Check for updates

DR. DEBRA DE SILVA (Orcid ID : 0000-0001-8413-5487)
DR. PABLO RODRIGUEZ DEL RIO (Orcid ID : 0000-0002-0783-1988)
DR. EKATERINA KHALEVA (Orcid ID : 0000-0002-2220-7745)
DR. ANNA NOWAK-WEGRZYN (Orcid ID : 0000-0002-0960-9854)
DR. PHILIPPE BÉGIN (Orcid ID : 0000-0002-9089-4604)
DR. ALESSANDRO FIOCCHI (Orcid ID : 0000-0002-2549-0523)
DR. GARY WK WONG (Orcid ID : 0000-0001-5939-812X)
DR. MONTSERRAT FERNANDEZ-RIVAS (Orcid ID : 0000-0003-1748-2328)
DR. ROSAN MEYER (Orcid ID : 0000-0002-5710-5570)
DR. SUSANNE LAU (Orcid ID : 0000-0002-5189-4265)
PROF. GRAHAM C ROBERTS (Orcid ID : 0000-0003-2252-1248)

Article type : Original article

Title

Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: systematic review and meta-analysis

Short running title

Immunotherapy and/or biologicals in food allergy

Full names of authors and institutional affiliations

Debra de Silva, The Evidence Centre, England
Pablo Rodríguez del Río, Niño Jesus University Children's Hospital, Spain
Nicolette W. de Jong, University Medical Centre Rotterdam, the Netherlands
Ekaterina Khaleva, University of Southampton, England
Chris Singh, The Evidence Centre, New Zealand
Anna Nowak-Wegrzyn, NYU Langone Health, USA

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ALL.15211

This article is protected by copyright. All rights reserved

Accepted Article

Antonella Muraro, Padua University Hospital, Italy
Philippe Begin, Univerisite de Montreal, Canada
Giovanni Pajno, Policlinico Hospital-University of Messina, Italy
Alessandro Fiocchi, Bambino Gesù Childrens' Hospital IRCCS, Italy
Angel Sanchez, AEPNAA Spanish Association for People with Food and Latex Allergy, Spain
Carla Jones, Allergy UK, England
Caroline Nilsson, Karolinska Institutet and Sachs´ Children and Youth Hospital, Sweden
Carsten Bindslev-Jensen, Odense University Hospital, Denmark
Gary Wong, Chinese University of Hong Kong, Hong Kong
Hugh Sampson, Mount Sinai School of Medicine, USA
Kirsten Beyer, Charité-Universitätsmedizin Berlin, Germany
Mary-Jane Marchisotto, EAACI Patient Organisation Committee Chair, USA
Montserrat Fernandez Rivas, Hospital Clínico San Carlos, Spain
Rosan Meyer, Imperial College, England
Susanne Lau, Charité - Universitätsmedizin Berlin, Germany
Ulugbek Nurmatov, Cardiff University, Wales
Graham Roberts, University of Southampton, England

Author citation

de Silva D, Rodríguez del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, Muraro A, Begin P, Pajno G, Fiocchi A, Sanchez A, Jones C, Nilsson C, Bindslev-Jensen C, Wong G, Sampson H, Beyer K, Marchisotto M-J. Fernandez Rivas M, Meyer R, Lau S, Nurmatov U, Roberts G on behalf of the GA^{2}LEN Food Allergy Guidelines Group.

Corresponding author: Debra de Silva, debra@evidencecentre.com

Author contributions

All authors conceptualised the work, extracted or checked data, undertook risk of bias assessments, provided substantive comments and approved the review for submission. In addition, CS and DdS undertook searches and meta-analysis and constructed summary of findings tables. PRdR, NdJ, GR, EK, ANW, PB and ADG extracted additional data and contributed to analysis. DdS, GR and EK managed the process.

This article is protected by copyright. All rights reserved

Conflicts of interest

Debra de Silva, none declared. Organisation received GA^{2}LEN funding to support review process.
Pablo Rodríguez del Río, Personal fees: Aimmune,
Nicolette W. de Jong, none declared
Ekaterina Khaleva, none declared
Chris Singh, none declared. Organisation received GA^{2}LEN funding to support review process.
Anna Nowak-Wegrzyn, Personal fees: Nestle, Novartis, Sanofil
Antonella Muraro, Personal fees: Aimmune, DVB, Mylan, ALK, Nestle, Novartis, Nutricia Research. Grant: Aimmune, Sanofil
Philippe Begin, Personal fees: ALK, DBV, Novartis, Sanofil,
Giovanni Pajno, none declared
Alessandro Fiocchi, Personal fees: Ferrero. Grant: Danone, HIPP
Angel Sanchez, none declared
Carla Jones, none declared. Organisation received funding to support projects
Caroline Nilsson, Grant: Aimmune, Thermofisher
Carsten Bindslev-Jensen, Personal fees: Allakos, CEV SA. Grant: Novartis
Gary Wong, none declared
Hugh Sampson, Personal fees: DBV, N-fold, Siolta
Kirsten Beyer, Personal fees: Aimmune, Bencard, Danone, DBV, HIPP, Hycor, Infectopharm, Jenapharma, Mylan/Meda, Nestle, Novartis, Nutricia Research, Thermofisher. Grants: Aimmune, Danone/Nutricia/Milipa, DBV, Hipp, Hycor, Infectopharm
Mary-Jane Marchisotto, none declared
Montserrat Fernandez Rivas, Personal fees: Therapeutics, ALK, Allergy Therapeutics, DBV, Diater, GSK, Thermofisher Scientific, SPRIM
Rosan Meyer, Personal fees: Abbott, Danone, Nestle, Mead Johnson
Susanne Lau, none declared
Ulugbek Nurmatov, none declared
Graham Roberts, Grant: UK Food Standards Agency, DBV, European Union

Acknowledgements

The Global Allergy and Asthma European Network (GA2LEN) contributed funding towards the systematic review process. Authors and contributors volunteered their time.

