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# Severity and threshold of peanut reactivity during hospital-based open oral food challenges: An international multicenter survey

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## Abstract

**Background**: Peanut allergy is classically managed by food avoidance. Immunotherapy programs are available at some academic centers for selected patients reacting to small amounts of peanut during food challenge. We aimed to determine and compare reaction thresholds and prevalence of anaphylaxis during peanut oral challenges at multiple specialist allergy centers.

**Methods**: A retrospective, international survey of anonymized case records from seven specialist pediatric allergy centers from the UK and Ireland, as well as the Australian HealthNuts study. Demographic information, allergy test results, reaction severity and threshold during open oral peanut challenges were collated and analyzed.

**Results**: Of the 1634 children aged 1-18 years old included, 525 (32%) failed their peanut challenge. Twenty-eight percent reacted to 25 mg, while 38% only reacted after consuming 1 g or more of whole peanut. Anaphylaxis (55 [11%]) was 3 times more common in teenagers than younger children and the likelihood increased at all ages as children consuming more peanut at the challenge. Children who developed anaphylaxis to 25-200 mg of whole peanut were significantly older. Previous history of reaction did not predict reaction threshold or severity.

**Conclusions**: More than a third of the children in this large international cohort tolerated the equivalent of one peanut in an oral challenge. Anaphylaxis, particularly to small amounts of peanut, was more common in older children. Tailored immunotherapy programs might be considered not only for children with low, but also higher reaction thresholds. Whether these programs could prevent heightened sensitivity and anaphylaxis to peanut with age also deserves further study.

KEYWORDS

anaphylaxis, children, food allergy, oral food challenge, peanut, threshold

**Abbreviations:** DBPCFC, double-blind, placebo-controlled food challenge; IT, immunotherapy; OFC, oral food challenge; SPT, skin prick test.

## 1 | INTRODUCTION

Standard clinical practice based on the latest management guidelines recommends that patients with peanut allergy avoid all food containing peanut.[1-3] This is in contrast to milk and egg allergy where baked food products may be recommended where tolerated in select patients as the first stage of milk/egg introduction to promote tolerance and resolution of the allergies.[2,4,5]

Immunotherapy (IT) for peanut allergy currently is largely in the domain of research clinical trials. Numerous trials have been shown to successfully increase the amount of peanut that patients tolerate.[6-8] Possible routes of administration include oral, sublingual, or epicutaneous. The oral route, although associated with a greater risk of adverse allergic reactions, has the advantage of allowing larger amounts of peanut to be administered and a greater degree of tolerance.[9,10]

Eligibility for enrollment in peanut IT clinical trials is usually,[9-12] but not always[13,14] determined after a formal double-blind placebo-controlled food challenge (DBPCFC) to confirm the clinical allergy and the threshold of clinical reactivity. Most regulatory and research studies have focused on clinical reactivity for the lowest 5%-10% of the population ($ED_{05}$-$ED_{10}$), calculating it to be between 20 and 70 mg of whole peanut (5-20 mg of peanut protein based on chemical analysis that has previously shown that peanut kernels contain 29% protein).[15-18] The proportion of patients with higher thresholds of reactivity are less well studied, but it is suggested that 50% of peanut allergic subjects only react to cumulative doses above 100 mg of peanut protein.[19] Patients who react to one peanut are generally excluded from IT clinical trials, as these patients would not be expected to meet the common secondary outcome of an IT-associated increase in the eliciting threshold dose of peanut. These patients are still advised to avoid peanuts as rigorously as those who react to smaller amounts of peanut and carry adrenaline kits.

