



Probiotic peanut oral immunotherapy versus oral immunotherapy and placebo in children with peanut allergy in Australia (PPOIT-003): a multicentre, randomised, phase 2b trial

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Summary

Background Oral immunotherapy is effective at inducing desensitisation to allergens and induces sustained unresponsiveness (ie, clinical remission) in a subset of patients, but causes frequent reactions. We aimed to investigate whether addition of a probiotic adjuvant improved the efficacy or safety of peanut oral immunotherapy.

Methods PPOIT-003, a multicentre, randomised, phase 2b trial, was conducted in three tertiary hospitals in Australia (Adelaide [SA], Melbourne [VIC], and Perth [WA]) in children aged 1–10 years, weighing more than 7 kg, with peanut allergy confirmed by a double-blind placebo-controlled food challenge (cumulative 4950 mg dose of peanut protein) and positive peanut skin prick test (≥ 3 mm) or peanut-specific IgE (≥ 0.35 kU/L). Children were randomly assigned (2:2:1) to receive probiotic and peanut oral immunotherapy (PPOIT), placebo probiotic and peanut oral immunotherapy (OIT), or placebo probiotic and placebo OIT (placebo) for 18 months, and were followed up until 12 months after completion of treatment. Oral immunotherapy consisted of increasing doses of peanut protein (commercially available food-grade 12% defatted peanut flour [50% peanut protein]) until a 2000 mg daily maintenance dose was reached. The probiotic adjuvant was a daily dose of 2×10^{10} colony-forming units of the probiotic *Lactobacillus rhamnosus* ATCC 53103. Placebo immunotherapy comprised maltodextrin, brown food colouring, and peanut essence, and placebo probiotic was maltodextrin. Dual primary outcomes were 8-week sustained unresponsiveness, defined as no reaction to a cumulative dose of 4950 mg peanut protein at treatment completion and 8 weeks after treatment completion, in the PPOIT versus placebo groups and the PPOIT versus OIT groups, analysed by intention to treat. Safety endpoints were adverse events during the treatment phase, and peanut ingestion and reactions in the 12-month post-treatment period. This study is registered with the Australian New Zealand Clinical Trials Registry, 12616000322437.

Findings Between July 4, 2016, and Sept 21, 2020, 201 participants were enrolled and included in the intention-to-treat analysis. 36 (46%) of 79 children in the PPOIT group and 42 (51%) of 83 children in the OIT group achieved sustained unresponsiveness compared with two (5%) of 39 children in the placebo group (risk difference 40.44% [95% CI 27.46 to 53.42] for PPOIT vs placebo, $p < 0.0001$), with no difference between PPOIT and OIT (-5.03% [-20.40 to 10.34], $p = 0.52$). Treatment-related adverse events were reported in 72 (91%) of 79 children in the PPOIT group, 73 (88%) of 83 children in the OIT group, and 28 (72%) of 39 children in the placebo group. Exposure-adjusted incidence of adverse events was 10.58 in the PPOIT group, 11.36 in the OIT, and 2.09 in the placebo group (ratio 0.92 [95% CI 0.85 to 0.99] for PPOIT vs OIT, $p = 0.042$; 4.98 [4.11–6.03] for PPOIT vs placebo, $p < 0.0001$; 5.42 [4.48–6.56] for OIT vs placebo, $p < 0.0001$), with differences seen primarily in gastrointestinal symptoms and in children aged 1–5 years. During the 12-month post-treatment period, 60 (85%) of 71 participants in the PPOIT group, 60 (86%) of 70 participants in the OIT group, and six (18%) of 34 participants in the placebo group were eating peanut; rescue epinephrine use was infrequent (two [3%] of 71 in the PPOIT group, four [6%] of 70 in the OIT group, and none in the placebo group).

Interpretation Both PPOIT and OIT were effective at inducing sustained unresponsiveness. Addition of a probiotic did not improve efficacy of OIT, but might offer a safety benefit compared with OIT alone, particularly in preschool children.

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Introduction

Food allergy affects 5–8% of children in high-income countries.^{1,2} Because there is currently no cure, patients must adhere to strict allergen avoidance, which leads to

psychological distress and reduced health-related quality of life (HRQOL).³

Peanut oral immunotherapy (OIT) is effective at inducing desensitisation (a temporary increase in reaction

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Research in context

Evidence before this study

We actively monitored relevant publications and regularly performed literature searches to ensure the most relevant, evidence-based information was included in the study design and manuscript. A PubMed review of the literature using search terms "OIT", "oral immunotherapy" and "peanut allergy" before Jan 1, 2016, showed that peanut oral immunotherapy (OIT) was highly effective at inducing desensitisation (a temporary increase in reaction threshold while on therapy) but only induced clinical remission (sustained unresponsiveness) in a subset of patients (about 30% of treated patients in randomised controlled trials). In January, 2015, we reported that a combination therapy, probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT (PPOIT) induced high rates of 2–6-week sustained unresponsiveness. PPOIT was associated with a favourable safety profile, suggesting potential safety benefits. However, the absence of a peanut OIT group prevented evaluation of the added benefit from a probiotic. Before the PPOIT-003 trial, the effects of food immunotherapy on health-related quality of life (HRQOL) were unclear, and there were no studies comparing benefits to patients from desensitisation versus sustained unresponsiveness. A 2019 meta-analysis of peanut OIT found a three times increased risk of anaphylaxis, two times increased risk of rescue epinephrine use, and insufficient evidence of improved HRQOL compared with allergen avoidance, leading to a question of whether desensitisation with OIT provides greater benefit than allergen avoidance (current standard care).

Added value of this study

Our study found that both PPOIT and OIT are highly effective at inducing sustained unresponsiveness compared with placebo and led to significant improvement in HRQOL. Addition of probiotic did not improve efficacy of OIT but might provide a meaningful safety benefit, particularly for children aged 1–5 years, by reducing the burden of gastrointestinal symptoms and systemic reactions. Post-treatment follow-up of participants showed greater benefit to patients from achieving sustained unresponsiveness over desensitisation alone. Moreover, sustained unresponsiveness provided significantly greater improvement in HRQOL compared with both desensitisation alone and remaining allergic.

Implications of all the available evidence

Both PPOIT and OIT represent potential treatments for children with peanut allergy, and addition of a probiotic to peanut OIT might improve safety and tolerability of OIT, particularly for children aged 1–5 years. Sustained unresponsiveness is a preferred outcome for patients compared with desensitisation without sustained unresponsiveness; it allows patients to cease treatment and introduce peanut into the diet if desired, whereas desensitisation requires continued daily treatment and allergen avoidance. Future trials focusing on sustained unresponsiveness as a primary endpoint are required. Recent studies have identified markers that predict likely persistence of peanut allergy and could be used to identify suitable patients for early intervention.

threshold while on therapy) and induces sustained unresponsiveness (ie, clinical remission) in a subset (about 30%) of patients.⁴ Desensitisation confers protection against accidental ingestion; however, disadvantages include the need for indefinite maintenance dosing, continued allergen avoidance, and frequent treatment-related reactions that paradoxically exceed the number of reactions associated with avoidance.^{4,5} A meta-analysis of peanut OIT found a three times increased risk of anaphylaxis, two times increased risk of rescue epinephrine use, and insufficient evidence of improved HRQOL compared with allergen avoidance.⁶ Improved therapies that induce remission, have fewer side-effects, and improve HRQOL are needed.

Sustained unresponsiveness is the absence of clinical reactivity after treatment is stopped for a period of time.⁴ Patients with sustained unresponsiveness are able to cease treatment, incorporate peanut into the diet, and experience substantial and significant improvement in HRQOL compared with placebo.^{6,7} Few clinical trials of peanut OIT have assessed sustained unresponsiveness or HRQOL. Meta-analyses show a limited ability to induce sustained unresponsiveness and highlight concerns regarding safety and the lack of improvement in HRQOL with OIT.^{8,9}

Addition of adjuvants such as immune response modifiers (probiotics or Toll-like receptor agonists) has been suggested to improve the effectiveness or safety of OIT.^{10,11} We previously reported high rates of long-term sustained unresponsiveness with a combination therapy consisting of probiotic (*Lactobacillus rhamnosus* CGMCC 1.3724) and peanut OIT (PPOIT); in the PPOIT-001 randomised trial, 23 (74%) of 31 patients treated with PPOIT versus one (4%) of 31 patients who received placebo achieved 2–6-week sustained unresponsiveness after 18 months of treatment ($p < 0.001$),¹² and seven (70%) of ten initial responders retained challenge-confirmed 8-week sustained unresponsiveness 4 years after the end of treatment.⁷ PPOIT was well tolerated, with low rates of treatment withdrawal, few gastrointestinal adverse events, and no cases of eosinophilic oesophagitis.¹² Additionally, PPOIT was associated with lasting significant improvement in HRQOL at 4 years after treatment, with benefits linked specifically to attainment of sustained unresponsiveness.^{6,13} The absence of a peanut OIT group in PPOIT-001 prevented evaluation of the added benefit from a probiotic.¹² We aimed to evaluate the efficacy and safety of PPOIT at inducing sustained unresponsiveness compared with placebo and with peanut OIT alone in children with peanut allergy.

