

Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety



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Summary

Background Oral immunotherapy is an emerging experimental treatment for peanut allergy, but its benefits and harms are unclear. We systematically reviewed the efficacy and safety of oral immunotherapy versus allergen avoidance or placebo (no oral immunotherapy) for peanut allergy.

Methods In the Peanut Allergen immunotherapy, Clarifying the Evidence (PACE) systematic review and meta-analysis, we searched MEDLINE, EMBASE, Cochrane Controlled Register of Trials, Latin American & Caribbean Health Sciences Literature, China National Knowledge Infrastructure, WHO's Clinical Trials Registry Platform, US Food and Drug Administration, and European Medicines Agency databases from inception to Dec 6, 2018, for randomised controlled trials comparing oral immunotherapy versus no oral immunotherapy for peanut allergy, without language restrictions. We screened studies, extracted data, and assessed risk of bias independently in duplicate. Main outcomes included anaphylaxis, allergic or adverse reactions, epinephrine use, and quality of life, meta-analysed by random effects. We assessed certainty (quality) of evidence by the GRADE approach. This study is registered with PROSPERO, number CRD42019117930.

Results 12 trials (n=1041; median age across trials 8·7 years [IQR 5·9–11·2]) showed that oral immunotherapy versus no oral immunotherapy increased anaphylaxis risk (risk ratio [RR] 3·12 [95% CI 1·76–5·55], $P=0\%$, risk difference [RD] 15·1%, high-certainty), anaphylaxis frequency (incidence rate ratio [IRR] 2·72 [1·57–4·72], $P=0\%$, RD 12·2%, high-certainty), and epinephrine use (RR 2·21 [1·27–3·83], $P=0\%$, RD 4·5%, high-certainty) similarly during build-up and maintenance ($p_{\text{interaction}}=0\cdot92$). Oral immunotherapy increased serious adverse events (RR 1·92 [1·00–3·66], $P=0\%$, RD 5·7%, moderate-certainty), and non-anaphylactic reactions (vomiting: RR 1·79 [95%CI 1·35–2·38], $P=0\%$, high-certainty; angioedema: 2·25 [1·13–4·47], $P=0\%$, high-certainty; upper tract respiratory reactions: 1·36 [1·02–1·81], $P=0\%$, moderate-certainty; lower tract respiratory reactions: 1·55 [0·96–2·50], $P=28\%$, moderate-certainty). Passing a supervised challenge, a surrogate for preventing out-of-clinic reactions, was more likely with oral immunotherapy (RR 12·42 [95% CI 6·82–22·61], $P=0\%$, RD 36·5%, high-certainty). Quality of life was not different between groups (combined parents and self report RR 1·21 [0·87–1·69], $P=0\%$, RD 0·03%, low-certainty). Findings were robust to IRR, trial sequential, subgroup, and sensitivity analyses.

Interpretation In patients with peanut allergy, high-certainty evidence shows that available peanut oral immunotherapy regimens considerably increase allergic and anaphylactic reactions over avoidance or placebo, despite effectively inducing desensitisation. Safer peanut allergy treatment approaches and rigorous randomised controlled trials that evaluate patient-important outcomes are needed.

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Introduction

Food allergy is a growing global problem.^{1,2} In Europe and North America, more than 6 million people are affected, including up to 8% of children and 2–3% of adults.^{1,3,4} Although allergy to milk and egg are commonly outgrown by school-age (5–10 years), allergies such as to peanut are lifelong in most cases (80–85%).⁵ The standard of care is allergen avoidance and rescue medication for allergic reactions or anaphylaxis, an acute systemic and potentially life-threatening allergic reaction.^{2,3,6} Without any other treatment options, there is a growing public, medical, and commercial interest in the therapeutic potential of oral immunotherapy for food allergies.⁷

Allergen immunotherapy was first established in 1911 by Noon and Freeman^{8,9} who used grass pollen extracts to treat hay fever. It involves repeated exposure over time to incrementally increasing doses of the allergen to which the patient is allergic. The principal aim of immunotherapy is to reduce disease-related allergic reactions. For inhalant allergies, this reduction entails less nasal congestion and rhinorrhoea in allergic rhinoconjunctivitis, or fewer exacerbations in asthma.¹⁰ Randomised-controlled trials (RCTs) and meta-analyses support the safety and efficacy of sublingual and subcutaneous immunotherapy for these respiratory allergic conditions.¹¹ In contrast, narrative reviews, observational studies, and a historical lack of randomised trials^{12,13} drive the debate on whether oral

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Research in context

Evidence before this study

Peanut allergy affects millions of people around the world. It is a rising global problem, lifelong in most cases, and associated with potentially life-threatening allergic reactions and anaphylaxis. There is growing interest in oral immunotherapy, an incremental controlled exposure to peanut allergen to reduce allergic reactions by desensitisation. However, the health benefits and harms of this therapy are not clear.

We searched MEDLINE, Embase, Cochrane Controlled Register of Trials, Latin American & Caribbean Health Sciences Literature, China National Knowledge Infrastructure, WHO's International Clinical Trials Registry Platform, US Food and Drug Administration Drugs, and European Medicines Agency databases for randomised controlled trials studies comparing oral immunotherapy versus no oral immunotherapy for the treatment of peanut allergy, without language restrictions. Three previous meta-analyses are available, each including one to three studies enrolling a total of 28–185 participants, being up to date only to 2016, and none has examined comprehensively both benefits and harms.

Added value of this study

This systematic review and meta-analysis of more than 1000 patients (12 studies) with peanut allergy followed for up to 5.8 years shows with high-certainty evidence that, compared with allergen avoidance or placebo (no oral immunotherapy), current oral immunotherapy regimens achieve immunological desensitisation, but also result in a large increase in anaphylaxis and other allergic reactions, rather than preventing them as intended. To the best of our knowledge, this study is the first comprehensive synthesis showing the disconnect between desensitisation and patient-centred outcomes of available oral immunotherapy for peanut allergy. With high-certainty and moderate-certainty evidence, peanut oral immunotherapy compared with no oral immunotherapy increased the risk and frequency of anaphylaxis, epinephrine use, serious adverse

events (as defined by the US Food and Drug Administration), and allergic reactions involving the gastrointestinal tract (vomiting, abdominal pain, mouth itching), skin and mucous membranes (hives or urticaria and swelling or angioedema), nose (congestion or rhinitis), and lungs (wheeze or asthma) to a similar extent during build-up and maintenance. These data favour allergen avoidance over current forms of oral immunotherapy if the desired outcome is less peanut-induced anaphylaxis and allergic reactions. Hence, the safety profile of these regimens might be a substantial barrier to widespread adoption by patients with peanut allergies, their caregivers, and health-care providers.