This international survey aimed to study the full range of thresholds to which patients react to peanut during open oral food challenge (OFC), as well as the prevalence of anaphylaxis during these challenges. Data from open OFC rather than DBPCFC were used, as open OFC is routinely practiced in most specialist allergy centers, while resource-intensive DBPCFC is largely confined to clinical trials. The survey provides information not only regarding the proportion of children who may be suitable for future peanut IT trials, but also a detailed picture of the prevalence of anaphylaxis and the proportion of patients who only react to larger amounts of peanut and thus require alternative approaches to desensitization to those offered in current FDA-approved trials.[20]

## 2 | METHODS

### 2.1 | Study design and patient selection

A retrospective, international, multicenter case review of hospital-based OFC to peanut and peanut-containing food was conducted. Anonymized data from children who had undergone hospital-based OFC to peanut between 2008 and 2017 were collected from pediatric allergy centers that were either part of the North West Paediatric Allergy Network (Alder-Hey Children's Hospital, Arrowe-Park Hospital, Liverpool, Royal Manchester Children's Hospital, University Hospital of South Manchester, Manchester, Royal Preston Hospital, Preston), or large pediatric allergy centers in other parts of the UK (Great North Children's Hospital, Newcastle upon Tyne, Guy's & St Thomas' Hospitals London, Southampton General Hospital, Southampton), Ireland (Cork University Hospital, Cork, Ireland), and Australia (Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia [HealthNuts study]). Anonymized data relating to children's demographics, previous clinical history of peanut allergy, results of allergy tests, and clinical outcome of peanut OFC were collated from all centers. Anaphylaxis was defined as allergic reactions associated with objective respiratory (wheeze, tachypnea, cough, drooling, stridor), or circulatory signs (hypotension, reduced conscious level).

HealthNuts is a birth cohort (2006-2009) study, which recruited 12-month-old infants at childhood immunization sessions in Melbourne, Australia. History of allergy or allergic reactions to peanut were not selection criteria.[21,22] Approval to conduct the HealthNuts study was obtained from the Victorian State Government Office for Children (reference no. CDF/07/492), the Victorian State Government Department of Human Services (reference no. 10/07), and the Royal Children's Hospital Human Research Ethics Committee (reference no. 27047). Parents provided informed written consent for their child to participate in the study and OFC.

In contrast to the limited age range of children and the lack of selection based on allergy history in the Australian cohort, Irish and UK children were aged 0-18 years old and attended pediatric allergy centers because of concerns about peanut allergy. These patients all underwent routine clinically indicated hospital-based peanut OFC after taking written consent. They either had a history of suffering an allergic reaction to peanut but had not had any allergic reactions for a number of years, or alternatively, there were concerns about possible peanut allergy but doubt about the diagnosis because of an unclear history or inconclusive allergy tests. Information regarding the Manchester cohort has been published previously.[23] Ethical permission was not required in Ireland or the UK for this anonymized case note review of routine clinical practice.

### 2.2 | Allergy testing

Peanut skin prick, peanut-specific IgE, and peanut Ara h 2 component test results were collected. IgE concentrations were measured by automated Immuno-CAP processor (Phadia AB, Uppsala, Sweden). Sensitization was defined as peanut, or peanut component IgE level of ≥0.35 $KU_A$/L, or a skin prick test (SPT) wheal size of ≥3 mm.

### 2.3 | Hospital-based peanut OFC

Peanut OFC was performed and directly supervised by the clinical teams at the respective pediatric allergy centers. Open OFC to peanut-containing foods (peanuts, peanut butter, peanut flour, or

Bamba snacks) was performed using OFC protocols, increasing the amount of peanut every 15-20 minutes. As such, the amount of peanut quoted in this study refers to weight of whole peanut product, rather than purified peanut protein. A positive challenge at all centers was defined as objective clinical signs (rather than just subjective symptoms) of allergy (urticaria, angioedema, vomiting, wheeze). The number of steps within the OFC protocol varied slightly between the centers. For example, as all the children attending the Melbourne center were all aged 1-2 years old, the maximum amount of peanut butter given during the OFC was 1 teaspoon (4.2 g). Southampton also only challenged patients to a maximum of 4 g. Other centers used a maximum of 20 g. For comparison, data regarding the threshold amount of peanut to which the children reacted were standardized using the weight of peanut used by centers at each stage of the OFC.