Methods

Study design and participants

PPOIT-003, a multicentre, randomised, placebo-controlled, phase 2b study, was conducted at three tertiary hospitals in Australia (Women's and Children's Hospital in Adelaide [SA], Royal Children's Hospital Melbourne [VIC], and Perth Children's Hospital [WA]). The trial included children aged 1–10 years, weighing more than 7 kg, with peanut allergy confirmed by a double-blind, placebo-controlled food challenge (cumulative 4950 mg peanut protein) and positive peanut skin prick test (≥ 3 mm) or peanut-specific IgE (≥ 0.35 kU/L) at screening. Exclusion criteria were history of severe anaphylaxis; severe anaphylaxis in the double-blind, placebo-controlled food challenge at screening; forced expiratory volume in 1 s of less than 85% predicted at rest and a ratio of forced expiratory volume in 1 s to forced vital capacity of 85% or less than predicted at rest or ongoing chronic persistent asthma; underlying medical conditions (eg, cardiac disease) that increase the risks associated with anaphylaxis; use of β -blockers or angiotensin-converting enzyme inhibitors; inflammatory intestinal conditions, indwelling catheters, gastrostomies, immunocompromised states, post-cardiac or gastrointestinal tract surgery, critical illnesses and those requiring prolonged hospital stays, or other conditions that might increase the risks of probiotic-associated sepsis; use of probiotic supplements within the past 6 months (does not include formula); reaction to the placebo component during the double-blind, placebo-controlled challenge at screening; other food immunotherapy in the preceding 12 months; current immunomodulatory therapy (including allergen immunotherapy); past or current major illness that in the opinion of the site investigator might affect the participant's ability to participate in the study; unable to follow the protocol according to site investigator's opinion; and another family member already enrolled in the trial (to maintain safety and blinding; appendix pp 50–51). Parents or guardians provided written informed consent. The investigators and research team enrolled the participants. This study was approved by the Human Research Ethics Committee at the Royal Children's Hospital Melbourne (HREC 35246) and the Child and Adolescent Health Service Perth (RGS 2543). The protocol is available in the appendix (pp 26–97).

Randomisation and masking

Participants were assigned (2:2:1) to receive PPOIT, OIT, or placebo, stratified by site (Melbourne, Adelaide, and Perth), age (1–5 years and 6–10 years), and peanut skin prick test (≤ 10 mm and >10 mm), in randomly permuted blocks of size five. An independent statistician provided one computer-generated randomisation list at each site's pharmacy. The pharmacist assigned the next available unique randomisation number, notified the study personnel, then prepared the participant's allocated study treatment, and labelled the treatment with the participant's randomisation number. Parti-

cipants, investigators, and research team were masked to treatment allocation. Placebo and OIT products were similar in appearance, taste, and smell.

Procedures

In the two-part, double-blind placebo-controlled food challenge, peanut protein or placebo doses (80 mg, 160 mg, 320 mg, 640 mg, 1250 mg, and 2500 mg) were administered at 15 min intervals if patients did not have dose-limiting symptoms to the previous dose (for more details see the appendix p 91). Predefined stopping criteria were based on the PRACTALL consensus report, with minor modification.^{14,15} Patients who had no reactions in the double-blind, placebo-controlled food challenge at the screening visit were excluded from randomisation. Participants who reacted to the peanut component, but not the placebo component, of the challenge were randomly assigned to one of the three groups and proceeded to day 1 (the rush induction phase), which comprised administration of increasing doses of peanut protein or placebo every 20 min until a dose of 12 mg (cumulative 24 mg) peanut protein was reached. Doses were given in hospital, and patients were monitored until 2 h after the last dose in this phase. The PPOIT group received the probiotic (2×10^{10} colony-forming units of *L rhamnosus* ATCC 53103) and peanut protein (commercially available food-grade 12% defatted peanut flour [50% peanut protein]), the OIT group received probiotic placebo (maltodextrin) and peanut protein, and the placebo group received probiotic placebo and OIT placebo (maltodextrin, brown food colouring, and peanut essence, with similar taste and appearance to peanut OIT). The probiotic (or the probiotic placebo) was administered daily, before OIT, throughout the study period.

The build-up phase, starting on day 2, comprised a daily dose commencing at the highest tolerated dose during the rush induction phase, with dose increases every 2 weeks until the 2000 mg peanut protein (or placebo) maintenance dose was reached. Dose increases were administered in hospital under medical supervision. The maintenance daily dose was continued at home until 18 months of treatment was completed; participants were required to complete a minimum of 6 months on maintenance dosing (appendix p 55).

The double-blind, placebo-controlled food challenge (cumulative 4950 mg peanut protein) was repeated at the end of 18 months of treatment to determine desensitisation. Participants who passed this double-blind, placebo-controlled food challenge (ie, had no dose-limiting symptoms) proceeded to a second double-blind, placebo-controlled food challenge (cumulative 4950 mg peanut protein) at 8 weeks after treatment completion to determine sustained unresponsiveness, with strict peanut elimination between the end of treatment and 8 weeks after treatment completion. At this timepoint, participants were classified into one of three clinical outcomes:

See Online for appendix

sustained unresponsiveness (passed both double-blind, placebo-controlled food challenges), desensitised without sustained unresponsiveness (passed the first, but not second, double-blind, placebo-controlled food challenge), allergic (had reactions to the peanut component but not the placebo component in the first double-blind, placebo-controlled food challenge). Instructions on peanut ingestion and avoidance during the 12-month post-treatment monitoring phase were then provided according to the clinical outcome achieved. Participants with sustained unresponsiveness were advised to incorporate peanut into their diet *ad libitum* without specific instructions on amount or frequency of ingestion; if additional guidance was requested, study staff suggested one to two standard serves of peanut every 2–4 weeks with additional explanation that it is not possible to define *ad libitum* intake. Participants with desensitisation alone (ie, without sustained unresponsiveness) were instructed to take a daily treatment dose of one to two peanuts. Participants who were allergic were instructed to continue strict peanut avoidance. Allergic reactions to peanut (and other foods) and peanut ingestion during the post-treatment monitoring phase were recorded in patient diaries reviewed at the follow-up visit at 12 months after treatment completion. Participants with sustained unresponsiveness recorded the frequency and amount of peanut ingested as ranges on a weekly basis (appendix p 24), and those with desensitisation alone kept a daily record of their daily peanut dose intake. All participants were followed up until 12 months after treatment completion.

Treatment-emergent adverse events from commencement of treatment to 8 weeks after treatment completion and adherence during the treatment phase were monitored by patient diaries reviewed at study visits. Study visits during the treatment were every 2 weeks during the build-up phase, then every 12 weeks during the maintenance phase. There were no study visits from 8 weeks after treatment completion to 12 months after treatment completion. Telephone contact was made at 6 months after the end of treatment (phone assessment only). Causality, severity, and association of treatment-emergent adverse events with study treatment were assessed by site investigators. Severity of immediate allergic reactions was categorised according to criteria adapted from the US National Institute of Allergy and Infectious Diseases (NIAID) Consortium for Food Allergy Research grading system (appendix p 4). For other treatment-emergent adverse events, severity was classified according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guidelines. Treatment-emergent adverse events were categorised as treatment related, accidental food exposure related, double-blind placebo-controlled food challenge related, or unrelated to any of the above. Treatment-emergent adverse events were presented according to medical dictionary for regulatory activities (MedDRA)

terms, grouped by system organ class, and preferred term.

HRQOL was assessed with the Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF),¹⁶ which was completed by parents or guardians at baseline, treatment completion (or withdrawal from the study), and 12 months after treatment completion. The FAQLQ-PF comprises a total score (mean of up to 30 items) and three subscale scores (emotional impact, food anxiety, and social and dietary limitations), and the response scale is from 0 (minimal impairment in HRQOL) to 6 (maximal impairment in HRQOL); a reduced score indicates an improvement in the child's HRQOL. The minimal clinically important difference for the total score is 0.45–0.5.¹⁷

Outcomes

The primary outcome was the proportion of participants with 8-week sustained unresponsiveness, defined as passing both double-blind placebo-controlled food challenges at treatment completion and 8 weeks after treatment completion in the PPOIT versus placebo groups and the PPOIT versus OIT groups. Secondary outcomes were the proportion of participants with 8-week sustained unresponsiveness in the OIT versus placebo groups; full desensitisation to 4950 mg peanut protein (defined as passing the double-blind placebo-controlled food challenge at treatment completion); total cumulative dose of peanut protein tolerated at the end of treatment; adverse events during the treatment phase; peanut skin prick test wheal size, and peanut-specific and peanut component (Ara h 1, h 2, and h 3)-specific IgE and IgG₄ at treatment completion, at 8 weeks after treatment completion, and at 12 months after treatment completion, and their changes from baseline; and peanut ingestion and reactions at 12 months after treatment completion. A prespecified exploratory outcome was HRQOL assessed by the FAQLQ-PF at the end of treatment and at 12 months after treatment completion. An additional prespecified exploratory objective relating to cost-effectiveness outlined in the study protocol will be reported separately.

Statistical analysis

The planned study sample was 200 participants (80 in the PPOIT group, 80 in the OIT group, and 40 in the placebo group). We used a hierarchical fixed-sequence testing strategy to maintain a global type I error of 5% for two primary outcomes: for PPOIT versus placebo, sample sizes of 70 and 35 participants provided more than 99% power with two-tailed 0.05 significance to detect a difference between 60% and 15% sustained unresponsiveness, respectively; and for PPOIT versus OIT, sample sizes of 70 participants in each group provided 85% power with two-tailed 0.05 significance to detect the difference between 60% and 35% sustained unresponsiveness, respectively. A sample size of 200 participants allowed for 12.5% loss to follow-up.