Implications of all the available evidence

These findings have several potential implications for multiple stakeholders. For patients, health-care providers, and policy makers, safer peanut allergy treatments that are rigorously tested in randomised-controlled trials are needed before peanut oral immunotherapy or other approaches can be used routinely. In this regard, the values and preferences of patients regarding their desired outcomes and acceptable trade-offs with peanut allergy treatments in general need clarification. For researchers, these data show the disconnect between passing an in-clinic supervised food challenge (a provocation test) and out-of-clinic allergic and anaphylactic reactions to everyday exposures. As recommended by the US National Institute of Allergy and Infectious Diseases, The Grading of Recommendations Assessment, Development and Evaluation approach, and already established for respiratory allergies, future trials evaluating the efficacy and safety of food allergy treatments should focus on the risk and frequency of anaphylaxis and allergic reactions over time to real-world exposures rather than solely patient responses to provocation testing (supervised food challenges). In view of peanut allergy as a model for other food allergies, their global burden, and the unmet need for therapies, these findings have immediate and important implications.

immunotherapy for food allergy is ready for routine and widespread clinical use, or whether it should remain an investigational therapy (ie, more research is needed).^{14–16} Oral immunotherapy for peanut allergy has been the subject of intense research, serving as a model for other food allergies.

Peanut allergy affects 2% of children and 1% of adults in high-income countries^{1,3,4} and is a leading cause of food-related allergic reactions, anaphylaxis, and deaths.¹⁷ Peanut oral immunotherapy aims to desensitise patients to decrease the risk of allergic reactions (12% per year) and anaphylaxis (7% per year).^{18,19} The often unpredictable and potentially life-threatening nature of food allergic reactions is associated with substantial anxiety and impaired quality of life in patients and their caregivers.^{20–22}

Although multiple RCTs on peanut oral immunotherapy have been completed,^{23–28} eight in 2018 (unpublished

NCT00597675, NCT00815035, NCT01324401),^{29–35} no rigorous systematic synthesis of all relevant data is available to date, to our knowledge. The most recent Cochrane review³⁶ was published in 2012 and included a single study; the same group's meta-analysis in 2017 included three studies (n=185).¹³ Thus, the principal aim of this study was to systematically review and meta-analyse the health benefits and harms of oral immunotherapy compared with allergen avoidance or placebo (no oral immunotherapy) for the treatment of peanut allergy.

Methods

Search strategy and selection criteria

We undertook and reported this systematic review and meta-analysis in accordance with PRISMA; Grading of Recommendations, Assessment, Development and Evaluation (GRADE); and Cochrane guidelines.^{37–40} This

study is registered with PROSPERO, number CRD42019117930.

From inception to Dec 6, 2018, we searched MEDLINE, EMBASE, Cochrane Controlled Register of Trials, Latin American & Caribbean Health Sciences Literature, China National Knowledge Infrastructure, WHO's Clinical Trials Registry Platform (ICTRP), US Food and Drug Administration (FDA), and European Medicines Agency databases for published and unpublished RCTs comparing oral immunotherapy with placebo or allergen avoidance for the treatment of peanut allergy (a full list of the search terms is available in the appendix). We did not use any language restrictions and translated non-English studies. We included a study comparing oral immunotherapy versus sublingual immunotherapy as described in further detail in the appendix, because we hypothesised that the incidence of anaphylactic and non-gastrointestinal allergic reactions in the sublingual immunotherapy cohort would be comparable to placebo.¹¹ For commercial oral immunotherapy products, we checked company websites and presentations for additional data. We checked all reference lists and articles citing included studies and recent reviews^{13,14,41,42} for any additional relevant studies.

Data collection

We screened titles and abstracts, reviewed full-texts, extracted data, and assessed risk of bias independently in duplicate (DKC, SF), using standardised pre-piloted forms (Covidence; Veritas Health Innovation, Melbourne, VIC, Australia). We resolved disagreements by consensus and, if necessary, discussion with a third reviewer (JLB). We collected characteristics on trial, setting, eligibility criteria, population studied, intervention, comparator, and outcomes.

Outcomes

We prioritised outcomes that were patient-important events of food allergy outside a clinic provocation test setting,^{20–22} consistent with the established approach for respiratory allergy immunotherapy,^{43,44} and as advocated by the US FDA as highly informative of food allergy treatment efficacy and safety.⁴⁵ A surrogate outcome for treatment efficacy is the proportion of patients who pass a supervised graded in-clinic oral food challenge (a provocation test); passing was defined per each study. Because we hypothesised that peanut immunotherapy would decrease food allergic reactions, more direct measures were included: peanut-induced anaphylaxis (accepted if reported by the study and otherwise defined by The National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network 2005–06 criteria⁶ as 2 or more organ system involvement after possible allergen exposure, or isolated hypotension with known allergen exposure), peanut-induced allergic reactions, epinephrine use, and quality of life. We stratified allergic reactions by organ system involvement and their severity (serious adverse events defined by US FDA as

causing death, a life-threatening state, hospitalisation, disability, congenital abnormality, or an important medical event such as an urgent intervention to prevent the other outcomes);⁴⁶ and if they caused treatment discontinuation.

Data analysis

We analysed outcomes by intention-to-treat (ITT).⁴⁷ In cases of multiple reports of the same trial, we used all relevant data and analysed it as a single study. We pooled summary measures using DerSimonian and Laird random-effects, estimating heterogeneity using the Mantel-Haenszel model. For dichotomous outcomes, we combined data using risk ratio (RR) and if the outcome could happen more than once in the same patient, incidence rate ratio (IRR). We combined continuous outcomes across studies using the mean difference, or the standardised mean difference if the outcomes were measured with different scales.

We used the Cochrane risk of bias tool for randomised trials⁴⁸ with modified responses as “Definitely yes”, “Probably yes”, “Probably no”, or “Definitely no”,^{49,50} to examine risk of bias per outcome. We classified studies as high risk of bias if at least one domain was high risk. We evaluated the certainty (quality) of evidence using the GRADE approach.⁵¹ GRADE defines high certainty evidence when confidence that the true effect lies close to that of the estimate of the effect is very high; moderate certainty evidence when confidence in the effect estimate is moderate (ie, the true effect is likely to be close to the estimate, but there is a possibility that it is substantially different); low certainty evidence when the confidence in the effect estimate is limited (ie, the true effect might be substantially different from the estimate of the effect); and very low certainty when confidence in the effect estimate is very low (ie, the true effect is likely to be substantially different from the estimate of effect).