### 2.4 | Statistical analysis

Most analyses were performed using the IBM SPSS Statistics 22 program. Continuous variables were quoted as medians and interquartile ranges. Statistical differences between groups were determined by chi-square or Mann-Whitney *U* tests. Differences were considered statistically significant with a *P* value <0.05. Multivariate analysis was performed using binary logistic regression. Receiving operating characteristic (ROC) curve analysis was used to display sensitivity and specificity of allergy tests. Dose-distribution modeling was performed using the fitdist function in R v3.4.1. Log-normal, Weibull, and logistic distribution models of the minimum amount of peanut that triggered an allergic reaction on OFC were compared using the Akaike information criteria (AIC). As the log-normal model provided the best fit, this model was used to estimate the amount of peanut (Effective Dose) that resulted in 10% (ED10) or 50% (ED50) of the cohort reacting to peanut on OFC. Difference between the log-normal dose-distribution between Australian and European centers was assessed using the likelihood-ratio test by first fitting the model to all the data and then introducing region as a covariate. A *P* value <0.05 was deemed statistically significant.

## 3 | RESULTS

### 3.1 | Demographics

A total of 1634 children aged 0-18 years old (75% ≤6 years old) underwent ward-based OFC to peanut-containing food between 2008 and 2017 (Table 1). A total of 601 (37%) were from Ireland, 554 (34%) from Australia, and 479 (29%) from the UK. A total of 882 (54%) were male. A total of 1160 (71%) were white European, and the remainder were Asian and Afro-Caribbean. Australian children were all 2 years old or less, while UK and Irish children were aged 0-18 years old. Only 5% of Australian children had experienced previous allergic reactions to peanut compared to 36% of British and Irish children.

### 3.2 | Previous history of clinical allergic reactions and sensitization to peanuts

A total of 396 (24%) patients had a history of previous allergic reactions to peanut (Table 1). Fifty-five (10%) had previously developed respiratory/circulatory signs (anaphylaxis). A total of 879 (54%) patients had never eaten peanuts but had a positive skin prick test (SPT) ≥3 mm, peanut-specific IgE ≥0.35 $KU_A$/L, or both. The remaining 359 (22%) patients had never eaten peanut-containing food and were not sensitized but because they were unwilling to try peanut for the first time at home, were challenged in hospital.

Of the total cohort, 1193 (73%) patients had evidence of allergic sensitization to peanuts. Sixty percent had a SPT of ≥3 mm, and 20% had a test result ≥8 mm. Fifty-four percent had a positive specific peanut IgE of ≥0.35 $KU_A$/L and 20% a positive peanut Ara h 2 of ≥0.35 $KU_A$/L. Irish children were significantly more likely to be sensitized to peanut (94%) than Australian (55%) or British children (68%).

The predictive values of allergy tests in relation to the outcome of peanut OFC are shown in Figure 1 and Table 2. Fifty-six percent of children who passed their OFC had evidence of allergic sensitization, either on SPT, blood peanut-specific IgE, or both. SPT <3 mm provided the best negative predictive value (94%), while Ara h 2 ≥ 0.35 $AU_K$/L provided the best positive predictive value (87%;

**TABLE 1** Demography and previous investigations

| Parameter | Total cohort | Australia | UK | Ireland | *P* value |
|---|---|---|---|---|---|
| Number | 1634 | 554 | 479 | 601 | |
| Age range (median) (y) | 0-18 (2) | 0-2 (1) | 0-18 (5) | 0-18 (3) | <0.001 |
| Male gender | 59% | 57% | 42% | 61% | 0.3 |
| White European | 72% | 70% | 74% | 100% | 0.3 |
| Clinical history of allergic reaction | 24% | 5% | 36% | 36% | <0.001 |
| SPT ≥3 mm | 60% | 44% | 43% | 85% | <0.001 |
| Peanut-specific IgE ≥0.35 $KU_A$/L | 54% | 42% | 41% | 74% | <0.001 |
| Ara h 2 ≥0.35 $KU_A$/L | 20% | 13% | 18% | 60% | <0.001 |

*P* value calculated using chi-square analysis for discrete variables and Mann-Whitney *U* test for continuous variables.