Continuous outcomes are presented as mean (SD) with the range (or median [IQR] with the range for skewed data) and categorical outcomes as absolute and relative frequencies. The primary outcome is summarised as number and proportion of participants with sustained unresponsiveness, with the primary pairwise comparisons (PPOIT vs placebo and PPOIT vs OIT) presented as risk differences (95% CI), calculated using Pearson χ^2 statistic, as prespecified in the accompanying protocol and statistical analysis plan (appendix pp 26–126). Limitations of the Pearson χ^2 statistic when applied to 2×2 contingency tables include the possibility of smaller p values and narrower CIs. Therefore, as a post-hoc sensitivity analysis, Wallenstein's 95% CI were calculated to include the continuity correction. Secondary binary outcomes are presented and analysed as for the primary outcomes, with the addition of the Fisher exact test as a post-hoc sensitivity analysis, computed as double the exact one-tailed probability. For categorical outcomes with more than two categories, the two-tailed Fisher exact test probability is presented. Normally distributed continuous outcomes (including changes from baseline in peanut skin prick test wheal size, and peanut-specific and peanut component-specific IgE and IgG₄ concentrations at the end of treatment, and at 8 weeks and 12 months after treatment completion) were pairwise compared between groups using Student's *t* test or Wilcoxon rank-sum test (also known as the Mann-Whitney *U* test) was used when outcomes had a skewed distribution (peanut-specific and peanut component-specific IgE and IgG₄ at treatment completion, 8 weeks after treatment completion, and 12 months after treatment completion). Cumulative doses tolerated at the end of treatment are presented as geometric means and 95% CIs within each group. Efficacy analyses were done in the intention-to-treat population (all participants analysed according to the group to which they were randomly assigned). Prespecified sensitivity analyses of sustained unresponsiveness and desensitisation were done in the per-protocol and complete case populations. A priori subgroup analysis by age (1–5 years vs 6–10 years) was conducted by interaction modelling followed by stratification.

Treatment-emergent adverse events are reported as proportion of participants reporting events and as exposure-adjusted incidence rates, by preferred term and by treatment group. We calculated the exposure-adjusted incidence rate by dividing the total number of treatment-related adverse events by the time on treatment in patient-years. We calculated ratios between exposure-adjusted event rates to allow pairwise treatment comparisons. Relative risk ratios and 95% CIs of exposure-adjusted event rates are based on a Poisson regression model using a log-linear model with terms for treatment group and age group, and an interaction term for treatment by age group and the

natural logarithm of years of exposure to treatment as the offset. Peanut ingestion and reactions between 8 weeks and 12 months after treatment completion, and HRQOL were analysed by clinical outcome and treatment groups. The p value for the change in HRQOL total score from baseline to 12 months after treatment completion was derived from a linear regression model adjusted for the baseline FAQLQ-PF total score. Safety and HRQOL outcomes were analysed in the intention-to-treat population, which coincided with the safety population. As a post-hoc analysis, anaphylaxis was presented first according to the NIAID and Food Allergy and Anaphylaxis Network (FAAN) criteria¹⁸ and second in a sensitivity analysis in which hoarse voice was included as a symptom of anaphylaxis. Severity of anaphylaxis events was graded according to the European Academy of Allergy and Clinical Immunology criteria.¹⁹

Statistical analyses were done with SAS (version 9.4; efficacy and safety), Stata (version 16; subgroup analyses), and R (version 3.6.1; HRQOL analysis). Further details are in the appendix (p 3). An independent data and safety monitoring committee provided trial oversight. This trial is registered with the Australian New Zealand Clinical Trials Registry, 12616000322437.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between July 4, 2016, and Sept 21, 2020, 248 participants were screened, 201 were enrolled (104 aged 1–5 years and 97 aged 6–10 years; 72 girls and 129 boys), 178 (89%) completed 18 months of treatment, 176 (88%) completed 8-week follow-up after treatment completion, and 175 (87%) completed the 12-month follow-up after treatment completion (table 1; figure). The intention-to-treat population included 79 participants in the PPOIT group, 83 in the OIT group, and 39 in the placebo group. Mean age for the study population was 5.9 years (SD 2.8), mean peanut skin prick test wheal size was 12.7 mm (5.5), median peanut-specific IgE was 11.95 kU/L (IQR 2.0–60.7), and median reaction-eliciting dose was 320 mg (160–1250) peanut protein.

Sustained unresponsiveness was achieved in 36 (46%) of 79 participants in the PPOIT group, 42 (51%) of 83 participants in the OIT group, and two (5%) of 39 participants in the placebo group (risk difference 40.44% [95% CI 27.46 to 53.42] for PPOIT vs placebo, $p < 0.0001$; –5.03% [–20.40 to 10.34] for PPOIT vs OIT, $p = 0.52$; and 45.47% [32.68 to 58.27] for OIT vs placebo, $p < 0.0001$; table 2). There was no evidence of a difference in sustained unresponsiveness between the PPOIT and OIT groups. Both PPOIT and OIT were effective at inducing desensitisation to 4950 mg peanut protein

	PPOIT group (n=79)	OIT group (n=83)	Placebo group (n=39)
Age, years	6.0 (3.0; range 1–10)	5.8 (2.7; range 1–10)	6.0 (2.7; range 1–10)
Age 1–5	41 (52%)	43 (52%)	20 (51%)
Age 6–10	38 (48%)	40 (48%)	19 (49%)
Sex			
Female	30 (38%)	28 (34%)	14 (36%)
Male	49 (62%)	55 (66%)	25 (64%)
Reaction-eliciting peanut protein dose, mg	320 (160–640; range 80–2500)	320 (160–1250; range 80–2500)	320 (160–1250; range 80–2500)
History of asthma	18 (23%)	31 (37%)	14 (36%)
History of eczema	60 (76%)	61 (74%)	27 (69%)
History of wheeze	43 (54%)	51 (61%)	23 (59%)
Other food allergies diagnosed	54 (68%)	52 (63%)	32 (82%)
Anaphylaxis to peanut	28 (35%)	32 (39%)	14 (36%)
Anaphylaxis to other food	19 (24%)	18 (22%)	9 (23%)
Peanut-specific IgE*, kU/L	10.4 (1.9–85.0; range 0.1–1115.8)	11.0 (2.0–44.0; range 0.1–1861.0)	18.0 (3.8–59.7; range 0.2–306.0)
Peanut-specific IgG ₄ †, mgA/L	0.38 (0.1–1.0; range 0.0–53.5)	0.36 (0.1–0.8; range 0.0–48.8)	0.63 (0.2–1.9; range 0.0–5.5)
Peanut skin prick test, mm	12.7 (5.6; range 4.0–30.0)	12.6 (5.2; range 3.0–27.0)	12.7 (5.8; range 5.0–31.0)
Food Allergy Quality of Life Questionnaire-Parent Form‡§			
Emotional impact	1.8 (1.4)	1.7 (1.5)	2.5 (1.6)
Food anxiety	2.3 (1.9)	2.1 (1.7)	2.9 (2.0)
Social and dietary restrictions	2.5 (1.6)	2.2 (1.6)	2.6 (1.5)
Total score¶	2.2 (1.5)	2.0 (1.4)	2.6 (1.6)

Data are mean (SD), n (%), or median (IQR), unless otherwise specified. OIT=oral immunotherapy. PPOIT=probiotic and peanut oral immunotherapy. *Data missing for two participants in the PPOIT group, two participants in the OIT group, and one participant in the placebo group. †Data missing for two participants in the PPOIT group, one participant in the OIT group, and one participant in the placebo group. ‡Data missing for one participant in the PPOIT group. §The response scale is from 0 (minimal impairment in health-related quality of life) to 6 (maximal impairment in health-related quality of life), as perceived by the caregiver. ¶The minimal clinically important difference for the total score is 0.45–0.5.

Table 1: Participant demographics and baseline characteristics

compared with placebo (table 2). Subgroup analysis by age and sensitivity analyses on per-protocol and complete case populations provided similar results (table 2; appendix p 6). For the PPOIT versus placebo and OIT versus placebo comparisons, there were no estimates of the interaction term because no children had sustained unresponsiveness or desensitisation in the age group of 6–10 years in the placebo group. For PPOIT versus OIT, the interaction term p value was 0.16 for sustained unresponsiveness and 0.44 for desensitisation. At the end-of-treatment double-blind, placebo-controlled food challenge, the median cumulative tolerated dose was 4950 mg (IQR 4950–4950) in the PPOIT group (n=70), 4950 mg (4950–4950) in the OIT group (n=68), and 240 mg (80–560) in the placebo group (n=36). Both PPOIT and OIT led to an increased total cumulative tolerated dose compared with placebo (both p<0.0001), with no difference between PPOIT and OIT (p=0.60). The geometric mean total cumulative tolerated dose was 4232.1 mg (95% CI 3116.9 to 5746.0) in the PPOIT group, 4604.3 mg (3376.0 to 6279.4) in the OIT group, and 101.1 mg (65.6 to 155.3) in the placebo group.