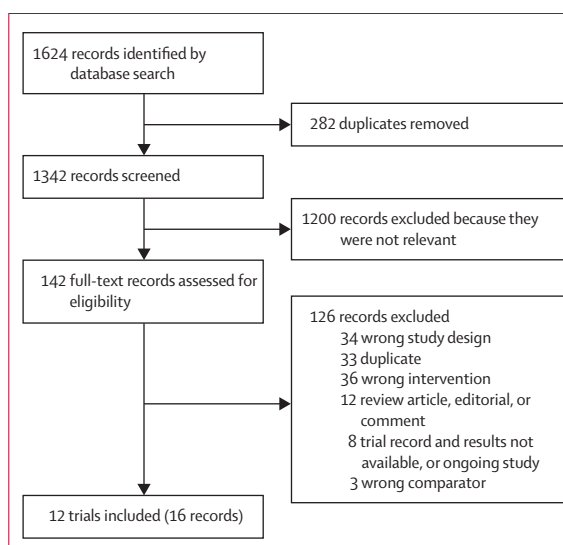


Figure 1: Study selection

	Country		Setting		Intervention and comparator assignments						Restrictions			Participants	
	Country	Entry OFC	Median follow-up, years	OIT group	Proprietary	No OIT group	Starting dose (mg)	Target dose (mg)	Time to achieve maintenance (weeks), median	Strictly avoid peanut?	Other restrictions	Sample size, n	Median age, years	Women, n (%)	
Varshney et al (2011) ³³	USA	No	1.00	OIT	No	Placebo	0.1	4000	50	Yes	No dose if fever, infection, or otherwise feeling ill; dose on full stomach	28	5.75	10 (36%)	
STOP II (2014) ²⁴	UK	Yes	0.50	OIT	Yes	Avoidance	2	800	26	No	Dose with food; no exercise for 2 h after dose	99	12.4	29 (29%)	
PPOIT (2015) ³⁵⁻²⁷	Australia	No	5.80	OIT and probiotic	Yes	Placebo	0.1	2000	36	Yes	-	62	5.95	25 (40%)	
Naniset et al (2015) ³⁸	USA	Yes	1.33	OIT	No	Sublingual immunotherapy	0.1	2000	16	Yes	No exercise for 2 h after dose; call for individualised instructions during fever, and either full dose or skip dose	21	11.1	10 (48%)	
ARCO01 (2017) ³⁹	USA	Yes	0.42	OIT	Yes	Placebo	0.5	300	22	Yes	No exercising, or taking hot showers or baths within 4 h; dose reduction during menstrual period	55	7.5	19 (35%)	
PMIT (NCT00597675; 2017)	USA	No	1.00	OIT	No	Placebo	2	4000	..	No	..	10	5.4	3 (30%)	
PnOIT3 (NCT00815035; 2017)	USA	No	0.85	OIT	No	Placebo	..	4000	..	No	..	16	5	10 (63%)	
PNOIT (NCT01324401; 2018)	USA	No	1.08	OIT	No	Avoidance	..	4000	44	No	..	30	9	12 (40%)	
Blumchen et al (2018) ³⁹	Germany	Yes	1.33	OIT	No	Placebo	0.5	125-250	56	Yes	No exercise activity for 2 h	62	6.8	24 (39%)	
PALISADE (2018) ^{39,33,34}	North America and Europe	Yes	1.00	OIT	Yes	Placebo	0.5	300	26	Yes	No exercise, or showering or bathing within 3 h; dose reduction during menstrual period; no dose within 2 h of bedtime; no dose without food; must dose daily	551	11.3	236 (43%)	
PITA (2018) ³⁵	France	Yes	0.46	OIT	No	Placebo	2	400	24	Yes	No sports for 2 h after dose nor any condition of stress likely to be induced either by effort or sun exposure	30	14.75	8 (27%)	
TAKE-AWAY (2018) ^{33,32}	Norway	Yes	1.07	OIT	No	Avoidance	1	5000	56	Yes	No exercise within 2 h after dose; monitor during menses; no dose if ongoing infections, asthma exacerbations, excessive tiredness, or vaccinations	77	9.5	33 (43%)	

OFC=oral food challenge. OIT=oral immunotherapy.

Table 1: Characteristics of included oral immunotherapy studies

	Sample size	Risk ratio* (95% CI)	Anticipated absolute effects (95% CI) per 1000 individuals			Grades of evidence	Main findings†‡§
			No OIT	OIT	Risk difference		
Anaphylaxis	9 RCTs; 891 participants	3.12 (1.76–5.55)	71¶	222 (125–394)	151 (54–323)	High	Peanut OIT results in large increase in anaphylaxis; NNT _H 7 (3–19); IRR 2.72 (1.57–4.72)
Epinephrine use‡	9 RCTs; 984 participants	2.21 (1.27–3.83)	37	82 (47 to 142)	45 (10–105)	High	Peanut OIT results in large increase in epinephrine use; NNT _H 22 (10–100); IRR 2.87 (1.70–4.85)
Serious adverse events	12 RCTs; 1041 participants	1.92 (1.00–3.66)	62	119 (62–227)	57 (0–165)	Moderate**	Peanut OIT probably increases serious adverse events (death, life threatening, disability, or requiring urgent medical intervention or hospitalisation to prevent these events); NNT _H 18 (6–5376)
Vomiting, representative of gastrointestinal reactions††	6 RCTs; 755 participants	1.79 (1.35–2.38)	186	334 (252–444)	147 (65 to 257 more)	High	Peanut OIT results in large increase in vomiting frequency; NNT _H 6 (4–14); IRR 2.11 (1.54–2.89)
Angioedema, representative of mucocutaneous reactions‡‡	5 RCTs; 694 participants	2.25 (1.13–4.47)	39	88 (44–174)	49 (5 to 135 more)	High§§	Peanut OIT increases angioedema; NNT _H 20 (7–200); IRR 2.51 (1.79–3.51)
Nasal congestion or blockage, representative of respiratory reactions§§	6 RCTs; 724 participants	1.36 (1.02–1.81)	178	241 (181–321)	64 (4 to 144 more)	Moderate¶¶	Peanut OIT probably increases nasal congestion or blockage (rhinitis); NNT _H 16 (7–250); IRR 1.48 (1.04–2.10)
Surrogate for exposure to peanut outside of clinic without a reaction: passing a supervised food challenge in-clinic	9 RCTs; 917 participants	12.42 (6.82–22.61)	32	397 (218–723)	365 (186 to 691 more)	High	Peanut OIT results in large increase in completing a supervised oral food challenge without an allergic reaction, but this does not translate into less reactions outside of clinic; for every gram increase in total cumulative challenge dose, the chance of passing decreases by 26%; NNT 3 (1–5)