Contributors

This article is protected by copyright. All rights reserved

Susanne Halken, Hans Christian Andersen Children's Hospital, Odense University Hospital, Denmark
Margitta Worm, Charité - Universitätsmedizin Berlin, Germany
Audrey Dunn-Galvin, University College Cork, Ireland.
Liz Angier, University of Southampton, England
Amena Warner, Allergy UK, England
Antoine Deschildre, University Lille, France
Antonella Cianferoni, University of Florence, Italy
Barbara Ballmer, UniversitätsSpital Zürich, Switzerland
Berber Vlieg-Boerstra, OLVG Hospital, the Netherlands
Bertine Flokstra-de Blok, University of Groningen, the Netherlands
Bright Nwaru, University of Gothenburg, Sweden
Carina Venter, Children's Hospital Colorado, USA
Celine Demoulin, Association Française pour la Prévention des Allergies Siège social, France
Clare Mills, University of Manchester, England
Gary Wong, Chinese University of Hong Kong, Hong Kong
Giovanni Pajno, Policlinico Hospital-University of Messina, Italy
Hania Szajewska, Medical University of Warsaw, Poland
Hasan Arshad, University of Southampton, England
Jennifer Gerdts, Food Allergy Canada, Canada
Josefine Gradman, Hans Christian Andersen Children's Hospital, Odense University Hospital, Denmark
Kate Grimshaw, Salford Care Organisation, England
Lars K. Poulsen, Copenhagen University Hospital, Denmark
Lynne Regent, Anaphylaxis Campaign, England
Marcia Podestà, Food Allergy Italia, Italy
Matthew Geromi, The Evidence Centre, USA
Mika Makela, Helsinki University Hospital, Finland
Montserrat Alvaro Lozano, Hospital Sant Joan de Déu, Esplugues, Spain
Montserrat Fernandez Rivas, Hospital Clínico San Carlos, Spain
Motohiro Ebisawa, Sagamihari National Hospital, Japan
Paul Turner, Imperial College, England
Pete Smith, Griffith University School of Medicine, Australia
Richard Loh, Perth Children's Hospital, Australia
Robert Wood, John Hopkins Bloomberg School of Public Health, USA

Accepted Article

This article is protected by copyright. All rights reserved

Ronald Van Ree, Amsterdam UMC, the Netherlands
Sabine Schnadt, DAAB, Deutscher Allergie- und Asthmabund e.V, Germany
Stefania Arasi, Bambino Gesù Children's Research Hospital, Italy
Torsten Zuberbier, Charité - Universitätsmedizin Berlin, Germany

Main text word count

3,729 words, including headings and referring in the text to tables, figures and supplements

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Abstract and keywords

Background

There is substantial interest in immunotherapy and biologicals in IgE-mediated food allergy.

Methods

We searched six databases for randomised controlled trials about immunotherapy alone or with biologicals (to April 2021) or biological monotherapy (to September 2021) in food allergy confirmed by oral food challenge. We pooled the data using random-effects meta-analysis.

Results

We included 36 trials about immunotherapy with 2,126 mainly child participants. Oral immunotherapy increased tolerance whilst on therapy for peanut (RR 9.9, 95% CI 4.5. to 21.4, high certainty); cow's milk (RR 5.7, 1.9 to 16.7, moderate certainty) and hen's egg allergy (RR 8.9, 4.4 to 18, moderate certainty). The number needed to treat to increase tolerance to a single dose of 300mg or 1000mg peanut protein was 2.

Oral immunotherapy did not increase adverse reactions (RR 1.1, 1.0 to 1.2, low certainty) or severe reactions in peanut allergy (RR 1,6, 0.7 to 3.5, low certainty), but may increase (mild) adverse reactions in cow's milk (RR 3.9, 2.1 to 7.5, low certainty) and hen's egg allergy (RR 7.0, 2.4 to 19.8, moderate certainty). Epicutaneous immunotherapy increased tolerance whilst on therapy for peanut (RR 2.6, 1.8 to 3.8, moderate certainty). Results were unclear for other allergies and administration routes.

There were too few trials of biologicals alone (3) or with immunotherapy (1) to draw conclusions.

Conclusions

Oral immunotherapy improves tolerance whilst on therapy and is probably safe in peanut, cow's milk and hen's egg allergy. More research is needed about quality of life, cost and biologicals.

Keywords: Biological, Food allergy, IgE-mediated, Immunotherapy, Peanut

Word count: 247

This article is protected by copyright. All rights reserved

Accepted Article

Main text

INTRODUCTION

Background

Around 6% of people live with immunoglobulin E (IgE)-mediated food allergy[1] which affects quality of life, social activities, anxiety and nutrition.[2,3] Patients are advised to avoid the allergen and use medications to relieve symptoms, but accidental exposure is common and can be life-threatening.[4]

There is growing interest in allergen-specific immunotherapy (hereafter immunotherapy) and biological therapies. However, there are conflicting results, with some studies finding improved allergen tolerance and others emphasising increased adverse reactions.[5]

Past reviews sometimes combined studies of various designs and therapies, focused on only one type of food allergy or are outdated.[6,7,8,9,10] We compiled an up-to-date systematic review about the efficacy and safety of immunotherapy and/or biologicals to inform forthcoming Global Allergy and Asthma European Network (GA^{2}LEN) guidelines and add to existing guidelines.[11,12]

Objectives

We prioritised the following review questions after feedback from people with food allergy, patient advocates, healthcare professionals, teachers and policy makers. No industry representatives were involved.