Both PPOIT and OIT groups were associated with significantly greater reduction from baseline (ie, screening) in peanut skin prick test wheal size and peanut-specific IgE, and significantly greater increase from baseline in peanut-specific IgG₄, compared with placebo at treatment completion, 8 weeks after treatment completion, and 12 months after treatment completion (appendix p 8). Reduced peanut-specific IgE concentrations in the PPOIT and OIT groups persisted to 12 months after treatment completion (median reduction of 5.8 kU/L [IQR –49.9 to –1.0] and 4.1 kU/L [–20.9 to –1.0]; appendix p 8). Peanut-specific IgG₄ concentrations in the PPOIT and OIT groups increased significantly from baseline to treatment completion but regressed towards baseline by 12 months after treatment completion, although remained significantly higher than placebo (appendix p 8). Similar changes were observed for Ara h 2-specific IgE and Ara h 1, h 2, and h 3-specific IgG₄ (appendix pp 9–12). There were no significant differences in immunological parameters at any timepoint between the PPOIT and OIT groups.

Treatment-emergent adverse events were reported in 197 (98%) participants (77 [97%] of 79 in the PPOIT group,

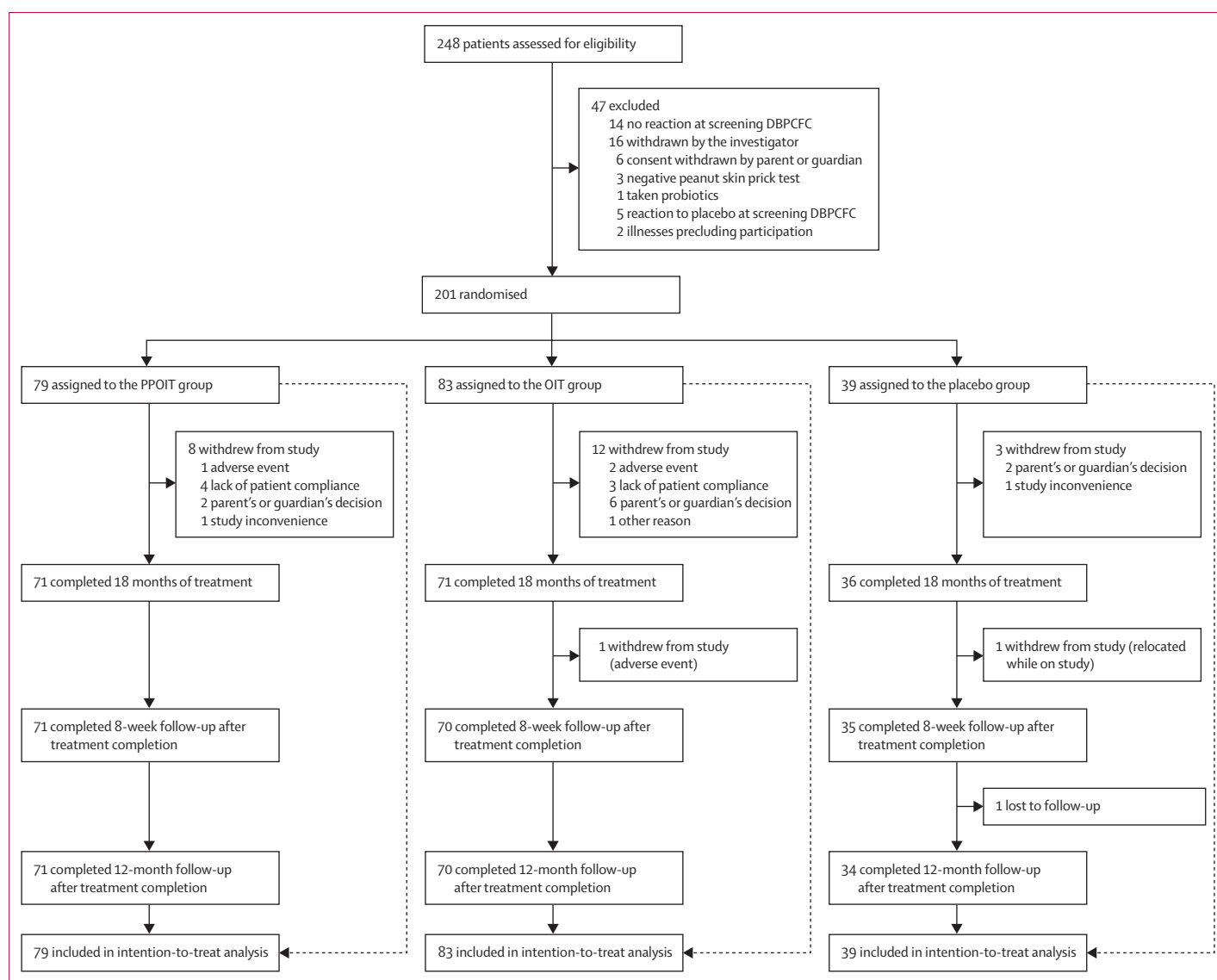


Figure: Trial profile

DBPCFC=double-blind, placebo-controlled food challenge. OIT=oral immunotherapy. PPOIT=probiotic and peanut oral immunotherapy.

81 [98%] of 83 in the OIT group, and all 39 in the placebo group; appendix p 13), and treatment-related adverse events were reported in 173 (86%) participants (72 [91%] in the PPOIT group, 73 [88%] in the OIT group, and 28 [72%] in the placebo group; table 3). 2291 (93%) of 2473 treatment-related adverse events (1042 in the PPOIT group, 1141 in the OIT group, and 108 in the placebo group) were mild, 152 (6%) were moderate (75 in the PPOIT group, 70 in the OIT group, and seven in the placebo group), and 30 (1%) were severe (13 in the PPOIT group, 16 in the OIT group, and one in the placebo group). Abdominal pain was a frequent treatment-related adverse event across all treatment groups. Hypersensitivity (ie, systemic reactions involving two or more organ systems) were reported in 44 (56%) of 79 participants in the PPOIT

group, 47 (57%) of 83 participants in the OIT group, and nine (23%) of 39 participants in the placebo group. Anaphylaxis defined according to the NIAID-FAAN criteria occurred in 11 (14%) of 79 participants in the PPOIT group, 14 (17%) of 83 participants in the OIT group, and one (3%) of 39 participants in the placebo group. Expanding the definition of anaphylaxis to include hoarse voice as a symptom of respiratory compromise identified six additional participants (two in the PPOIT group and four in the OIT group) who had urticaria or angio-oedema and hoarse voice without other symptoms of respiratory or cardiovascular compromise, yielding anaphylaxis frequencies of 13 (16%) of 79 participants in the PPOIT group, 18 (22%) of 83 participants in the OIT group, and one (3%) of 39 participants in the

PPOIT group (n=79)			OIT group (n=83)			Placebo group (n=39)			PPOIT group vs placebo group			PPOIT group vs OIT group			OIT group vs placebo group		
									Risk difference (95% CI); p value	Wallenstein's 95% CI*	Fisher's p value	Risk difference (95% CI); p value	Wallenstein's 95% CI*	Fisher's p value	Risk difference (95% CI); p value	Wallenstein's 95% CI*	Fisher's p value
All age groups																	
Sustained unresponsiveness	36 (46%)	42 (51%)	2 (5%)	40.44% (27.46 to 53.42); p<0.0001	22.52 to 53.36	<0.0001	-5.03% (-20.40 to 10.34); p=0.52	-21.30 to 11.50	0.63	45.47% (32.68 to 58.27); p<0.0001	27.61 to 57.98	<0.0001					
Desensitisation	61 (77%)	61 (73%)	2 (5%)	72.09% (60.53 to 83.64); p<0.0001	54.81 to 82.40	<0.0001	37.2% (-9.53 to 16.98); p=0.58	-10.74 to 17.87	0.71	68.37% (56.61 to 80.12); p<0.0001	51.01 to 79.01	<0.0001					
Age 1-5 years																	
Sustained unresponsiveness	25/41 (61%)	24/43 (56%)	2/20 (10%)	50.98% (31.08 to 70.87); p=0.0002	22.10 to 68.87	0.0003	5.16% (-15.89 to 26.22); p=0.63	-17.99 to 27.73	0.80	45.81% (25.99 to 65.64); p=0.00058	17.21 to 63.84	0.0009					
Desensitisation	36/41 (88%)	34/43 (79%)	2/20 (10%)	77.80% (61.28 to 94.33); p<0.0001	50.75 to 90.99	<0.0001	8.74% (-7.02 to 24.49); p=0.28	-9.55 to 25.82	0.44	69.07% (51.16 to 86.98); p<0.0001	41.28 to 83.76	<0.0001					
Age 6-10 years																	
Sustained unresponsiveness	11/38 (29%)	18/40 (45%)	0/19	28.95% (14.53 to 43.37); p=0.0090	3.86 to 48.79	0.013	-16.05% (-37.16 to 5.06); p=0.14	-38.20 to 7.92	0.22	45.00% (29.58 to 60.42); p=0.0005	18.26 to 63.78	0.0004					
Desensitisation	25/38 (66%)	27/40 (68%)	0/19	65.79% (50.71 to 80.87); p<0.0001	44.83 to 80.86	<0.0001	-1.71% (-22.64 to 19.22); p=0.87	-24.58 to 19.54	1.00	67.50% (52.99 to 82.01); p<0.0001	40.49 to 83.02	<0.0001					
OIT=oral immunotherapy. PPOIT=probiotic and peanutoral immunotherapy. *Includes the continuity correction.																	
Table 2: Sustained unresponsiveness and desensitisation in the intention-to-treat population and stratified by age group																	

OIT=oral immunotherapy. PPOIT=probiotic and peanut oral immunotherapy. *Includes the continuity correction.