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). IRR=incidence rate ratio. MID=minimally important difference. NNT=number needed to treat. NNT_H=number needed to treat to harm. OIT=oral immunotherapy. RCT=randomised controlled trial. *Similar findings for all outcomes were found when accounting for if patients could have more than one event using IRR analysis. †Three events of eosinophilic esophagitis occurred across five trials, all in the oral immunotherapy group, precluding an accurate estimate of the relative and absolute effect between groups on the risk of eosinophilic esophagitis. ‡Likelihood of improving quality of life by the MID by parent report (risk ratio [RR] to achieve MID 1.14 [0.66–1.99], risk difference [RD] 0.01 [–0.16 to 0.17]), self-report (RR to achieve MID 1.20 [0.80–1.81]; RD 0.09 [–0.10 to 0.27]), or combined (RR 1.21 [0.87–1.69], RD 0.03 [–0.12 to 0.18]); weighted mean quality of life scores between oral immunotherapy and no oral immunotherapy groups by either parent report (weighted mean difference in change from baseline –0.23 [–0.62 to 0.16]) or child self-report (standardised mean difference in change from baseline 0.23 [–0.15 to 0.61]). §Similar findings were obtained when analysed by incidence rate. ¶Vander and colleagues¹⁸ leak observational study estimates, which are similar to those of Cherkouai and colleagues.¹⁹ ||Similar findings for reactions severe enough to cause study discontinuation. **Rated down for imprecision because of wide CIs. ††Similar findings for abdominal pain, mouth itching, and any allergic or adverse reaction. ‡‡Similar findings for urticaria. §§We did not rate down for imprecision despite the lower limit of the risk difference approaching no effect because of the large number of events and sufficient information size in trial sequential analysis. ¶¶Similar findings for asthma attack or wheeze. |||A substantial proportion of trials and their contributing information were either unblinded or terminated early for benefit specifically with this oral food challenge outcome; although the true effect estimate might be smaller than the presented estimate, sensitivity analyses that adjusted for risk of bias and early termination yielded similar results to the main analysis; we did not rate down the evidence given the very strong association.

Table 2: Summary of findings in studies comparing oral immunotherapy with no oral immunotherapy (avoidance or placebo) for peanut allergy

Prespecified subgroup analyses for the main outcomes included analysis by median age, oral immunotherapy formulation (proprietary or not), confirmation of peanut allergy at study entry by food challenge, duration of oral immunotherapy, starting and target dose, and sublingual immunotherapy versus no oral immunotherapy. We also evaluated outcomes according to which of the two phases—build up or maintenance—allergic reactions occurred. Post-hoc analyses were by assignment of the control groups to either placebo or avoidance, and by entry and exit challenge threshold.

Sensitivity analyses to test the robustness of the findings included worst-case or various plausible scenarios for missing participants;⁵² disregarding excluded participants or missing data (ie, available case analysis); fixed-effect meta-analysis; excluding unpublished trials; adjusting potentially overestimated outcomes for trials terminated early by reducing their effect size;⁵³ restricting anaphylaxis analyses to only those with moderate-to-severe severity; excluding sublingual immunotherapy from the control arm; and using the more conservative Knapp-Hartung-Sidik-Jonkman random effects meta-analytic method,⁵⁴ or potentially more appropriate empirical continuity

correction.⁵⁵ We used trial sequential analysis to account for multiple testing, and objectively assessed imprecision by examining for sufficient data to avoid type 1 (false-positive) and type 2 (false-negative) errors.

We tested between-study heterogeneity using χ^2 (threshold $p=0.10$) and quantified it using I^2 . We assessed publication bias by inspecting funnel plots, statistically by the Harbord modification of Egger test.⁵⁶ We also assessed both qualitatively applying GRADE guidance.^{57,58} We did all statistical analyses using STATA version 14.3. We used GRADEpro GDT to create the summary of findings table.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our database searches yielded 1624 records. After removal of duplicates, we screened 1342 publications, reviewed 142 in full-text, and included 16 reports of 12 RCTs

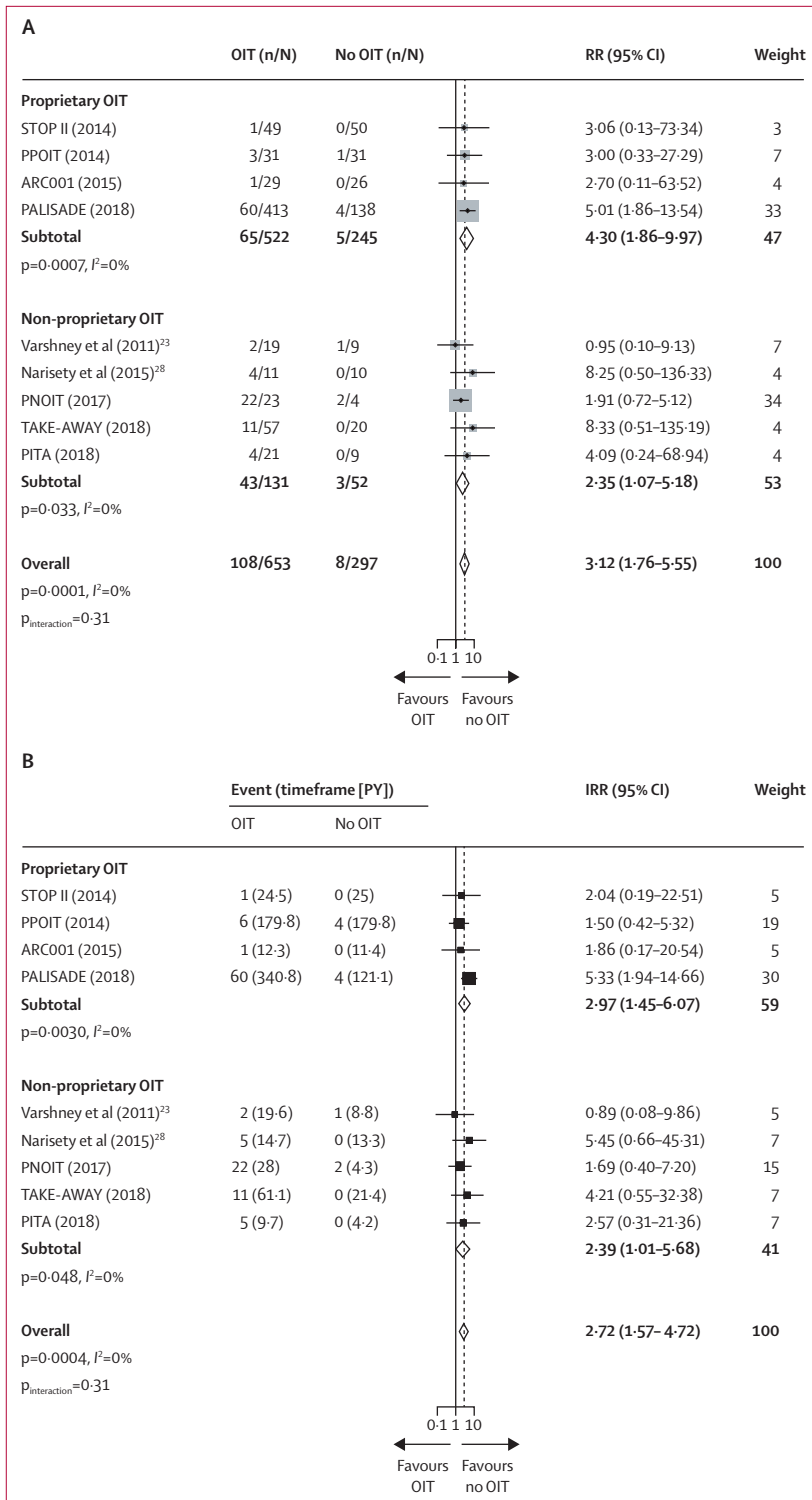


Figure 2: Anaphylaxis events with peanut oral immunotherapy versus no oral immunotherapy
 (A) Anaphylaxis risk. (B) Anaphylaxis frequency. IRR=incidence rate ratio. OIT=oral immunotherapy. PY=patient-years.
 RR=risk ratio.