1. What is the efficacy, safety and cost-effectiveness of a) immunotherapy alone, b) immunotherapy with a biological or c) biologicals alone for children and adults with any IgE-mediated food allergy compared to no active treatment agent?

2. What is the efficacy, safety and cost-effectiveness of immunotherapy administered by different routes for children and adults with any IgE-mediated food allergy?

METHODS

A task force of allergy specialists, patient representatives, primary care doctors, psychologists, other clinicians, teachers and methodologists from 19 countries undertook the review.

This article is protected by copyright. All rights reserved

The full methods are available in the protocol (International Prospective Register of Systematic Reviews PROSPERO registration: CRD42021250940) so methods are only briefly summarised here.

Accepted Article

This article is protected by copyright. All rights reserved

Eligibility criteria

Studies meeting the following criteria were eligible:

- Population: infants (< 3 years), children (3-17 years) or adults (18+ years) with IgE-mediated food allergy confirmed using oral food challenge.

- Intervention: allergen-specific immunotherapy alone, with a biological or biological alone.

- Comparator: placebo, no intervention or routine management without active treatment. For review question 2 the compactor was immunotherapy using a different route.

- Outcomes: quality of life, desensitisation (ability to tolerate the allergen whilst being treated), sustained unresponsiveness (ability to tolerate the allergen after discontinuing therapy), adverse reactions, severe adverse reactions and cost-effectiveness, all as defined by the original studies.

- Study types: randomised controlled trials (hereafter trials) published from the beginning of databases (1946) to 30 April 2021 for immunotherapy and trials and controlled comparisons up to 30 September 2021 for biological monotherapy.

Study selection

Clinicians, patients and information specialists developed a search strategy (Supplement S1). Methodologists (CS, DdS) searched six databases (CINAHL, Cochrane Library, EMBASE, ISI Web of Science, MEDLINE, Scopus), reviewed bibliographies of reviews, guidelines and identified studies and contacted experts in the field for additional research.

Two methodologists independently screened the titles, abstracts and full text of potentially relevant studies (CS, DdS). Shortlisted studies were rescreened by the task force for consensus. Some studies included in previous reviews did not meet our stringent criteria (S2).

Data extraction

Pairs of methodologists (MG, DdS, CS) and task force members (all authors) extracted study characteristics and outcomes independently. Clinicians independently extracted additional data about adverse reactions and thresholds (PRdR, EK, GR, PB, AWN, ADG, SA, ME, TZ), including

This article is protected by copyright. All rights reserved

the different definitions used (S3). A senior clinician acted as an arbitrator if needed, but there was consensus (GR).

We had most data about peanut allergy so we compiled the proportion able to tolerate 300mg (level at which there is a substantial reduction in risk from products labelled with "may contain")[13] and 1000mg peanut protein as both a single last tolerated and cumulative dose. Our approach was conservative, so when someone was reported to tolerate 300mg to 600mg peanut protein we classified them as tolerating a 300mg dose. We used a range of 1000mg to 2000mg for the 1000mg threshold. We used these ranges because an individual's threshold may vary by at least a factor of two when they are challenged twice within a short time.[14]

Risk of bias in individual studies

Four methodologists and clinicians independently assessed the risk of bias in individual studies using the Cochrane Risk of Bias tool 2 (ROB2)[15] (pairs of all authors). Arbitration was available if needed from a senior clinician (GR) but there was agreement in the risk of bias assessments.

Synthesis of results

We used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to synthesise data about each outcome.[16]

We pooled intention-to-treat data using random effects Mantel-Haenszel meta-analysis (Revman 5.4) because the studies included different populations, regimes and time periods and to avoid overweighting large but imprecise studies.

We divided studies based on the food allergy and therapy route. We undertook subgroup analysis based on risk of bias, age, allergy severity, comparator and threshold tolerated. In sensitivity analysis, we used a continuity correction (adding 0.05 to numerators and denominators) where there were no events in each study arm for severe or life-threatening events, anaphylaxis and adrenaline use.

We used funnel plots to help assess publication bias. We quantified the heterogeneity of studies using the I2 statistic, with values less than 25% indicating low heterogeneity.[17]

All task force members developed conclusions by consensus, recognising any potential conflicts of interest, which were declared in advance. We used standardised GRADE statements to

This article is protected by copyright. All rights reserved

summarise the conclusions[18] (S4 lists our wording conventions). We used the word 'may' to represent low certainty evidence, 'probably' for moderate certainty and 'resulted in' for high certainty evidence.

RESULTS

Study characteristics

We included 36 trials of immunotherapy with 2,126, mainly child, participants, and 3 trials about biological monotherapy with 118 participants, mainly teenagers and adults. (Table 1 and Figure 1).

The GRADE certainty of evidence was generally low to moderate (S6). The certainty of evidence was mainly downgraded due to risk of bias (S5), indirectness and imprecision. About one quarter of studies were at low risk of bias (28%), half at moderate risk (47%) and quarter at high risk (25%).

Tables 2-4 list the key findings, with details in S6 and S7. Trends were broadly similar for people with mild/moderate or severe allergy and studies at lower and higher risk of bias (S7). There was insufficient information to be able to distinguish immunotherapy with raw versus cooked foods or to draw conclusions about the most effective regimen or duration of treatment.