**TABLE 2** Accuracy of clinical history and allergy tests in predicting peanut OFC outcome

| Test | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|
| Clinical history of previous allergic reaction to peanut | 50% | 68% | 47% | 70% |
| Skin prick test ≥3 mm | 93% | 56% | 50% | 94% |
| Skin prick test ≥8 mm | 47% | 94% | 81% | 79% |
| Peanut-specific IgE ≥0.35 $KU_A/L$ | 80% | 58% | 48% | 86% |
| Peanut Ara h 2 IgE ≥0.35 $kU_A/L$ | 57% | 96% | 87% | 84% |

Table 2). Fifty-three percent of patients with a clear history of previous allergic reactions to peanut passed their OFC, while 30% of patients who had no history of reacting to peanuts failed their OFC.

## 3.3 | Reaction threshold during peanut OFC

A total of 525 (32%) patients developed clinical signs of allergy during the peanut OFC. Demographic factors and allergy test results associated with passing an OFC or failing the challenge after eating >200 and ≤200 mg of peanut are shown in Table 3. Patients reacting to larger amounts of peanut were significantly older than the other two groups ($P < 0.01$), and this was independent of other variables in multivariate analysis. Irish children were more likely to react on OFC than children from the UK or Australia. A total of 144 (28%) patients reacted to 25 mg of peanut, while 283 (54%) reacted to 200 mg or more of peanut, 199 (38%) to 1 g or more, and 121 (22%) to 5 g or more.

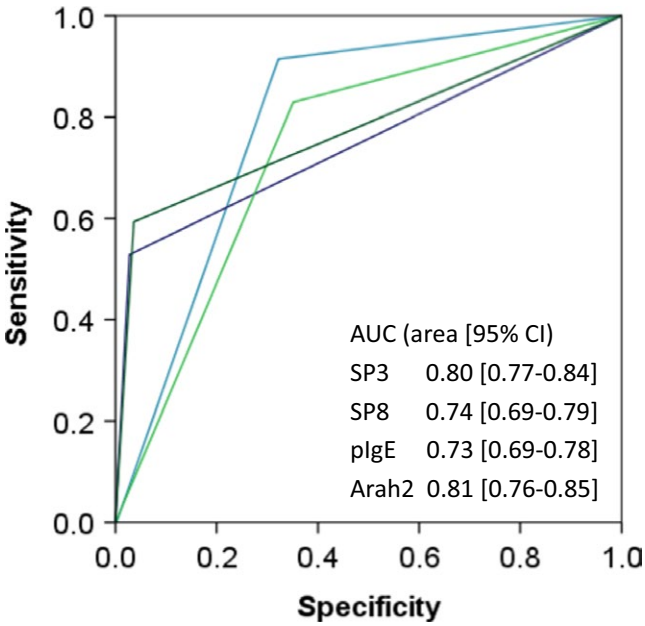


**FIGURE 1** Receiver operating characteristic (ROC) curve linking outcome of peanut OFC (pass vs fail) to positive peanut SPT, peanut-specific IgE, and peanut Ara h 2 component. Light blue line: peanut SPT ≥3 mm; Dark blue line: peanut SPT ≥8 mm; Light green line: peanut-specific IgE ≥0.35 $KU_A/L$; Dark green line: peanut Ara h 2 IgE ≥0.35 $KU_A/L$. Area (95% CI) is given as text within the figure [Colour figure can be viewed at wileyonlinelibrary.com]

Threshold of reactivity to peanuts during OFC was determined using dose-distribution modeling (Figure 2). Assessment of how well different models fitted the empirical cumulative distribution of the whole data, as determined using Akaike information criteria (AIC), showed that a log-normal (AIC score 8139) was better than either a Weibull (8251) or logistic (10 143) distribution. The ED10 and ED50 derived from the log-normal distribution were 20 mg (95% CI: 15-25) and 300 mg (95% CI: 250-370), respectively. In view of the different age distributions of the Australian and European cohorts, analyses of these two subgroups were performed. The ED10 for the Australians was 15 mg of peanut (95% CI: 10-25) and for the Europeans 20 mg of peanut (95% CI: 15-25). The ED50 for the Australians was 220 mg of peanut (150-310) and for the Europeans 340 mg of peanut (95% CI: 270-425; $P = 0.05$).