(nine published;²³⁻³⁵ three unpublished [NCT00597675, NCT00815035, and NCT01324401] for meta-analysis (figure 1).

The characteristics of each trial included in this study are summarised in table 1 and are described narratively in the appendix. Trial eligibility criteria is tabulated in the appendix. Briefly, studies enrolled 1041 participants (median number of participants across trials 43 [IQR 26-66]; median of median age across trials 8.7 years [5.9-11.2]; 39% women, 61% men) undergoing peanut oral immunotherapy (four trials with proprietary products and eight with non-proprietary products) versus no oral immunotherapy (eight placebo trials, three avoidance trials, and one sublingual immunotherapy trial) for a median follow up of 1.0 year (IQR 0.8-1.4; overall 1027 patient-years;). Peanut oral immunotherapy involved defatted lightly roasted peanut flour in ten trials (for the remaining trials, peanut paste, extract, or ground and defatted peanut were used) and, across all trials, the median starting dose was 0.5 mg (IQR 0.2-1.75) daily, with a median target dose of 2000 mg (375-4000), and a median time to achieve the maintenance phase of 31 weeks (25-51). In all trials, both groups were instructed to strictly avoid peanut consumption other than that provided in the study. Most studies also had restrictions or needed to modify how the study medications were taken to prevent an allergic reaction to a previously tolerated dose, including: no exertion or exercise within 2-4 h; taking medication after food; no dosing within 2 h of waking, going to sleep, or being tired; lower dose during menstruation; no showering or bathing within 3-4 h; no or lower dose if fever, infection, or otherwise feeling ill; and no dose if uncontrolled asthma symptoms.

Study characteristics that did not modify the findings below included threshold of oral food challenge at study entry, control cohort assignment, median participant age, and oral immunotherapy regimen (proprietary formulation or not, starting dose, target dose, and treatment duration; appendix). Overall, the risk of bias for all outcomes across the included trials was low (appendix). We had some suspicion of reporting bias for urticaria with oral immunotherapy versus no oral immunotherapy (appendix); one pharmaceutical company-run trial³³ did not fully report outcome data for their adult participants. We did not detect publication bias for any outcome (appendix). Summary of these findings with absolute risks for all outcomes is available interactive online.

Nine trials (n=950) reported anaphylaxis data (NCT01324401).^{23-25,27-29,31,33,35} Oral immunotherapy increased the risk of anaphylaxis compared with no oral immunotherapy (table 2 and figure 2). Oral immunotherapy also increased the incidence of anaphylactic reactions over 968 person-years (table 2 and figure 2). This effect was seen irrespective of entry challenge threshold, starting or target dose, oral immunotherapy duration, age, control group assignment, or whether the formulation was a

proprietary product or not (figure 3). The increased rate of anaphylaxis was similar irrespective of phase of immunotherapy (figure 3). Compared with trials that confirmed peanut allergy diagnosis at study entry by oral food challenge, trials that did not had a 2·68-times lower risk of anaphylaxis with oral immunotherapy versus no oral immunotherapy (moderate credibility; figure 3).

Nine trials (n=984) reported epinephrine use.^{23–25,27–29,31,33,35} Oral immunotherapy compared with no oral immunotherapy increased the risk for epinephrine use (figure 3) and its frequency over 936 person-years. We found no subgroup effects (appendix).

Oral immunotherapy increased serious adverse events compared with no oral immunotherapy (figure 4; NCT00597675, NCT00815035, and NCT01324401).^{23–25,27–31,33,35} No participant died in any trial. The risk of allergic or adverse reactions severe enough to cause study discontinuation was higher with oral immunotherapy versus no oral immunotherapy (figure 4). Trials not requiring an entry challenge had a 6·31-times lower risk for adverse reactions causing study discontinuation compared with those that did (moderate credibility; appendix). Trials with proprietary formulations were 4·96-times more likely to cause reactions that resulted in participant drop-out (low credibility; appendix).

In ten trials (n=919, 941 person-years; NCT00597675, NCT00815035, and NCT01324401),^{23,25,27,29–31,33,34} oral immunotherapy increased the RR and IRR of any allergic or adverse reaction compared with no oral immunotherapy (figure 4). The high *I*² was probably falsely inflated by the narrow CIs and high frequency of events.^{58,59} Findings for specific allergic or adverse reactions are summarised by organ system involvement (vomiting, representative of gastrointestinal reactions; angioedema, indicative of mucocutaneous; and respiratory reactions) in figure 4 and table 2. Across organ systems, oral immunotherapy increased the risk and frequency of allergic and adverse reactions (appendix).

Three events of eosinophilic esophagitis were diagnosed across five trials (n=719),^{28–30,33,35} all in the oral immunotherapy groups, but too few to determine with confidence the magnitude, variability, and direction of treatment effect.

A surrogate outcome for preventing out-of-clinic allergic reactions and anaphylaxis, passing a supervised graded in-clinic oral challenge, was more likely in the oral immunotherapy group than in the no oral immunotherapy group (9 trials [n=858 917], RR 12·42 [95%CI 6·82–22·61], *I*²=0%, *p*<0·0001, table 2; NCT01324401).^{23–25,29,30,33,35} For every gram increase in oral food challenge dose, the RR of passing a challenge decreased by 26% (slope 0·74 [0·52–1·06], *p*_{interaction}=0·05, moderate credibility; appendix).