Peanut allergy (Table 2)

Desensitisation

Most studies about peanut allergy enrolled children. Oral immunotherapy resulted in a large increase in the proportion able to tolerate peanut during therapy (absolute difference 62%, relative risk (RR) 9.9, 95% confidence interval (CI) 4.5 to 21.4, high certainty). Those receiving oral immunotherapy were six times more likely than controls to tolerate a single dose of 300mg peanut (roughly one peanut, number needed to treat (NNT) 2) and 17 times more likely to tolerate 1000mg (NNT 2). Before immunotherapy, the mean maximum tolerated dose was only about 34mg (S5)

Epicutaneous immunotherapy probably increased the proportion able to tolerate peanut during therapy (absolute difference 29%, RR 2.6, 95% CI 1.8 to 3.8, moderate certainty). Those

This article is protected by copyright. All rights reserved

receiving epicutaneous immunotherapy were twice as likely as controls to be able to tolerate a single dose of 300mg peanut (NNT 6)

Sublingual immunotherapy may result in a large increase in the proportion able to tolerate peanut during therapy (absolute difference 55%, RR 4.7, 95% CI 1.6 to 13.8, low certainty). It is unclear whether subcutaneous immunotherapy had any impact because the certainty of evidence was very low.

Sustained unresponsiveness

Peanut oral immunotherapy may increase the proportion of children able to tolerate peanut after stopping therapy (absolute difference 31%, RR 8.8, 05% CI 1.2 to 61.6, low certainty). No data were available about sustained unresponsiveness using other administration routes.

Accepted Article

This article is protected by copyright. All rights reserved

Adverse reactions

There was no statistically significant increase in adverse reactions due to peanut immunotherapy, regardless of the administration route, though oral immunotherapy was on the borderline for increasing adverse reactions (RR 1.1, 95% CI 1.0 to 1.2, p=0.06, low certainty).

The most common adverse reactions were gastrointestinal, including swelling and itching in the mouth, vomiting, abdominal pain and diarrhoea. Most symptoms (80-90%) were mild in severity and less than 10% withdrew from treatment as a result. Some experienced respiratory and skin symptoms such as rhinitis, wheezing, dyspnoea, asthma, laryngeal oedema, urticaria, angioedema and erythema. These ranged in severity but were usually responsive to treatment. Immune system disorders, infections, eye symptoms, ear and labyrinth disorders and cardiovascular events were not frequently reported. Eosinophilic esophagitis was rare. The frequency of adverse reactions appeared to reduce with increasing duration of immunotherapy.

Skin reactions were the most common adverse reactions to peanut epicutaneous immunotherapy. Most cutaneous reactions were mild, limited to the patch site and generally occurred in the first month of treatment. Skin manifestations extending beyond the borders of the patch were uncommon, as were extra-cutaneous reactions (respiratory, thoracic and mediastinal disorders, immune reactions or eye symptoms).

No deaths were reported due to immunotherapy, and there was no increase in anaphylaxis or life-threatening reactions (S7).

Cow's milk allergy (Table 3)

All but one study about cow's milk allergy enrolled children. Oral immunotherapy probably resulted in a higher proportion able to tolerate cow's milk protein during therapy (absolute difference 53%, RR 5.7, 95% CI 1.9 to 16.7, moderate certainty).

An increased proportion may have experienced adverse reactions (absolute difference 67%, RR 3.9, 95% CI 2.1 to 7.5, low certainty), but few studies focused solely on reactions caused by the therapy (S7) and there was no significant difference in the 3 studies comparing with placebo.

The most common adverse reactions were mild gastrointestinal symptoms. A small number experienced respiratory symptoms. It was unclear whether oral immunotherapy increased severe reactions because the certainty of evidence was very low. Reports of severe reactions,

This article is protected by copyright. All rights reserved

anaphylaxis, use of adrenaline and discontinuation were rare. No hospital admissions or deaths were reported due to treatment.

There was insufficient evidence to draw conclusions about other administration routes in cow's milk allergy.

Hen's egg allergy (Table 4)

All studies about hen's egg allergy were in children and all but one compared with an elimination diet. Oral immunotherapy probably resulted in a large increase in the proportion of children able to tolerate hen's egg during therapy (absolute difference 79%, RR 8.9, 95% CI 4.4 to 18, moderate certainty). It may increase the proportion able to continue tolerating hen's egg after therapy ends (absolute difference in sustained unresponsiveness 30%, RR 7.1, 95% CI 1.7 to 29.4, low certainty).

Egg oral immunotherapy probably resulted in a large increase in the proportion of children experiencing adverse reactions (absolute difference 71%, RR 7.0, 95% CI 2.4 to 19.8, moderate certainty), but few studies focused only on reactions caused by the treatment. The one study that compared with placebo found no significant difference in adverse reactions. It was unclear whether there was any impact on severe reactions because the certainty of evidence was very low.

Accepted Article

This article is protected by copyright. All rights reserved

Around 95% of reactions were mild. They occurred in about 1 in 20 doses during the build-up phase and decreased to 1 in 40 doses during the first months of maintenance. The most frequently reported symptoms were oral pruritus and gastrointestinal pain. Anaphylaxis or symptoms that were severe enough to discontinue immunotherapy were rare.

Other food allergies and outcomes

We identified too few studies about other food allergies or directly comparing immunotherapy routes to present meaningful results (see S6 and S7). There was also little information about the impact on quality of life, despite being key to whether people are motivated to continue immunotherapy (S6). None of the included studies reported cost-effectiveness. We did not find a clear relationship between the duration of treatment and desensitisation, sustained responsiveness or safety (S7).