## 3.4 | Prevalence of anaphylaxis during peanut OFC

Fifty-five (10% of positive challenges; 3% of total challenges) patients suffered from anaphylaxis (mainly wheeze and tachypnea) during the peanut OFC and treated with intramuscular adrenaline. Progression up the food challenge protocol was associated with higher rates of anaphylaxis: 9% of patients who reacted to 25-100 mg developed signs of anaphylaxis, compared with 27% of patients who reacted to 200 mg-1 g and 40% of patients who reacted 5-20 g of peanut ($P < 0.001$; Figure 3A).

Children suffering anaphylactic reactions were significantly older (median (interquartile range) 8 (5-14) years) than those who had milder allergic reactions during the OFC (3 (1-8) years) ($P < 0.001$), and this was particularly so for those with lower thresholds of reactivity (25-200 mg of peanut; Figure 3B). Clinical history of previous anaphylaxis to peanut was not significantly associated with more severe allergic reactions during OFC, neither was SPT nor peanut-specific IgE result.

The association between anaphylaxis and the child's age, stage at which they failed their OFC, and the recruiting center was further investigated using multivariate analysis. The age of the child and stage at which they failed their OFC were independently associated with anaphylaxis (Table 4). Teenagers were three times more likely to develop anaphylaxis than younger children. Patients who failed their challenge at the last two stages of the OFC were 13 times more likely to develop clinical features of anaphylaxis, independent of their age.

**TABLE 3** Parameters associated with the outcome of peanut OFC

| Parameter | Degree of sensitivity to whole peanut | | | Relative risk (95% CI) comparing >200 and ≤200 mg of peanut |
|---|---|---|---|---|
| | No reaction | Reacted to >200 mg | Reacted to ≤200 mg | |
| Number | 1111 | 280 | 243 | |
| Age (y) | 2 (1-6) | 5 (1-10) | 2 (1-6) | 0.9 (0.9-0.9) 0.001 |
| Gender (males) | 663 (57%) | 181 (65%) | 152 (62%) | 1.0 (0.7-1.5) 0.6 |
| Country | | | | |
| Australia | 421 (76%) | 65 (12%) | 69 (13%) | 1.0 |
| UK | 354 (75%) | 78 (17%) | 40 (8%) | 0.8 (0.4-1.7) 0.6 |
| Ireland | 336 (56%) | 137 (23%) | 125 (21%) | 1.9 (1.1-3.2) 0.01 |
| Evidence of sensitization on SPT and/or IgE | 636/1038 (61%) | 257/265 (97%) | 227/232 (98%) | 1.8 (0.3-12.2) 0.5 |
| Skin prick test ≥3 mm | 454/1038 (44%) | 237/259 (92%) | 217/230 (94%) | 0.7 (0.2-2.4) 0.6 |
| Skin prick test ≥8 mm | 43/995 (4%) | 129/262 (49%) | 122/219 (56%) | 1.3 (0.9-1.9) 0.2 |
| Peanut-specific IgE ≥0.35 $KU_A/L$ | 451/1074 (42%) | 215/274 (78%) | 189/232 (82%) | 1.3 (0.7- 2.2) 0.4 |
| Peanut Ara h 2 IgE ≥0.35 $kU_A/L$ | 23/639 (4%) | 82/151 (54%) | 68/114 (60%) | 1.2 (0.8-2.0) 0.4 |

Continuous variable (age) is listed as median (interquartile range). Discrete variables are listed as number/denominator (percentage). Statistical analysis between the two groups that reacted on OFC used binary logistic regression multivariate analysis.