Two placebo-controlled studies^{26,30} assessed participant quality of life by parent proxy using Food Allergy Quality of Life Questionnaire-Parent Form (FAQLQ-PF).^{20,60} Another two studies^{30,32} used self-reported FAQLQ-CF

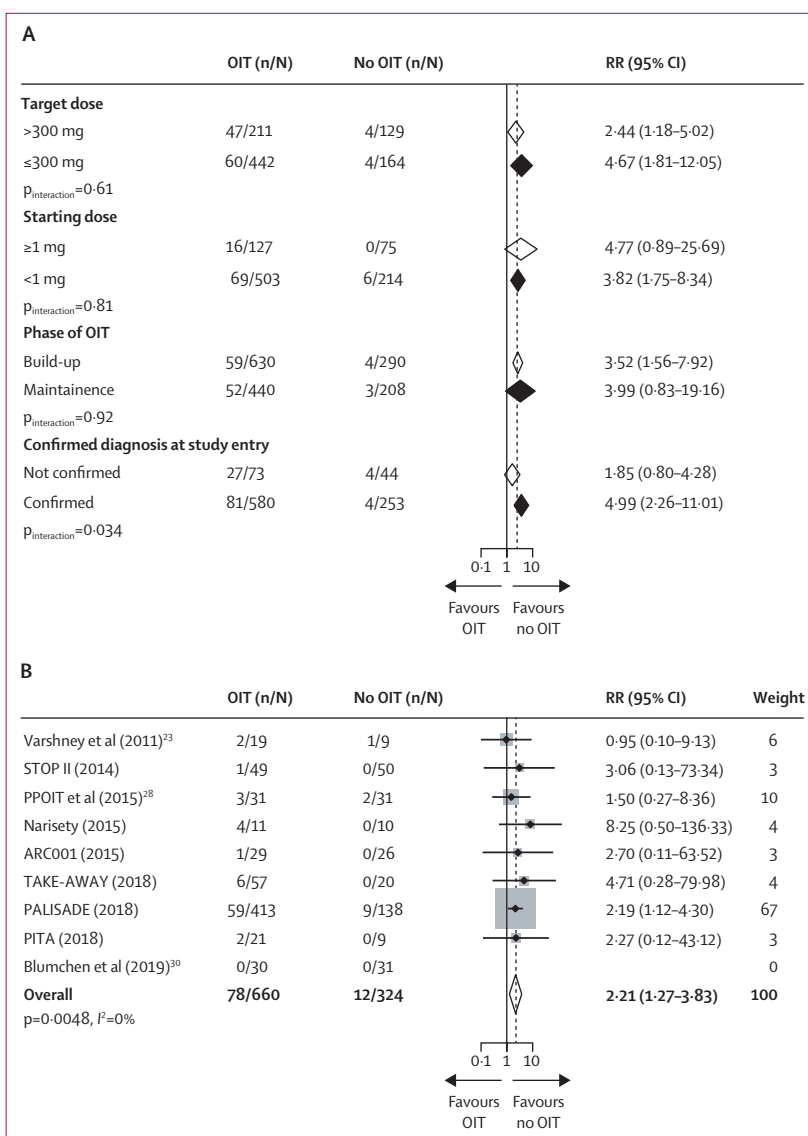


Figure 3: Anaphylaxis subgroup analyses by immunotherapy regimen and epinephrine use with peanut oral immunotherapy versus no oral immunotherapy

(A) Anaphylaxis risk. (B) Epinephrine use. OIT=oral immunotherapy. RR=risk ratio.

or Pediatric QoL [Quality of Life] Inventory version 4·0. Oral immunotherapy did not improve quality of life in participants by the minimally important difference (MID) compared with no oral immunotherapy by any measure (combined parent and self-report RR to achieve MID 1·21 [0·87–1·69], *I*²=0%, *p*=0·26; risk difference 0·03 [−0·12–0·18], *I*²=0%, *p*=0·71, low-certainty). Similarly, there was no difference in quality of life scores between groups by any measure.

Trial sequential, subgroup, and sensitivity analyses supported the overall findings (appendix). Sensitivity analyses showed that the findings were consistent whether the control group was placebo, avoidance, or sublingual immunotherapy (appendix).

See Online for appendix

For more on the findings for this study see https://gdt.gradeapro.org/presentations/#/isof/isof_49c0f323-9446-4436-bf16-c2a71ed4b7e2?_k=lrj8i or <https://bit.ly/LancetOIT>

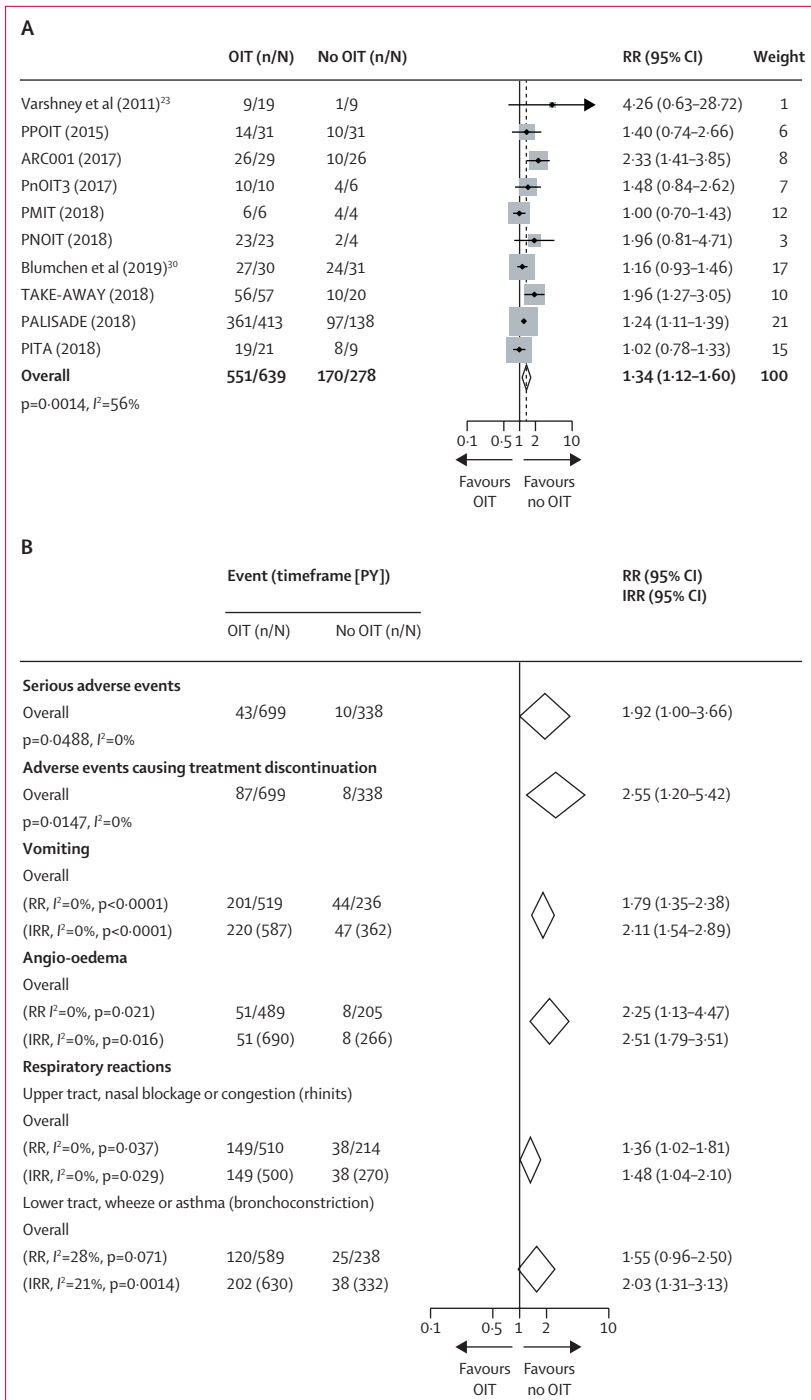


Figure 4: Serious adverse events, reactions causing study discontinuation, and allergic reactions by organ system involvement with peanut oral immunotherapy versus no oral immunotherapy
IRR=incidence rate ratio. OIT=oral immunotherapy. PY=patient-years. RR=risk ratio.