Biological therapies

There were too few studies to draw meaningful conclusions about biologicals alone or added to immunotherapy (S6). In those aged 13+ years, there was a trend towards improved tolerance of peanut during biological monotherapy, with few side effects. However the certainty of evidence was very low, with only three studies, each about different therapy.[19, 20,21]

DISCUSSION

Summary of evidence

Proactive treatments are needed to reduce the burden of food allergy. Our review suggests that oral immunotherapy may be safe and effective for increasing tolerance whilst on therapy in children allergic to peanut, cow's milk or hen's egg. Three-quarters receiving peanut oral immunotherapy tolerated a single dose of 300mg peanut protein at the end of therapy and a half a single dose of 1000mg, which would protect against most accidental exposure. About one third may maintain tolerance after stopping therapy, at least in the short term (3 months). Oral immunotherapy was usually well tolerated. It is likely to result in more adverse reactions, but mainly mild. Clinicians and families will need to weigh up the benefits versus harms when considering whether immunotherapy is appropriate for individuals.

Epicutaneous immunotherapy may also be safe and effective amongst children with peanut allergy, but less is known about this for other food allergies, or about sublingual or subcutaneous

This article is protected by copyright. All rights reserved

immunotherapy for any food allergy. We found insufficient evidence to draw conclusions about benefits or harms from biologicals.

Comparison with previous research

Many studies, reviews and opinion pieces have explored immunotherapy for people with food allergy, sometimes with inconsistent results.[22] Our review differs from others because it includes the highest quality and most up-to-date evidence, divided by type of food allergy and administration route. We excluded trials that did not use food challenges to confirm food allergy before treatment, as this may introduce bias into absolute event rates. We examined tolerated thresholds in detail, which we believe is the first analysis of its kind. Our review supports others suggesting that clinicians could consider immunotherapy for some groups of patients.[6,7]

Implications for research

There is now a good pool of studies about oral immunotherapy for peanut allergy, but we can only draw limited conclusions about other food allergies, administration routes and biologicals due to sparse good quality evidence.

An important area not explored in our review is patient preferences and motivation to use immunotherapy and/or biologicals. Our findings suggest that (oral) immunotherapy may improve tolerance whilst people continue the therapy, but gains may not be sustained after stopping therapy. Therefore people need to consider whether they are willing to continue therapy for an extended period. Future research using standardised threshold levels for each allergen may help patients make more informed decisions.

Future studies could create core outcome sets[23] and use standardised definitions and measures of quality of life, desensitisation, sustained unresponsiveness and adverse reactions to allow robust comparisons across populations, regions and types of immunotherapy. Standardised immunotherapy regimens would also assist comparisons. More high quality trials are needed to directly compare different administration routes and to explore the impacts of adding biologicals.

Strengths and limitations

A strength of our review is that it was conducted by a large group of clinicians, allied health professionals, patient representatives, teachers and researchers from different parts of the world.

Accepted Article

This article is protected by copyright. All rights reserved

By analysing detailed data about desensitisation thresholds, we showed that only 2 children needed to be treated with peanut oral immunotherapy to increase 1 child's reactivity threshold up to 300mg and 1000mg. This would reduce the chance of reactions from accidental consumption of packaged food containing peanut.[11] Given variability in reactivity thresholds,[12] achieving tolerance to a single dose of 1000mg is likely protective to real-life exposures.

However, our conclusions are limited by methodological variations in the available studies and a lack of eligible studies about many topics. We found that adverse reactions tended to increase, but we do not know whether these reactions were due to the therapy, accidental exposure or unrelated causes. This limits conclusions about the safety profile. Some studies excluded patients with previous anaphylaxis, which may also affect generalisability.

A number of trials have pragmatic designs and do not confirm food allergy at the outset using oral food challenges. We excluded these studies to ensure that participants definitely had food allergy, but there is an argument for including such research in decision-making if the selection criteria reflect real-life clinical practice.

Conclusions

There may be merit in allergen-specific immunotherapy and/or biologicals for a carefully selected group of patients, but there are also downsides including (mainly mild) reactions to manage, relatively long treatment periods and benefits potentially only lasting whilst people maintain the regimen.

Immunotherapy is also specific to the culprit food(s) and requires exposure to allergens, which may be off-putting for some. We know little about how patient motivation to sustain the therapy may differ in various parts on the world or based on patient characteristics. When making patient-centred shared decisions about whether to offer immunotherapy and/or biologicals to an individual, clinicians and patients need to weigh up factors such as patient preferences, motivation, accessibility and cost alongside the evidence about safety and effectiveness.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

Tables

Table 1: Characteristics of included studies

Allergy	Administration	Studies	Participants	Allergy severity	Region
Peanut (13 studies)	Oral[24,25,26,27,28,29,30]	7	1031 children 55 mixed age	1 study moderate 6 studies mixed	4 studies Europe 2 studies USA 1 study multiple
	Epicutaneous[31,32,33]	3	356 children 295 mixed age	2 studies mild/moderate 1 study mixed	1 study USA 2 studies multiple
	Sublingual[34]	1	40 adults	Mild/moderate	1 study USA
	Subcutaneous[35]	1	8 mixed age	Severe	1 study USA
	Oral vs sublingual[36]	1	21 children	Mild/moderate	1 study USA
Cow's milk (11 studies)	Oral[37,38,39,40,41,42,43,44]	8	91 infants 144 children 42 mixed age	3 studies mild/moderate 2 studies severe 3 studies mixed	1 study Asia 6 studies Europe 1 study USA
	Epicutaneous[45]	1	19 mixed age	Mixed	1 study Europe
	Oral vs sublingual[46]	1	30 children	Mixed	1 study USA
	Oral + biological[47]	1	16 children	Severe	1 study Asia
Hen's egg (7 trials)	Oral[48,49,50,51,52,53,54]	7	327 children	3 studies mild/moderate 1 study severe 1 study mixed	2 studies Asia 5 studies Europe
Other (1 hazelnut. 1 peach, 1 wheat, 2 multiple foods)	Oral[55,56,57]	3	69 children 49 mixed age	2 studies mild/moderate 1 study mixed	2 studies Europe 1 study USA
	Sublingual[58,59]	2	78 adults	Mixed	1 study Europe

This article is protected by copyright. All rights reserved

Total immunotherapy	25 studies oral 4 epicutaneous 1 subcutaneous 3 sublingual 2 oral versus sublingual 1 oral + biological	36	2,126 2 studies infants 23 children 3 adults 8 mixed age	12 studies mild/moderate 1 moderate 5 severe 18 mixed	4 studies Asia 20 studies Europe 9 studies USA 3 studies multiple
Biological monotherapy	1 etokimab[19] 1 omalizumab[20] 1 TNX-901[21]	3	118 2 studies 13+ years 1 study half children and half 13+ years	3 studies mixed	3 studies USA

Note: allergy severity was based on definitions in individual studies and descriptions of inclusion criteria.