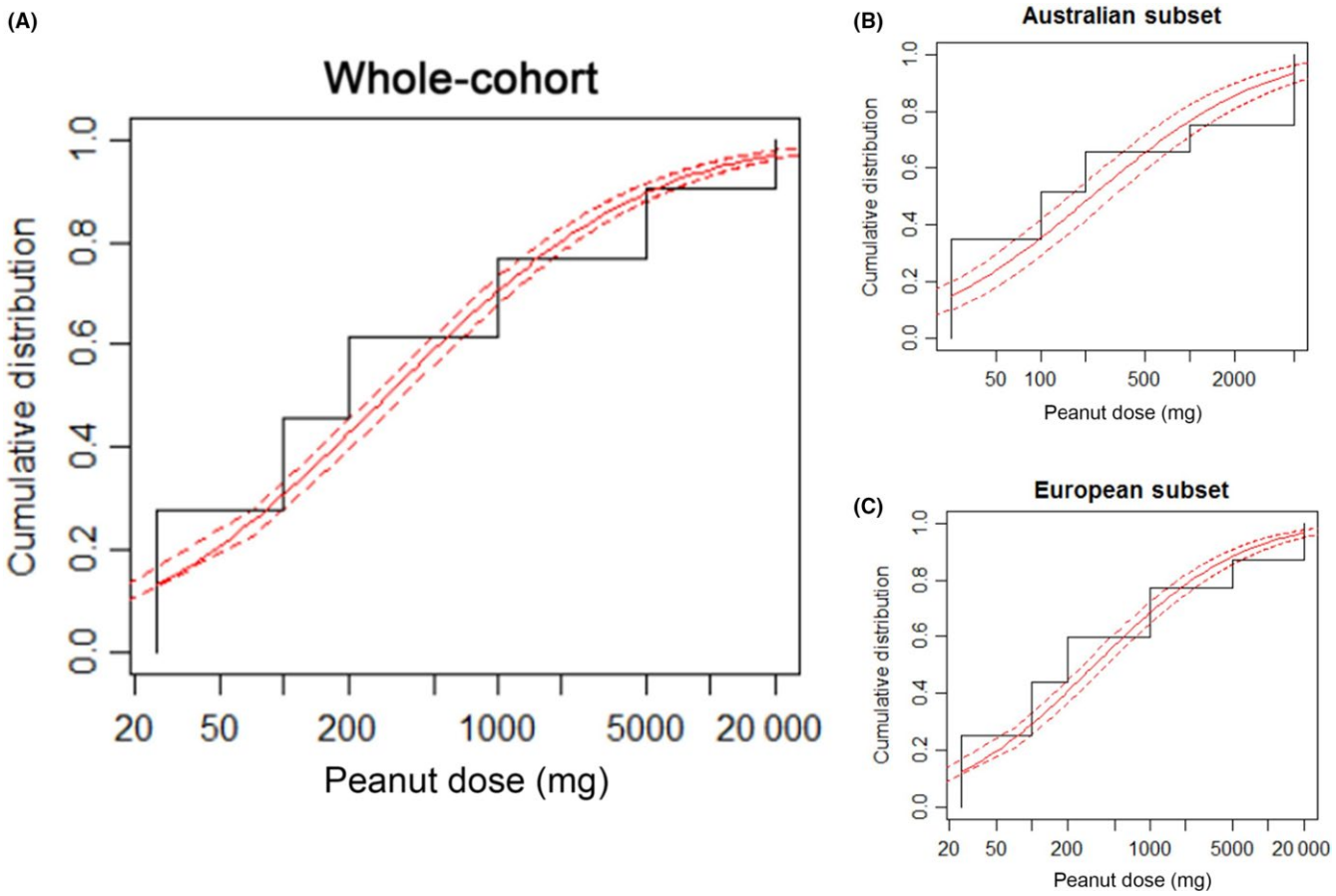


**FIGURE 2** Plots showing cumulative distribution curves of smallest amount peanut that triggered an allergic reaction during OFC. Solid black line represents the empirical cumulative distribution. Solid and dashed red lines are the point estimate and 95% CI from a log-normal distribution model for (A) the whole cohort, (B) the Australian subgroup, and (C) the European subgroup [Colour figure can be viewed at wileyonlinelibrary.com]

