
PDF

[View The effect of sleep deprivation and exercise on reaction threshold in peanut-allergic adults: a randomised controlled study as PDF\(Open in a new window\)](#) (1.66 MB)