Accepted Article

This article is protected by copyright. All rights reserved

Table 2: Summary of findings about immunotherapy for peanut allergy

Outcome	% Active	% Control	Absolute difference	Relative risk (95% CI)	NNT	Certainty of evidence	Comparisons & participants
Oral immunotherapy							
Desensitisation	68	6	62%, p<0.05	9.9 (4.5 to 21.4)	2	High	7 (n=1023)
Tolerate single dose of 300mg	76	13	63%, p<0.05	5.7 (4.0 to 7.9)	2	Moderate	5 (n=820)
Tolerate single dose of 1000mg	56	2	54%, p<0.05	16.6 (8.0 to 34.4)	2	High	5 (n=906)
Sustained unresponsiveness	35	4	31%, p<0.05	8.8 (1.2 to 61.6)	4	Low	1 (n=85)
Adverse reactions	98	89	9% p>0.05	1.1 (1.0 to 1.2)	NA	Low	7 (n=953)
Severe adverse reactions	4	2	2%, p>0.05	1.6 (0.7 to 3.5)	NA	Low	6 (n=950)
Epicutaneous immunotherapy							
Desensitisation	46	17	29%, p<0.05	2.6 (1.8 to 3.8)	3	Moderate	3 (n=651)
Tolerate single dose of 300mg	30	13	18%, p<0.05	2.4 (1.5 to 3.8)	6	Low	3 (n=333)
Adverse reactions	78	61	17%, p>0.05	1.2 (0.95 to 1.6)	NA	Low	4 (n=676)
Severe adverse reactions	6	2	4%, p>0.05	2.0 (0.8 to 5.1)	NA	Low	4 (n=676)
Sublingual immunotherapy							
Desensitisation	70	15	55%, p<0.05	4.7 (1.6 to 13.8)	2	Very low	1 (n=40)
Tolerate single dose of 300mg	25	15	10%, p>0.05	1.7 (0.5 to 6.1)	NA	Very low	1 (n=40)
Severe adverse reactions	0	0	0	Not calculated	NA	Very low	1 (n=40
Subcutaneous immunotherapy							
Desensitisation	33	0	33%, p>0.05	1.5 (0.1 to 22.6)	NA	Very low	1 (n=4)

Accepted Article

This article is protected by copyright. All rights reserved

Note: Rounded to nearest whole number. Absolute difference is % active minus control. CI = confidence interval, NNT = number needed to treat. NA = not applicable as no statistically significant difference. Adverse reactions and severe adverse reactions are all reactions, not necessarily linked to the therapy. Multiple definitions of severe reactions were used (see S3). In general these involved marked impact on participants (e.g. symptomatic bronchospasm, hypotension) and need for medical intervention. Online supplement S7 contains additional data such as the proportion of doses experiencing reactions and adverse events linked to therapy. 'Comparisons' means the number of comparisons between active and control groups. In most cases this is the total number of trials contributing the meta-analysis but some studies compared different doses with placebo. Each comparison was included separately in the meta-analysis. Data about threshold reactivity at 1000mg peanut protein were only available for oral immunotherapy.

Accepted Article

This article is protected by copyright. All rights reserved

Table 3: Summary of findings about oral immunotherapy for cow's milk allergy

Outcome	% Active	% Control	Absolute difference	Relative risk (95% CI)	NNT	Certainty of evidence	Trials and participants
Desensitisation	68	15	53%, p<0.05	5.7 (1.9 to 16.7)	2	Moderate	7 (n=249)
Adverse reactions	85	17	67%. p<0.05	3.9 (2.1 to 7.5)	2	Low	6 (n=210)
Severe adverse reactions	3	0	3%, p>0.05	7.0 (0.4 to 124.8)	NA	Very low	4 (n=204)

Note: The note under Table 2 also applies to this table. There was one study about epicutaneous immunotherapy which reported events by dose (see supplement S7).

Table 4: Summary of findings about oral immunotherapy for hen's egg allergy

Outcome	% Active	% Control	Absolute difference	Relative risk (95% CI)	NNT	Certainty of evidence	Trials and participants
Desensitisation	84	5	79%, p<0.05	8.9 (4.4 to 18.0)	2	Moderate	6 (n=259)
Sustained unresponsiveness	35	4	30%, p<0.05	7.1 (1.7 to 29.4)	4	Low	2 (n=91)
Adverse reactions	79	8	71%, p<0.05	7.0 (2.4 to 19.8)	2	Moderate	6 (n=291)
Severe adverse reactions	6	0	6%, p>0.05	3.4 (0.6 to 19.6)	NA	Very low	4 (n=211)

Note: The note under Table 2 also applies to this table

Figure legends

Figure 1: PRISMA diagram showing study selection

This article is protected by copyright. All rights reserved

Accepted Article

Accepted Article

References

1 Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, Dubois AE, Halken S, Hoffmann-Sommergruber K, Poulsen LK, Roberts G, Van Ree R, Vlieg-Boerstra BJ, Sheikh A. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy 2014;69(1):62-75.