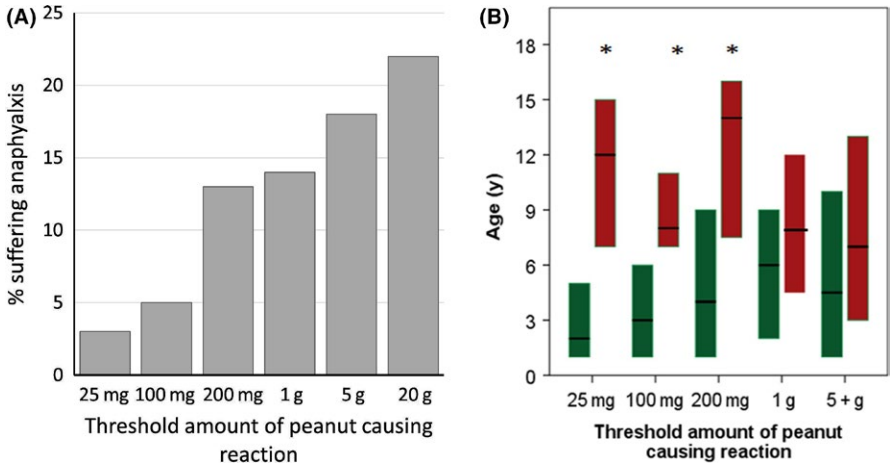


**FIGURE 3** Relationship between the amount of peanut consumed during peanut OFC, age of patients, and signs of anaphylaxis. A, Percentage of patients reacting with signs of anaphylaxis to different amounts of whole peanut in an OFC, B, Box plots showing median (interquartile range) of age of patients who had nonanaphylactic (green boxes) and anaphylactic reactions (red boxes) to different amounts of peanut during OFC. *$p < 0.05$ using Mann-Whitney *U* test [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 4** Parameters associated with anaphylaxis

| Parameter | Relative risk (95% CI) | *P* value |
|---|---|---|
| Stage of failure (reference stage 1) | | |
| Stage 2 | 1.5 (0.3-6.6) | 0.6 |
| Stage 3 | 4.7 (1.3-17.0) | 0.02 |
| Stage 4 | 5.2 (1.4-19.3) | 0.01 |
| Stage 5-6 | 13.2 (3.7-46.9) | 0.001 |
| Age (reference 0-5-y olds) | | |
| 6-12-y olds | 0.8 (0.4-2.0) | 0.7 |
| 13-18-y olds | 3.2 (1.3-8.2) | 0.02 |
| Country (reference Australia) | | |
| UK | 1.1 (0.2-5.1) | 0.9 |
| Ireland | 2.0 (0.6-6.6) | 0.3 |
| History of previous allergic reaction | 1.5 (0.8-3.0) | 0.2 |
| Peanut skin prick test | 1.2 (1.1-1.3) | 0.003 |
| Peanut-specific IgE | 1.0 (1.0-1.0) | 0.2 |

Analysis used binary logistic regression analysis comparing children who failed their OFC with and without clinical signs of anaphylaxis.

## 4 | DISCUSSION

This international, multicenter survey provides important results regarding the threshold of clinical reactivity and prevalence of anaphylaxis after a hospital-based peanut OFC. Although, in keeping with previous studies, we showed that the ED10 was only 20 mg of peanut,[15-17] we found that the ED50 was 300 mg of peanut and 38% of children only reacted after being given more than 1 g of whole peanut.