Table 2: Sustained unresponsiveness and desensitisation in the intention-to-treat population and stratified by age group

placebo group. There were no severe anaphylaxis events according to the European Academy of Allergy and Clinical Immunology grading criteria. Rescue epinephrine use was similar in the PPOIT group (14 [18%] of 79) and the OIT group (13 [16%] of 83), both higher than placebo (one [3%] of 39; appendix p 19). There were two cases of treatment-related eosinophilic oesophagitis in the OIT group and none in PPOIT or placebo groups. Seven participants (three in the PPOIT group and four in the OIT group) each reported one treatment-related serious adverse event (appendix p 17).

The exposure-adjusted incidence rate of adverse events provides more detailed insight into the frequency or burden of adverse events. Overall exposure-adjusted event rate of treatment-related adverse events was greater in both the PPOIT and OIT group compared with the placebo group (both $p<0.0001$), and was lower in the PPOIT group than in the OIT group ($p=0.042$; table 4). Comparing PPOIT and OIT groups, there was a significant reduction in exposure-adjusted incidence of abdominal pain, vomiting, and system organ class respiratory disorders, which include preferred terms allergic cough, allergic respiratory, and respiratory adverse events in the PPOIT group. A priori subgroup analysis by age showed reductions in exposure-adjusted incidence of abdominal pain, vomiting, hypersensitivity, and moderate or severe adverse events in participants aged 1–5 years in the PPOIT versus OIT groups. In participants aged 6–10 years, exposure-adjusted incidence of vomiting and respiratory events was lower in the PPOIT than in the OIT group, whereas that of hypersensitivity and urticaria was higher (table 4). Further adverse event information is available in the appendix (pp 13–19).

	PPOIT group (n=79)	OIT group (n=83)	Placebo group (n=39)
Overall summary	72 (91%)	73 (88%)	28 (72%)
Gastrointestinal disorder	19 (24%)	17 (21%)	5 (13%)
Abdominal pain	41 (52%)	40 (48%)	10 (26%)
Vomiting	18 (23%)	21 (25%)	4 (10%)
Hypersensitivity*	44 (56%)	47 (57%)	9 (23%)
Allergic cough	22 (28%)	19 (23%)	0
Allergic respiratory symptom†	25 (32%)	26 (31%)	1 (3%)
Respiratory symptom	17 (22%)	21 (25%)	3 (8%)
Angio-oedema	14 (18%)	19 (23%)	3 (8%)
Urticaria	39 (49%)	38 (46%)	14 (36%)

If a patient has more than one adverse event coded to the same medical dictionary for regulatory activities term per treatment, the patient is counted only once. OIT=oral immunotherapy. PPOIT=probiotic and peanut oral immunotherapy. *Hypersensitivity refers to involvement of two or more systems, with upper respiratory symptoms assigned to respiratory system. †Allergic respiratory symptom refers to multiple respiratory symptoms, whereas respiratory symptom refers to upper respiratory symptoms.

Table 3: Treatment-related adverse events by preferred term reported by at least 10% of the study population

A clinically and statistically significant improvement in HRQOL during the 12 months after treatment completion was observed in both the PPOIT and OIT groups compared with placebo, despite the higher frequencies of adverse events reported in both active treatment groups (difference in FAQLQ-PF total score from baseline to 12 months after treatment completion: -0.74 [95% CI -0.27 to -1.21] for PPOIT vs placebo, adjusted for baseline score $p=0.0016$; -0.75 [-0.28 to

-1.23] for OIT vs placebo, adjusted for baseline score $p=0.0022$; appendix p 20). No difference was observed in HRQOL change scores between PPOIT and OIT (0.01 [95% CI -0.37 to 0.39], adjusted for baseline score $p=0.95$). Results of unadjusted and sensitivity analyses of HRQOL are given in the appendix (pp 20–21). During the 12-month post-treatment period, 60 (85%) of 71 participants in the PPOIT group, 60 (86%) of 70 participants in the OIT group, and six (18%) of 34 participants

	Exposure-adjusted incidence*			PPOIT vs OIT		PPOIT vs placebo		OIT vs placebo	
	PPOIT group (n=79)	OIT group (n=83)	Placebo group (n=39)	Ratio† (95% CI)	p value	Ratio† (95% CI)	p value	Ratio† (95% CI)	p value
Overall									
1–5 years	7.67	10.05	1.88	0.76 (0.68–0.86)	<0.0001	4.08 (3.08–5.40)	<0.0001	5.34 (4.05–7.05)	<0.0001
6–10 years	14.13	12.79	2.33	1.11 (0.99–1.23)	0.068	6.08 (4.68–7.90)	<0.0001	5.50 (4.23–7.15)	<0.0001
All age groups	10.58	11.36	2.09	0.92 (0.85–0.99)	0.042	4.98 (4.11–6.03)	<0.0001	5.42 (4.48–6.56)	<0.0001
Abdominal pain									
1–5 years	1.76	2.60	0.27	0.68 (0.53–0.87)	0.0022	6.42 (3.13–13.18)	<0.0001	9.51 (4.67–19.37)	<0.0001
6–10 years	5.84	6.10	0.72	0.96 (0.82–1.13)	0.60	8.06 (5.07–12.83)	<0.0001	8.41 (5.29–13.37)	<0.0001
All age groups	3.60	4.27	0.49	0.80 (0.69–0.93)	0.0043	7.19 (4.69–11.04)	<0.0001	8.94 (5.85–13.67)	<0.0001
Diarrhoea									
1–5 years	0.12	0.09	0.07	1.35 (0.43–4.25)	0.61	1.75 (0.36–8.40)	0.49	1.29 (0.25–6.67)	0.76
6–10 years	0.23	0.02	0.08	11.78 (1.52–91.24)	0.018	2.99 (0.66–13.53)	0.15	0.26 (0.02–2.81)	0.26
All age groups	0.17	0.06	0.07	3.99 (1.23–12.89)	0.021	2.29 (0.77–6.79)	0.14	0.57 (0.13–2.46)	0.45
Multiple gastrointestinal symptoms									
1–5 years	0.22	0.35	0.14	0.63 (0.31–1.26)	0.19	1.62 (0.53–4.97)	0.39	2.59 (0.88–7.57)	0.082
6–10 years	1.31	0.99	0.04	1.32 (0.91–1.91)	0.14	34.34 (4.76–247.58)	0.0005	25.96 (3.59–187.85)	0.0013
All age groups	0.71	0.66	0.09	0.91 (0.61–1.35)	0.64	7.46 (2.40–23.22)	0.0005	8.20 (2.66–25.26)	0.0002
Vomiting									
1–5 years	0.17	0.35	0.14	0.48 (0.23–1.03)	0.059	1.25 (0.39–3.97)	0.71	2.59 (0.88–7.57)	0.082
6–10 years	0.39	0.78	0.00	0.51 (0.30–0.88)	0.015	..	..	..	..
All age groups	0.27	0.56	0.07	0.50 (0.31–0.79)	0.032	..	..	..	..
Hypersensitivity‡									
1–5 years	1.24	2.09	0.44	0.60 (0.45–0.80)	0.0005	2.80 (1.55–5.05)	0.0006	4.70 (2.65–8.33)	<0.0001
6–10 years	2.68	1.30	0.53	2.06 (1.54–2.77)	<0.0001	5.02 (2.89–8.72)	<0.0001	2.44 (1.40–4.33)	0.0024
All age groups	1.89	1.71	0.49	1.11 (0.90–1.36)	0.33	3.75 (2.50–5.62)	<0.0001	3.38 (2.25–5.08)	<0.0001
Allergic cough									
1–5 years	0.72	0.96	0.00	0.75 (0.50–1.12)	0.16	..	..	..	..
6–10 years	0.25	0.58	0.00	0.43 (0.22–0.84)	0.013	..	..	..	..
All age groups	0.51	0.78	0.00	0.57 (0.38–0.84)	0.0044	..	..	..	..
Allergic respiratory symptom§									
1–5 years	0.43	0.69	0.00	0.62 (0.37–1.02)	0.060	..	..	..	..
6–10 years	0.44	0.45	0.04	0.98 (0.54–1.77)	0.94	11.45 (1.54–85.09)	0.017	11.71 (1.58–86.69)	0.016
All age groups	0.43	0.57	0.02	0.78 (0.53–1.15)	0.20	..	..	..	..
Respiratory symptom									
1–5 years	0.58	0.37	0.00	1.56 (0.91–2.69)	0.11	..	..	..	..
6–10 years	0.15	1.01	0.23	0.14 (0.07–0.32)	<0.0001	0.64 (0.21–1.89)	0.42	4.41 (1.90–10.27)	0.0006
All age groups	0.38	0.68	0.11	0.47 (0.29–0.77)	0.0023	..	..	..	..
Dermatitis allergic									
1–5 years	0.02	0.14	0.03	0.12 (0.02–0.96)	0.046	0.50 (0.03–7.97)	0.62	4.14 (0.52–33.09)	0.18
6–10 years	0.06	0.02	0.00	3.21 (0.33–30.88)	0.31	..	..	..	..
All age groups	0.04	0.08	0.02	0.62 (0.13–2.89)	0.54	..	..	..	..