Discussion

This systematic review and meta-analysis of over 1000 peanut allergic patients in 12 randomised trials provides high and moderate certainty evidence that compared with allergen avoidance, current peanut oral

immunotherapy approaches increase the chance and frequency of allergic reactions, including anaphylaxis, need of epinephrine, and serious adverse events. This is despite oral immunotherapy being efficacious in increasing in-clinic supervised food challenge thresholds (ie, desensitisation). The findings were irrespective of oral immunotherapy protocol, proprietary formulation or not, and phase of immunotherapy (build up vs maintenance). We found low certainty evidence that oral immunotherapy might not improve quality of life compared with avoidance or placebo (which included allergen avoidance). For most outcomes, evidence of benefit or harm was apparent only after meta-analysis of all studies, whereas the single studies included yielded inconclusive results when analysed in isolation.

These data agree with the initial trial of peanut subcutaneous immunotherapy (SCIT),⁶¹ in which three of 11 treated participants passed an oral food challenge but systemic adverse reactions were frequent (13%). Systemic allergic reactions in the peanut SCIT trial⁶¹ and a cohort study⁶² were at a steady rate during both build up and maintenance phases, consistent with the findings of our meta-analysis and in contrast to the experience with aeroallergen immunotherapy.¹¹ Compared with a baseline risk of 7.1%, we estimated the risk of anaphylaxis with oral immunotherapy to be approximately 22% (incidence of 23%), which is consistent with retrospective case-series studies of oral immunotherapy reporting an allergic reaction or anaphylaxis rate requiring epinephrine of 23–27%.^{63,64} Altogether, these data contrast from the low-certainty evidence for benefits and harms in meta-analyses of oral immunotherapy for milk allergy because of imprecision and publication bias,¹² and the much lower rate of anaphylaxis (1–4%) during aeroallergen immunotherapy.¹¹

This meta-analysis shows that current peanut oral immunotherapy regimens can achieve the immunological goal of desensitisation, but that this outcome does not translate into achieving the clinical and patient-desired aim²⁰⁻²² of less allergic reactions and anaphylaxis. Instead, the opposite outcome occurs, with more allergic and adverse reactions with oral immunotherapy compared with avoidance or placebo. Rather than take the view that these data denounce current research in oral immunotherapy as not successful, we instead suggest that this research has reached an important milestone in mechanistic but not clinical efficacy. From a clinical or biological perspective, the apparently paradoxical desensitisation versus longitudinal clinical findings show the lability and unreliability of allergen thresholds identified during oral food challenges, because patients often unpredictably reacted to previously tolerated doses outside of clinic. Indeed, the degree of desensitisation with oral immunotherapy is variable and rarely complete, borne out by our meta-regression findings that the higher the dose of peanut at exit food challenge, the more patients reacted (26% higher chance

to react for every gram increase in cumulative challenge dose). In some cases, identifiable but often unavoidable factors were attributable for causing reactions. These include fever or infections, menstruation, exercise or exertion, temperature changes (including hot showers), dosing on an empty stomach, variability in asthma control, and non-compliance. Many reactions occurred with no identifiable co-factor. The contribution of study participants' allergen avoidance practices to our findings is uncertain because no study reported participants' adherence to this practice or any change in risk taking behaviours, albeit findings were similar in studies that used avoidance or placebo.

From a research perspective, these data question the utility of in-clinic oral food challenges as a primary (surrogate) measure of treatment efficacy in peanut allergy research. Studies currently measure treatment success by whether or not a treated patient can pass a supervised food challenge. Notwithstanding the known limitations of food challenge methods,⁴² supervised food challenges are diagnostic procedures with no validated utility in predicting a patient's future risk and frequency of allergic reactions to peanut as part of taking the daily oral immunotherapy dose or otherwise in the real world (ie, outside the clinic setting).^{45,65,66} An equally limited surrogate outcome is the severity of reaction elicited during oral food challenge because several studies have shown that the severity of one food allergic reaction does not predict the severity of the next.^{18,65,66} In turn, for future studies, as recommended by GRADE,⁵¹ the National Institute of Allergy and Infectious Diseases and FDA,⁴⁵ and others organisations,^{43,44} the primary measures to estimate health benefits and harms of interventions for IgE-mediated food allergies should be patient-centred outcomes, such as a risk and rate of allergic and anaphylactic reactions. This study shows the need for such an approach.

This meta-analysis shows with low certainty evidence that peanut oral immunotherapy might not improve the quality of life of patients with peanut allergy compared with allergen avoidance and placebo. This finding is in contrast to those generated by uncontrolled observational studies at high risk for confounding and bias that might have an influence on public opinion. Large, well done randomised controlled trials are required to clarify the effect, if any, of peanut oral immunotherapy on quality of life. Perhaps more important is to clarify patient values and preferences^{51,67} regarding food allergy therapies in general. This approach includes gaining a clear understanding of patients' therapeutic expectations and variability in decision making regarding the trade-offs between desirable and undesirable consequences of different treatment options.

Strengths of this review include its comprehensive search, identifying more than five times the sample size in ten additional studies than the most recent meta-analyses,^{13,36} and methodological rigour. Outcome

analyses, focused on patient-important outcomes rather than surrogate outcomes, were at overall low risk of bias; consistent across populations, interventions, and comparators; and were robust to IRR, subgroup, trial sequential, and sensitivity analyses.

Despite including all available RCTs, 12 studies including 1000 participants with a median sample size of 50 patients, this sample is comparatively small to standard cardiovascular or asthma trials. We addressed this issue by using trial sequential analysis, which showed that sufficient information was available to reach conclusions, and the formal GRADE approach, which provides a defined framework for assessing the certainty (quality) of the body of evidence for imprecision, among other domains. Secondly, we could not obtain data from some studies that did not fully report all their data for all the study participants. We contacted authors for additional information on outcome data but did not receive satisfactory responses. In cases of missing data, we made a range of plausible assumptions that did not materially change the overall findings. Although we observed some rational and plausible⁵⁸ subgroup effects using meta-regression, these relationships at the trial level should be confirmed with individual-patient level data analysis. Oral immunotherapy in the included studies was administered for a median 1 year but ranged up to 5·8 years, and mainly in children. Whether longer-term oral immunotherapy or delivery in adults has a different efficacy and safety profile than that observed in this study requires further investigation, albeit we found a similar risk and rate of allergic and anaphylactic events during build-up and maintenance phases, and irrespective of age. We used prospective observational studies with similar results to estimate the baseline risk of allergic reactions.^{18,19} For populations at a different baseline risk, the estimated relative treatment effects would still apply because they translate across levels of baseline risk.^{40,68} Studies did not uniformly and explicitly report antihistamine prophylaxis, which might be important because patients on immunotherapy could be taking antihistamines to try to reduce side-effects. Similarly, we found a high rate of gastrointestinal adverse events but only three cases of reported eosinophilic esophagitis, which might be because of underdiagnosis of eosinophilic esophagitis in the absence of uniform and systematic evaluation.