Ten percent of children who failed their peanut OFC developed signs of anaphylaxis (wheeze, tachypnea). Anaphylaxis during OFC did not correlate with the patient's medical history of allergic reactions, suggesting that past events do not always predict subsequent reaction severity. Three factors were independently associated with anaphylaxis. Firstly, the risk of anaphylaxis increased with the amount of peanut ingested during the OFC, with patients reaching the final two stages of the challenge having a 13-fold higher risk than those reacting at the first stage. Clinicians supervising patients should therefore carefully examine patients prior to proceeding to each subsequent stage of the OFC in order not to miss milder signs. Secondly, teenagers were three times more likely to develop anaphylaxis than younger children, particularly if they reacted to smaller amounts of peanut. Although the association between reaction severity and age has been noted previously,[24] the fact that older children with lower thresholds of reactivity were more likely to develop anaphylaxis than younger children is novel. It suggests that long-term avoidance of peanuts might increase the risk of severe allergic reactions to lower levels of allergen exposure. If correct, peanut IT at a younger age may not only help to maintain partial tolerance to peanut, but also reduce the risk of future anaphylaxis. This is in keeping with evidence from both prevention[25] and the disease-modifying IT studies[12] that introduction of peanut-containing food, particularly into the diets of young children, prevents and alleviates clinical allergy. Finally, there was a small but significant association between the magnitude of the skin prick test result (but not peanut-specific IgE) and anaphylaxis (relatively risk 1.2, 95% CI: 1.1-1.3), but the clinical relevance of this observations remains to be determined, particularly as numerous other studies have not found an association between allergy test results and clinical severity.

Although not the primary objective of the study, the data also highlight the fact that clinical history is an imprecise marker of peanut allergy, failing to accurately predict whether a sensitized patient will react to oral ingestion of peanut, the severity of the reaction, and the amount of peanut that will cause a reaction. Diagnosing peanut allergy solely on the basis of history may risk falsely labeling patients as having peanut allergy. Although OFC is considered the gold standard for diagnosing food allergy, Glaumann et al[26] suggest that there may be intra-individual variability in the threshold of reactivity defined by OFC, as they found differences in reactivity when blinded peanut challenges were repeated in the same children. However, this was a small study of only 27 children, which in contrast to our survey, assessed outcome of the OFC on not only clinical signs of allergy but also subjective symptoms of "mouth itch," "stomach ache," "tiredness."

Although collation of data from allergy centers across the UK, as well as from Ireland and Australia, is a definite strength of this survey in that it provides a much larger sample size and allows comparison in OFC outcome in different centers, it also introduces potential bias in terms of selection criteria, variations in OFC protocol, and inter-center criteria for determining the clinical features of a positive allergic reaction. The Australian HealthNuts cohort was a much younger group of children, specifically recruited to reduce bias caused by previous allergic reactions as it is expected, and indeed found, that very few (5%) had a history of peanut allergy. This is in contrast to the older children from the European centers selected specifically on a real or perceived concern about peanut allergy. Despite these differences, threshold of reactivity on the Australian toddlers was similar to that of large European centers (Cork and Southampton) suggesting the general relevance of our results. There is evidence that reintroduction of peanuts back into the diet as part of a regimented IT program can lead to both health economic and lifestyle improvements for patients and society.[27] Although there will always be the risk of adverse allergic reactions during tolerance induction,[12,28] this risk needs to be weighed against the physical and psychological impact of unavoidable allergic reactions associated with the constant vigilance of long-term avoidance.[29] For children reacting to milligram amounts, current options are either ongoing avoidance or engagement with one of the research-focused peanut IT clinical trials. For the sizable minority of patients who react to gram quantities of peanut, options other than maintaining the status quo with just long-term avoidance need to be developed. They may include the supervised introduction of dietary peanut at doses below threshold. Recent publications from our centers have demonstrated the clinical utility of these measures to maintain a level of tolerance, with the possibility of improving the degree of nonresponsiveness in some patients in a manner similar to a desensitization regime.[30,31] In summary, this survey highlights both the under-appreciated spectrum of reactivity to peanuts and that avoiding peanuts through childhood may well be a factor leading to increased clinical reactivity and severity. Further work is required to explore the impact and practicality of IT for these patients.

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## CONFLICT OF INTEREST

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