(Table 4 continues on next page)

Exposure-adjusted incidence*			PPOIT vs OIT		PPOIT vs placebo		OIT vs placebo		
PPOIT group (n=79)	OIT group (n=83)	Placebo group (n=39)	Ratio† (95% CI)	p value	Ratio† (95% CI)	p value	Ratio† (95% CI)	p value	
(Continued from previous page)									
Angio-oedema									
1-5 years	0.10	0.35	0.03	0.29 (0.12-0.72)	0.0077	2.99 (0.36-24.85)	0.31	10.35 (1.39-77.10)	0.023
6-10 years	0.58	0.33	0.08	1.76 (0.97-3.22)	0.065	7.63 (1.82-32.03)	0.0055	4.33 (1.00-18.73)	0.050
All age groups	0.32	0.34	0.05	0.71 (0.41-1.23)	0.23	4.78 (1.33-17.16)	0.017	6.69 (1.93-23.19)	0.0027
Urticaria									
1-5 years	2.13	1.98	0.68	1.08 (0.83-1.39)	0.58	3.12 (1.94-4.99)	<0.0001	2.90 (1.80-4.66)	<0.0001
6-10 years	1.89	0.91	0.53	2.07 (1.46-2.95)	<0.0001	3.54 (2.02-6.22)	<0.0001	1.71 (0.94-3.10)	0.078
All age groups	2.02	1.47	0.61	1.49 (1.20-1.86)	0.0003	3.32 (2.30-4.80)	<0.0001	2.23 (1.52-3.26)	<0.0001
Type 3 probability of interaction from regression model was <0.0001 overall, 0.070 for abdominal pain, 0.11 for diarrhoea, NA for multiple gastrointestinal symptoms and allergic cough, 0.015 for vomiting, <0.0001 for hypersensitivity and respiratory symptom, 0.21 for allergic respiratory symptom, 0.042 for dermatitis allergic, 0.0025 for angio-oedema, and 0.011 for urticaria. NA=not available. OIT=oral immunotherapy. PPOIT=probiotic and peanut oral immunotherapy. *The exposure-adjusted incidence rate is calculated by dividing the total number of adverse events by the total time on treatment in patient-years. †Ratio is calculated as the exposure-adjusted incidence rate of the first group divided by that of the second group; the ratio could not be calculated when the estimated event rate is zero. ‡Hypersensitivity indicates involvement of two or more systems, with upper respiratory symptoms assigned to respiratory system. §Allergic respiratory symptom refers to multiple respiratory symptoms, whereas respiratory symptom refers to upper respiratory symptoms.									
Table 4: Exposure-adjusted incidence rates of treatment-related adverse events, adjusted for time on study treatment in patient-years									

Table 4: Exposure-adjusted incidence rates of treatment-related adverse events, adjusted for time on study treatment in patient-years

in the placebo group were eating peanut (table 5). Rates of peanut reaction were similar in the PPOIT group (22 [31%] of 70) and OIT group (24 [34%] of 70), both higher than the placebo group (four [12%] of 34; table 5). Rescue epinephrine use was infrequent (two [3%] of 71 in the PPOIT group, four [6%] of 70 in the OIT group, and none in the placebo group; table 5).

Children with sustained unresponsiveness reported a significantly greater improvement in HRQOL between baseline and 12 months after treatment completion than participants with desensitisation alone (adjusted by baseline score $p=0.014$) and those who were allergic (adjusted by baseline score $p<0.0001$; mean change from baseline in FAQLQ-PF score -0.74 [SD 1.25] for participants with sustained unresponsiveness, -0.31 [1.38] for those with desensitisation alone, and -0.20 [1.32] for those with allergy; appendix pp 21, 23). For the sustained unresponsiveness group, improvement was seen across all subscales, with greatest improvement in social and dietary limitations. During the 12-month post-treatment period, participants with sustained unresponsiveness reported significantly fewer peanut reactions and two times less rescue epinephrine use than those with desensitisation alone (appendix p 23). 79 (99%) of 80 participants with sustained unresponsiveness were eating peanut according to their individual preference, with a median amount of 0.6–2 g peanut protein (three to ten peanuts) and median frequency of 1–2 times a week (appendix pp 23–24). By comparison, 41 (93%) of 44 participants with desensitisation alone and six (13%) of 46 participants who were allergic were eating peanut. Among participants with peanut allergy, five had accidental peanut ingestion and one commenced peanut consumption (against the study team's advice) based on an increase in their reaction threshold during the double-blind, placebo-controlled food challenge from baseline

to treatment completion (from 1250 mg to 2500 mg of peanut protein).

Discussion

PPOIT and OIT were similarly effective and both superior to placebo at inducing 8-week sustained unresponsiveness in children aged 1–10 years with peanut allergy. Both interventions provided similar substantial improvement in HRQOL compared with placebo. Children aged 1–5 years had higher rates of sustained unresponsiveness than those aged 6–10 years. Both PPOIT and OIT led to similar reductions in peanut skin prick test wheal size and peanut-specific IgE, as well as increases in peanut-specific IgG₄, with specific IgE changes from baseline maintained until 12 months after treatment completion. These findings suggest sustained modulation of the peanut allergic response rather than transient changes in effector pathways such as mast cell reactivity.^{20,21} Almost all (99%) children who achieved sustained unresponsiveness and ceased treatment were eating peanut *ad libitum* during the 12 months after treatment completion. Children with sustained unresponsiveness had significantly fewer reactions to peanut intake and greater improvement in HRQOL than children with desensitisation alone (without sustained unresponsiveness) in the 12-month post-treatment period. Importantly, despite a higher number of reactions, children with sustained unresponsiveness had significantly improved HRQOL compared with children who were allergic, suggesting that no longer having to avoid peanut and being able to eat peanut as and when one chooses provide greater benefit than continued allergen avoidance despite a higher likelihood of reaction.

The rates of sustained unresponsiveness achieved with both PPOIT and OIT in this study are higher than

in previous studies of peanut OIT (without probiotic), which report sustained unresponsiveness in only around a third of patients.^{9,22,23} The higher rate of sustained unresponsiveness in this trial might relate to lower baseline peanut-specific IgE or the younger age of participants, a higher OIT maintenance dose, and the accelerated dosing schedule. The rapid 16-week dose escalation applied in this study might be more effective at inducing anergy or deletion of peanut-specific Th2 cells.²⁴ The higher sustained unresponsiveness rate of 74% reported in the original proof-of-concept PPOIT-001 trial is likely to be related to a shorter period of elimination before the sustained unresponsiveness challenge.¹² There is currently no consensus on the length of time a patient should be off treatment before assessing for sustained unresponsiveness. Sufficient time should elapse to avoid residual desensitisation effects, yet longer times could result in regression of newly established (unstable) immune changes underpinning the remission state. An earlier readout on sustained unresponsiveness or remission might be appropriate to allow timely initiation of free allergen intake that is needed to consolidate nascent immune changes crucial to remission of allergy, and could lead to higher rates of long-term (durable) sustained unresponsiveness.

An a priori aim of this study was to assess whether addition of probiotic to peanut OIT provided safety benefits. Gastrointestinal adverse events from OIT are frequent and can lead to treatment discontinuation.²⁵ As OIT involves administering an allergen to patients who are allergic, it is not surprising that the majority of children reported at least one reaction during the course of 18 months of therapy. The proportion of participants reporting adverse events does not distinguish between children who have fewer reactions than those with more frequent reactions, whereas the exposure-adjusted incidence rate of adverse events describes the burden of adverse events experienced over the course of treatment. PPOIT was associated with a significantly lower exposure-adjusted incidence of adverse events overall, primarily related to reduced gastrointestinal adverse events. Addition of the probiotic provided greatest benefit to children aged 1–5 years, with a reduced withdrawal rate (5% in the PPOIT group and 14% in the OIT group) and 30–50% reduction in gastrointestinal symptoms, systemic reactions, and moderate and severe adverse events. Notably, two (2%) of 83 patients in the OIT group had biopsy-confirmed eosinophilic oesophagitis, in line with the incidence of eosinophilic oesophagitis (2.7–5.3%) in other OIT studies,^{26–28} whereas there were no cases of treatment-related eosinophilic oesophagitis in the PPOIT group, similar to the previous PPOIT-001 study.¹² These findings are consistent with the known effects of *L. rhamnosus* ATCC 53103 in inhibiting intestinal inflammation and a recent study suggesting a potential effect of probiotics in the treatment of eosinophilic oesophagitis.²⁹