2 Warren C, Dyer A, Lombard L, Dunn-Galvin A, Gupta R. The psychosocial burden of food allergy among adults: a us population-based study. J Allergy Clin Immunol Pract 2021;9(6):2452-2460.e3.

3 Polloni L, Muraro A. Anxiety and food allergy: A review of the last two decades. Clin Exp Allergy 2020;50(4):420-441.

4 Pouessel G, Turner PJ, Worm M, Cardona V, Deschildre A, Beaudouin E, Renaudin JM, Demoly P, Tanno LK. Food-induced fatal anaphylaxis: From epidemiological data to general prevention strategies. Clin Exp Allergy 2018;48(12):1584-1593.

5 Eiwegger T, Anagnostou K, Arasi S, Bégin P, Ben-Shoshan M, Beyer K, Blumchen K, Brough H, Caubet JC, Chan ES, Chen M, Chinthrajah S, Davis CM, Des Roches A, Du Toit G, Elizur A, Galli SJ, Håland G, Hoffmann-Sommergruber K, Kim H, Leung DYM, Long A, Muraro A, Nurmatov UB, Pajno GB, Sampath V, Saxena J, Sindher S, Upton J, Worm M, Nadeau KC. Conflicting verdicts on peanut oral immunotherapy from the Institute for Clinical and Economic Review and US Food and Drug Administration Advisory Committee: Where do we go from here? J Allergy Clin Immunol 2020;145:1153-1156.

6 Nurmatov U, Dhami S, Arasi S, Pajno GB, Fernandez-Rivas M, Muraro A, Roberts G, Akdis C, Alvaro-Lozano M, Beyer K, Bindslev-Jensen C, Burks W, du Toit G, Ebisawa M, Eigenmann P, Knol E, Makela M, Nadeau KC, O'Mahony L, Papadopoulos N, Poulsen LK, Sackesen C, Sampson H, Santos AF, van Ree R, Timmermans F, Sheikh A. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy 2017;72:1133-1147.

7 Romantsik O, Tosca MA, Zappettini S, Calevo MG. Oral and sublingual immunotherapy for egg allergy. Cochrane Database Syst Rev 2018;4(4):CD010638.

8 Xiong L, Lin J, Luo Y, Chen W, Dai J. The efficacy and safety of epicutaneous immunotherapy for allergic diseases: a systematic review and meta-analysis. Int Arch Allergy Immunol 2020;181(3):170-182.

9 Brożek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, Fiocchi A, Schünemann HJ. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clin Exp Allergy 2012;42(3):363-374.

10 Fisher HR, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?: a meta-analysis of published RCTs. Arch Dis Child 2011;96(3):259-264.

11 Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, Beyer K, Bindslev-Jensen C, Burks W, Ebisawa M, Eigenmann P, Knol E, Nadeau KC, Poulsen LK, van Ree R, Santos AF, du Toit G, Dhami S, Nurmatov U, Boloh Y, Makela M, O'Mahony L, Papadopoulos N, Sackesen C, Agache I, Angier E, Halken S, Jutel M, Lau S, Pfaar O, Ryan D, Sturm G, Varga EM, van Wijk RG, Sheikh A, Muraro A; EAACI Allergen Immunotherapy Guidelines Group. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy 2018;73(4):799-815.

12 Bégin P, Chan ES, Kim H, Wagner M, Cellier MS, Favron-Godbout C, Abrams EM, Ben-Shoshan M, Cameron SB, Carr S, Fischer D, Haynes A, Kapur S, Primeau MN, Upton J, Vander Leek TK, Goetghebeur MM. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy. Allergy Asthma Clin Immunol 2020;16:20.

This article is protected by copyright. All rights reserved

13 Remington BC, Krone T, Koppelman S. Quantitative risk reduction through peanut immunotherapy: Safety benefits of an increased threshold in Europe. Pediatr Allergy Immunol 2018;29(7):762-772.
14 Dua S, Ruiz-Garcia M, Bond S, Durham SR, Kimber I, Mills C, Roberts G, Skypala I, Wason J, Ewan P, Boyle R, Clark A. Effect of sleep deprivation and exercise on reaction threshold in adults with peanut allergy: A randomized controlled study. J Allergy Clin Immunol 2019;144(6):1584-1594.e2.
15 Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2, February 2021.
16 Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-394.
17 Melsen WG, Bootsma MCJ, Rovers MM, Bonten MJM. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clinical Microbiology Infection 2014;20(2):123-129.
18 Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, Brignardello-Petersen R, Carrasco-Labra A, De Beer H, Hultcrantz M, Kuijpers T, Meerpohl J, Morgan R, Mustafa R, Skoetz N, Sultan S, Wiysonge C, Guyatt G, Schünemann HJ. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126-135.
19 Chinthrajah S, Cao S, Liu C, Lyu SC, Sindher SB, Long A, Sampath V, Petroni D, Londei M, Nadeau KC. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight 2019 ;4(22):e131347.
20 Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, Wong DA. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol 2011 ;127(5):1309-10.e1.
21 Leung DYM, Sampson HA, Yunginger JW, Burks Jr AW., Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 2003;348:986-993.
22 Chu DK, Wood RA, French S, Fiocchi A, Jordana M, Waserman S, Brożek JL, Schünemann HJ. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet 2019;393(10187):2222-2232.
23 Sim K, Mijakoski D, Stoleski S, Del Rio PR, Sammut P, Le TM, Munblit D, Boyle RJ. Outcomes for clinical trials of food allergy treatments. Ann Allergy Asthma Immunol. 2020;125(5):535-542.
24 Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, Palmer C, Deighton J, Ewan P, Clark A. 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(9925):1297-1304.
25 Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, Leonard SA, Laubach SS, Kim EH, Vickery BP, Davis BP, Heimall J, Cianferoni A, MacGinnitie AJ, Crestani E, Burks AW. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of arc001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. J Allergy Clin Immunol Pract 2018;6(2):476-485.e3.
26 Blumchen K, Trendelenburg V, Ahrens F, Gruebl A, Hamelmann E, Hansen G, Heinzmann A, Nemat K, Holzhauser T, Roeder M, Rosenfeld L, Hartmann O, Niggemann B, Beyer K. Efficacy, safety, and quality of life in a multicenter, randomized, placebo-controlled trial of