This systematic review and meta-analysis, representing the most comprehensive and rigorous to date, to our knowledge, provides high and moderate certainty evidence that current approaches to oral immunotherapy effectively achieve a modest degree of desensitisation but, clinically, they promote net more allergic and anaphylactic reactions instead of preventing them as intended. These data support the need for improved food allergy treatment approaches with an enhanced safety profile and trials focused on patient-important outcomes. Considering the current view of peanut allergy oral

immunotherapy as a model for other food allergies combined with the rising global prevalence of food allergy, these findings are significant and important to the ongoing development of food allergy therapeutics and improved patient outcomes.

Contributors

SF and DKC did the literature search, screened records, evaluated full texts, extracted data, and evaluated risk of bias. DKC designed the literature search, did the statistical analyses, and wrote the first draft of the manuscript. JLB and HJS provided critical input for the methods. All authors reviewed the manuscript and provided critical intellectual contributions to the analysis and interpretation of the data, and revision of the manuscript.

Declaration of interests

DKC, SW, and MJ report being investigators on an ongoing peanut oral immunotherapy trial (NCT01601522) funded by a federal body (AllerGen NCE through Government of Canada) and all are blinded to the study. RAW reports grants from the US National Institutes for Health, Astellas, Aimmune, DBV Technologie, Sanofi, and Regeneron, and personal fees from American Academy of Allergy Asthma and Immunology and Up To Date, outside the submitted work. SW reports grants from Aimmune, and personal fees from Pfizer, Mylan, and Sanofi, outside of the submitted work. The other authors declare no competing interests.

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Peanut oral immunotherapy: balancing benefits and risks for individuals



Peanut allergy affects around 2% of the population.¹ Fatal anaphylactic reactions are rare but can occur.² It has a considerable negative impact on the quality of life of patients and their families,³ and all patients need to avoid peanuts and carry self-injectable adrenaline. With many foods being labelled as “may contain nuts”, complete avoidance is a challenge.⁴ Until this decade, no treatment for food allergy was available;^{5,6} hence considerable efforts were made to develop oral immunotherapy for food allergy.⁷

The systematic review and meta-analysis by Derek Chu and colleagues in *The Lancet* summarises the evidence for oral immunotherapy for peanut allergy.⁸ Traditionally, the primary outcome for food allergy oral immunotherapy trials is passing a graded oral food challenge because this is an objective outcome that can be carefully controlled. In contrast, for their primary outcome, Chu and colleagues have used the more patient-centred endpoint of peanut-induced anaphylaxis, either as a result of unplanned exposure to peanuts or as a result of the daily doses of peanuts in the oral immunotherapy. This endpoint arguably provides a much better summary of a patient’s experience in day-to-day living than one oral peanut challenge.

Their systematic review⁸ included 1041 participants (median age 8.7 years [IQR 5.9–11.2]; 39% female participants) across 12 randomised controlled trials of peanut oral immunotherapy. Participants in the oral immunotherapy groups in these trials were given increasing doses of peanuts on a daily basis until they reached a maintenance dose. The median starting dose of peanut protein was 0.5 mg and the median maintenance dose was 2000 mg (about four peanuts). The meta-analysis found that oral immunotherapy actually increased the risk of anaphylaxis (relative risk 3.12 [95% CI 1.76–5.55]; no important heterogeneity).⁸ This outcome contrasts with passing an oral peanut challenge, which was much more probable with oral immunotherapy (12.4 [6.82–22.61]). Oral immunotherapy also did not improve quality of life in the small number of studies that assessed it (1.21 [0.87–1.69]).

The key criticism of this systematic review⁸ is inherent in its method because studies with different

designs were grouped together. Although most of the trials compared immunotherapy with placebo, avoidance was the comparator in three studies and sublingual immunotherapy in one study. This might have been expected to add some heterogeneity to the results. However, there was minimal heterogeneity and no difference between the different designs in their preplanned sensitivity analyses. This lack of heterogeneity is even more surprising because of the different preparations of peanut products used and the more than ten-times difference in maintenance doses. Interestingly, the maintenance dose was not associated with the risk of anaphylaxis during follow-up in the trial. In addition, the systematic review focused on desensitisation and did not account for whether the therapy continued to be effective after it had been discontinued (ie, development of tolerance).

The authors estimated that peanut oral immunotherapy was associated with 151 (95% CI 54–323) more episodes of anaphylaxis per 1000 patients.⁸ They used a figure of 71 episodes of anaphylaxis per 1000 as the baseline risk on the basis of historical data. Such an approach overlooks the differing patterns of these events. Participants in the oral immunotherapy groups would have had anaphylaxis in association with daily doses of peanuts at home, where they would have felt more in control. Participants in the comparator groups would have had anaphylaxis mainly when they were away from home, where they would have felt less in control. Immunotherapy has always needed a consideration of the balance between efficacy and safety. Particularly, anxious patients with frequent reactions might benefit from exchanging reactions away from home for reactions at home.

Unfortunately, the trials have not provided information about which participants benefited most from the intervention. Only a few trials collected quality-of-life data and none reported cost-effectiveness data. These data are essential. A mixed-methods approach would be helpful to provide insights into the balance between the emotions of living with a severe allergy and with oral immunotherapy.

Undoubtedly oral immunotherapy reduces the likelihood of reacting to peanuts in a controlled clinic



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setting, its overall side-effect profile means that patients seem to have more allergic reactions while on therapy. Trading treatment-related side-effects at home for allergic reactions to accidental exposures out of the house (ie, in social situations) might be beneficial for some patients. However, it is not clear which patients might benefit most and what the relative balance of reactions in and out of patients' homes would be. It would also be useful to compare oral with epicutaneous immunotherapy. Although epicutaneous immunotherapy is less effective, it has a better safety profile than oral immunotherapy, which some patients might find more acceptable.⁹ Finally, we should not forget that we now know that the early introduction of peanut products into the infant diet can prevent most cases of peanut allergy.¹⁰ Moving forward we need to develop implementation strategies to reduce the number of patients with peanut allergy.

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