	PPOIT group	OIT group	Placebo group
Participants	71	70	34
Eating peanuts	60/71 (85%)	60/70 (86%)	6/34 (18%)
Reactions to peanuts*	22/71 (31%)	24/70 (34%)	4/34 (12%)
Reporting 1, 2, and ≥3 reactions†			
1	13/71 (18%)	15/70 (21%)	4/34 (12%)
2	4/71 (6%)	2/70 (3%)	0/34 (0%)
≥3	5/71 (7%)	7/70 (10%)	0/34 (0%)
Used rescue epinephrine	2/71 (3%)	4/70 (6%)	0
Number of reactions	58	52	4
Grade 1 (mild)	49/58 (85%)	47/52 (90%)	2/4 (50%)
Grade 2 (moderate)	7/58 (12%)	2/52 (4%)	2/4 (50%)
Grade 3 (severe)	2/58 (3%)	3/52 (6%)	0/4 (0%)
Food Allergy Quality of Life Questionnaire-Parent Form‡			
Participants assessed for change from baseline at treatment completion	70	71	36
Total score§	-0.10 (0.97)	0.05 (0.98)	-0.01 (1.34)
Emotional impact subscore	0.01 (1.02)	0.12 (0.96)	-0.11 (1.42)
Food anxiety subscore	0.05 (1.34)	0.20 (1.54)	0.01 (1.59)
Social and dietary limitations subscore	-0.34 (1.16)	-0.15 (1.11)	0.09 (1.37)
Participants assessed for change from baseline at 12 months after treatment completion	69	69	33
Total score§	-0.60 (1.22)	-0.57 (1.36)	-0.04 (1.34)
Emotional impact subscore	-0.41 (1.17)	-0.32 (1.36)	0.003 (1.32)
Food anxiety subscore	-0.41 (1.51)	-0.51 (1.89)	-0.05 (1.65)
Social and dietary limitations subscore	-0.97 (1.47)	-0.93 (1.50)	-0.07 (1.49)

Data are n/N (%) or mean (SD). FAQLQ-PF=Food Allergy Quality of Life Questionnaire-Parent Form. HRQOL=health-related quality of life. OIT=oral immunotherapy. PPOIT=probiotic and peanut oral immunotherapy. *Overall χ^2 p=0.049, Fisher p=0.043; PPOIT vs oral immunotherapy χ^2 p=0.68, Fisher p=0.81; PPOIT vs placebo χ^2 p=0.033, Fisher p=0.052; oral immunotherapy vs placebo χ^2 p=0.015, Fisher p=0.024. †Overall χ^2 p=0.21, Fisher two-sided p=0.23; no pairwise comparisons were done, as the overall p value is >0.05. ‡The response scale is from 0 (minimal impairment in HRQOL) to 6 (maximal impairment in HRQOL); a reduced score indicates an improvement in the child's HRQOL, as perceived by the caregiver. §The minimal clinically important difference for the total score is 0.45–0.5.

Table 5: Peanut ingestion and reactions in the 12-months post-treatment and mean change in FAQLQ-PF scores from baseline to 12 months after treatment completion, by treatment group

Of note, the preferred term hypersensitivity was assigned to any reaction involving two or more organ systems and the frequencies observed across all groups probably reflect the inclusion of upper airway symptoms (rhinorrhoea and sneezing) within respiratory system adverse events. We observed that rates of rescue epinephrine use aligned with anaphylaxis rates but were lower than hypersensitivity rates, likely reflecting the broad definition of systemic reactions. An unexpected finding was that the exposure-adjusted incidence of hypersensitivity was significantly higher with PPOIT than with OIT among participants aged 6–10 years. It is possible that although addition of the probiotic led to mitigation of gastrointestinal symptoms, allergic reactions overall were not avoided and instead manifested with cutaneous and respiratory symptoms. It remains unclear why this phenomenon would be specific to children aged 6–10 years, but might relate to greater plasticity of both microbiome and immune response patterns in the first years of life, supporting broader effects

of *L. rhamnosus* ATCC 53103 on airway inflammation and systemic reactions beyond the mitigation of localised gastrointestinal symptoms, as previously reported in mouse models of asthma.³⁰

An approach that reduces gastrointestinal adverse events associated with OIT would be especially useful in children aged 1–5 years because early intervention can increase the likelihood of sustained unresponsiveness. As children aged younger than 5 years have limited ability to articulate feeling pain or distress,³¹ a treatment that reduces gastrointestinal adverse events, even to a modest degree, would be beneficial. Studies evaluating the use of adjuvants alongside food OIT to reduce adverse reactions and enhance efficacy are underway (NCT03682770, NCT03881696).³² Addition of a probiotic offers a simple, low-cost approach to reduce adverse events associated with OIT in young children.

The principal objective of a food allergy treatment is to improve patient-important outcomes such as HRQOL, evidence of which was previously scarce.⁸ In this study, both PPOIT and OIT showed substantial and lasting HRQOL improvement compared with placebo, with greatest improvement in social and dietary limitations. Improvement in HRQOL following both treatments was specifically linked to acquisition of sustained unresponsiveness, with limited improvement in children who had desensitisation alone. Few studies have evaluated HRQOL outcomes with peanut OIT, and our own PPOIT-001 trial is the only study that examined long-term HRQOL effects of OIT.¹³ In the PPOIT-001 trial, PPOIT was shown to induce lasting and continuing improvement in parent-reported HRQOL up to 4 years after treatment completion, suggesting that the benefit might be linked to the ability to liberalise the diet or attainment of sustained unresponsiveness.^{6,13} A placebo-controlled study evaluating low-dose peanut OIT found mixed results, with parents reporting no improvement in their child's HRQOL (FAQLQ-PF), whereas children reported significant improvement (FAQLQ Child Form) compared with placebo.³³ Other open-label and cohort-controlled studies have reported HRQOL improvement from baseline following OIT; however, the absence of a placebo comparison precludes confidence in these findings, given that patients enrolled in placebo groups of OIT trials experience significant improvement in HRQOL.^{34–38} The present findings clearly show that both PPOIT and OIT provide substantial improvement in HRQOL compared with placebo (standard care) up to 12 months after treatment completion and, more importantly, establishes that sustained unresponsiveness provides greater HRQOL improvement than desensitisation alone (without sustained unresponsiveness) or remaining allergic.

PPOIT-003 is the first randomised trial that includes a 12-month post-treatment monitoring phase to comprehensively evaluate benefits and risks associated with the different clinical outcomes of sustained unresponsiveness, desensitisation alone, and persistent

allergy. With few exceptions, children followed specific advice regarding peanut intake or avoidance, reflecting real-world clinical care following immunotherapy. Results showed that children with sustained unresponsiveness who were eating peanut *ad libitum* had better outcomes than children who were desensitised without sustained unresponsiveness and continued on a daily treatment dose of one to two peanuts daily; specifically, sustained unresponsiveness provided fewer reactions and significantly improved HRQOL compared with desensitisation alone. Furthermore, despite a higher proportion of children with sustained unresponsiveness reporting reactions in the 12-month post-treatment period compared with children who were allergic, HRQOL was significantly improved compared with children with allergy, indicating that alleviating the lifestyle restrictions associated with peanut avoidance and being able to incorporate peanut in the diet provide meaningful benefit to patients and families, and outweighs concerns about reactions. It is also noteworthy that real-world data showed reactions in 45–50% of children with peanut allergy within a 12-month period,^{39,40} suggesting that sustained unresponsiveness might in fact lead to fewer reactions (26% of participants with sustained unresponsiveness reporting reactions) than living with allergy (45–50% reporting reactions) in the absence of a Hawthorne (placebo) effect. This result reinforces our previous reports of sustained HRQOL improvements in patients treated with PPOIT who achieved sustained unresponsiveness, and the greatest magnitude of improvement in those eating more peanut.^{6,13} These findings together suggest that removing the need for allergen avoidance and the ability to stop maintenance OIT drives HRQOL improvement beyond what is offered from protection against accidental exposure.

Strengths of this study include its randomised multi-centre design, robust criteria for sustained unresponsiveness (double-blind, placebo-controlled food challenge, 4950 mg peanut protein, and 8-week elimination), and a 12-month post-treatment follow-up period. Additionally, the distribution of reaction-eliciting doses in participants closely reflects that of the general population of people with peanut allergy,⁴¹ suggesting that findings can be generalised to the broader population of children aged 1–10 years with peanut allergy. Other trials of peanut immunotherapy have excluded enrolment of less sensitive participants (eliciting dose of 300 mg peanut protein or more), yet these patients also bear the considerable burden and HRQOL impact imposed by a peanut avoidance diet and are therefore in need of a disease-modifying treatment that improves HRQOL. A limitation is that patients with severe cardiovascular anaphylaxis or poorly controlled asthma were excluded. There is currently no consensus on the amount of allergen that should be tolerated or the duration of time off treatment to demonstrate sustained unresponsiveness,

although most published studies have used a standard diagnostic challenge of cumulative 4000–5000 mg and at least 4–12 weeks secondary elimination.^{4,21,22,42} Our study applied a robust measure of 8 weeks sustained unresponsiveness. It was not possible to adjust for frequency or amount of peanut ingestion when comparing reactions with peanut during the post-treatment monitoring phase because these data were collected using ranges (appendix p 24). Although differences in peanut ingestion frequency or amount might have contributed to the lower rate of reactions among participants with sustained unresponsiveness than those with desensitisation alone, these data represent the real-world patient experience associated with each clinical outcome. Moreover, about 95% of participants with sustained unresponsiveness were eating peanuts at least monthly (median frequency 1–2 times per week) and about 80% were eating equal or greater amounts than participants with desensitisation alone, indicating substantial peanut exposure.

In summary, the addition of a probiotic adjuvant to peanut OIT in this study did not improve efficacy of OIT as measured by sustained unresponsiveness, desensitisation, or immunological parameters such as peanut skin prick test, peanut-specific IgE, and peanut-specific IgG₄. However, a probiotic adjuvant might provide a meaningful safety benefit, particularly for children aged 1–5 years, by reducing the burden of gastrointestinal symptoms and systemic reactions. An adequately powered randomised trial comparing PPOIT versus OIT with safety measures as a primary endpoint is required to confirm these findings. Follow-up of participants for 12 months after treatment completion showed that sustained unresponsiveness leads to fewer reactions and greater HRQOL improvement than desensitisation alone, and moreover provided greater HRQOL improvement than persistent allergy.

Contributors

PL led the writing of the manuscript, with major contributions from FO, ACL, ML, SEA, and MLKT. MLKT led the funding application and conceived the trial design with MG, SLP, KJA, and FO. MDO'S, PQ, PL, and ADG contributed to trial design. FO led the statistical analysis at the 12-month post-treatment timepoint with contributions from ML and SEA. Study conduct was supervised by PL, ACL, MG, MDO'S, PQ, SP, CA, JRM, ELS, DT, MRN, SLP, and MLKT. PL and FO had full access to, and verified, the data. All authors reviewed the manuscript, assumed responsibility for accuracy of the data, and agreed with manuscript submission.

PPOIT-003 study group

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Declaration of interests

MDO'S reports having received grants from the Government of Western Australia Department of Health and Channel 7 Telethon Trust and is a director of the Australasian Society of Clinical Immunology and Allergy (ASCI). PQ reports having received grants from DBV Technologies. KJA is currently a member of the Australian Parliament, but all work for this Article was undertaken before April 12, 2019, by which time she had resigned from all paid and honorary appointments listed. SLP reports having received honoraria from

Swisse Biostime and Personal Lifestyle Medicine Institute. ADG reports having received consultant fees from Aimmune Therapeutics, DBV Technologies, and Nestle (research grant and advisory panel). MLKT declares consultant fees from Pfizer and Abbott Nutrition; inventorship on patents covering PPOIT; employee and scientific founder of, and holds share interest and options in, Prota Therapeutics; membership of the Medical Advisory Board of Anaphylaxis & Anaphylaxis Australia and past membership of the Board of Directors of the World Allergy Organization (WAO, ended 2019); membership of expert committees of the American Academy of Allergy Asthma and Immunology, Asia Pacific Association of Allergy Asthma and Clinical Immunology, Australasian Society of Clinical Immunology and Allergy, WHO, and past membership of the International Union of Immunological Societies (ended 2019). All other authors declare no competing interests.

Data sharing

The latest protocol version and statistical analysis plan are provided in the appendix (pp 26–126). Requests for any deidentified participant data, with justification and signed confidentiality agreement, can be sent to MLKT.

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References

- Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011; **128**: e9–17.
- Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J Allergy Clin Immunol* 2011; **127**: 668–76.
- Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. *Allergy* 2010; **65**: 933–45.
- Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. *J Allergy Clin Immunol* 2018; **141**: 1–9.
- Tang MLK, Lozinsky AC, Loke P. Peanut oral immunotherapy: state of the art. *Immunol Allergy Clin North Am* 2020; **40**: 97–110.
- Galvin AD, Lloyd M, Hsiao K-C, et al. Long-term benefit of probiotic peanut oral immunotherapy on quality of life in a randomized trial. *J Allergy Clin Immunol Pract* 2021; **9**: 4493–95.
- Hsiao KC, Ponsonby AL, Axelrad C, et al. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomised, double-blind, placebo-controlled trial. *Lancet Child Adolesc Health* 2017; **1**: 97–105.
- Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *Lancet* 2019; **393**: 2222–32.
- Nurmatov U, Dhimi S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017; **72**: 1133–47.
- Hsiao KC, Tang MLK. Novel treatments for established food allergies. *Curr Pediatr Rep* 2016; **4**: 178–85.
- Virkud YV, Wang J, Shreffler WG. Enhancing the safety and efficacy of food allergy immunotherapy: a review of adjunctive therapies. *Clin Rev Allergy Immunol* 2018; **55**: 172–89.

- 12 Tang ML, Ponsonby AL, Orsini F, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015; **135**: 737–44.
- 13 Dunn Galvin A, McMahon S, Ponsonby AL, Hsiao KC, Tang MLK. The longitudinal impact of probiotic and peanut oral immunotherapy on health-related quality of life. *Allergy* 2018; **73**: 560–68.
- 14 Chebar Lozinsky A, Loke P, Orsini F, et al. Study protocol of a multicentre, randomised, controlled trial evaluating the effectiveness of probiotic and peanut oral immunotherapy (PPOIT) in inducing desensitisation or tolerance in children with peanut allergy compared with oral immunotherapy (OIT) alone and with placebo (the PPOIT-003 study). *BMJ Open* 2020; **10**: e035871.
- 15 Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology–European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012; **130**: 1260–74.
- 16 DunnGalvin A, de BlokFlokstra BM, Burks AW, Dubois AE, Hourihane JO. Food allergy QoL questionnaire for children aged 0–12 years: content, construct, and cross-cultural validity. *Clin Exp Allergy* 2008; **38**: 977–86.
- 17 DunnGalvin A, Cullinan C, Daly DA, et al. Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire—Parent Form in children 0–12 years following positive and negative food challenges. *Clin Exp Allergy* 2010; **40**: 476–85.
- 18 Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *Ann Emerg Med* 2006; **47**: 373–80.
- 19 Muraro A, Dubois AE, DunnGalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. *Allergy* 2014; **69**: 845–53.
- 20 Narisety SD, Frischmeyer-Guerrero PA, Keet CA, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015; **135**: 1275–82.
- 21 Vickery BP, Scurlock AM, Kulis M, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014; **133**: 468–75.
- 22 Chinthrajah RS, Purington N, Andorf S, et al. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2019; **394**: 1437–49.
- 23 Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol* 2014; **133**: 500–10.
- 24 Bedoret D, Singh AK, Shaw V, et al. Changes in antigen-specific T-cell number and function during oral desensitization in cow's milk allergy enabled with omalizumab. *Mucosal Immunol* 2012; **5**: 267–76.
- 25 Nicolaides RE, Parrish CP, Bird JA. Food allergy immunotherapy with adjuvants. *Immunol Allergy Clin North Am* 2020; **40**: 149–73.
- 26 Echeverría-Zudaire LA, Fernández-Fernández S, Rayo-Fernández A, Muñoz-Archidona C, Checa-Rodríguez R. Primary eosinophilic gastrointestinal disorders in children who have received food oral immunotherapy. *Allergol Immunopathol* 2016; **44**: 531–36.
- 27 Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol* 2014; **113**: 624–29.
- 28 Petroni D, Spergel JM. Eosinophilic esophagitis and symptoms possibly related to eosinophilic esophagitis in oral immunotherapy. *Ann Allergy Asthma Immunol* 2018; **120**: 237–40.e4.
- 29 Mennini M, Tambucci R, Riccardi C, et al. Eosinophilic esophagitis and microbiota: state of the art. *Front Immunol* 2021; **12**: 595762.
- 30 Wu CT, Chen PJ, Lee YT, Ko JL, Lue KH. Effects of immunomodulatory supplementation with *Lactobacillus rhamnosus* on airway inflammation in a mouse asthma model. *J Microbiol Immunol Infect* 2016; **49**: 625–35.
- 31 Tottenham N. The brain's emotional development. *Cerebrum* 2017; **2017**: cer-08–17.
- 32 Loh W, Tang M. Adjuvant therapies in food immunotherapy. *Immunol Allergy Clin North Am* 2018; **38**: 89–101.
- 33 Blumchen K, Trendelenburg V, Ahrens F, et al. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol Pract* 2019; **7**: 479–91.
- 34 Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014; **383**: 1297–304.
- 35 Otani IM, Bégin P, Kearney C, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. *Allergy Asthma Clin Immunol* 2014; **10**: 25.
- 36 Epstein-Rigbi N, Goldberg MR, Levy MB, Nachshon L, Elizur A. Quality of life of food-allergic patients before, during and after oral immunotherapy. *J Allergy Clin Immunol Pract* 2019; **7**: 429–36.e2.
- 37 Reier-Nilsen T, Carlsen KCL, Michelsen MM, et al. Parent and child perception of quality of life in a randomized controlled peanut oral immunotherapy trial. *Pediatr Allergy Immunol* 2019; **30**: 638–45.
- 38 Fernandez-Rivas M, Vereda A, Vickery BP, et al. Open-label follow-on study evaluating the efficacy, safety, and quality of life with extended daily oral immunotherapy in children with peanut allergy. *Allergy* 2021; published online July 28. <https://doi.org/10.1111/all.15027>.
- 39 Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998; **102**: e6.
- 40 Wang Y, Peters RL, Perrett KP, et al. Community-based adverse food reactions and anaphylaxis in children with IgE-mediated food allergy at age 6 years: a population-based study. *J Allergy Clin Immunol Pract* 2020; **8**: 3515–24.
- 41 Houben GF, Baumert JL, Blom WM, et al. Full range of population eliciting dose values for 14 priority allergenic foods and recommendations for use in risk characterization. *Food Chem Toxicol* 2020; **146**: 111831.
- 42 Vickery BP, Berglund JP, Burk CM, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. *J Allergy Clin Immunol* 2017; **139**: 173–81.