Accepted Article

This article is protected by copyright. All rights reserved

low-dose peanut oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol Pract 2019;7(2):479-491.e10.
27 Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC, Manohar M, Boyd SD, Tibshirani R, Maecker H, Plaut M, Mukai K, Tsai M, Desai M, Galli SJ, Nadeau KC. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2019;394(10207):1437-1449.
28 Fauquert JL, Michaud E, Pereira B, Bernard L, Gourdon-Dubois N, Rouzaire PO, Rochette E, Merlin E, Evrard B. Peanut gastrointestinal delivery oral immunotherapy in adolescents: Results of the build-up phase of a randomized, double-blind, placebo-controlled trial (PITA study). Clin Exp Allergy 2018;48(7):862-874.
29 Hourihane J, Beyer K, Abbas A, Fernández-Rivas M, Turner PJ, Blumchen K, Nilsson C, Ibáñez MD, Deschildre A, Muraro A, Sharma V, Erlewyn-Lajeunesse M, Zubeldia JM, De Blay F, Sauvage CD, Byrne A, Chapman J, Boralevi F, DunnGalvin A, O'Neill C, Norval D, Vereda A, Skeel B, Adelman DC, du Toit G. Efficacy and safety of oral immunotherapy with AR101 in European children with a peanut allergy (ARTEMIS): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. Lancet Child Adolesc Health 2020;4(10):728-739.
30 Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO et al. AR101 oral immunotherapy for peanut allergy. N Engl J Med 2018;379(21):1991-2001.
31 Fleischer DM, Greenhawt M, Sussman G, Bégin P, Nowak-Wegrzyn A, Petroni D, Beyer K, Brown-Whitehorn T, Hebert J, Hourihane JO, Campbell DE, Leonard S, Chinthrajah RS, Pongracic JA, Jones SM, Lange L, Chong H, Green TD, Wood R, Cheema A, Prescott SL, Smith P, Yang W, Chan ES, Byrne A, Assa'ad A, Bird JA, Kim EH, Schneider L, Davis CM, Lanser BJ, Lambert R, Shreffler W. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: The PEPITES randomized clinical trial. JAMA 2019;321(10):946-955.
32 Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, Henning AK, Berin MC, Chiang D, Vickery BP, Pesek RD, Cho CB, Davidson WF, Plaut M, Sampson HA, Wood RA. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017;139(4):1242-1252.e9.
33 Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, Cheema AS, Leonard SA, Pongracic JA, Sauvage-Delebarre C, Assa'ad AH, de Blay F, Bird JA, Tilles SA, Boralevi F, Bourrier T, Hébert J, Green TD, Gerth van Wijk R, Knulst AC, Kanny G, Schneider LC, Kowalski ML, Dupont C. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA 2017;318(18):1798-1809.
34 Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, Sicherer SH, Liu AH, Stablein D, Henning AK, Mayer L, Lindblad R, Plaut M, Sampson HA. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013;131(1):119-27.e1-7.
35 Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992;90(2):256-62.
36 Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, Wood RA. 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(5):1275-82.e1-6.
37 Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R, Pajno GB. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. Allergy Asthma Proc 2009;30(4):443-448.

Accepted Article

This article is protected by copyright. All rights reserved

38 Lee JH, Kim WS, Kim H, Hahn YS. Increased cow's milk protein-specific IgG4 levels after oral desensitization in 7- to 12-month-old infants. Ann Allergy Asthma Immunol 2013;111(6):523-8.
39 Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008;121(2):343-347.
40 Martorell A, De la Hoz B, Ibáñez MD, Bone J, Terrados MS, Michavila A, Plaza AM, Alonso E, Garde J, Nevot S, Echeverria L, Santana C, Cerdá JC, Escudero C, Guallar I, Piquer M, Zapatero L, Ferré L, Bracamonte T, Muriel A, Martínez MI, Félix R. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011 Sep;41(9):1297-1304.
41 Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, Hanss Ch, Beaudouin E, Petit N, Kanny G. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol 2007;39(1):12-19.
42 Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, Passalacqua G. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol 2010;105(5):376-381.
43 Salmivesi S, Korppi M, Mäkelä MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatr 2013;102(2):172-176.
44 Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, Matsui EC, Burks AW, Wood RA. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008;122(6):1154-1160.
45 Dupont C, Kalach N, Soulaines P, Legoué-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol 2010;125(5):1165-1167.
46 Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, Steele P, Driggers S, Burks AW, Wood RA. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012;129(2):448-55, 455.e1-5.
47 Takahashi M, Soejima K, Taniuchi S, Hatano Y, Yamanouchi S, Ishikawa H, Irahara M, Sasaki Y, Kido H, Kaneko K. Oral immunotherapy combined with omalizumab for high-risk cow's milk allergy: a randomized controlled trial. Sci Rep 2017;7(1):17453.
48 Akashi M, Yasudo H, Narita M, Nomura I, Akasawa A, Ebisawa M, Takahashi T, Ohya Y. Randomized controlled trial of oral immunotherapy for egg allergy in Japanese patients. Pediatr Int 2017;59(5):534-539.
49 Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, Ruggeri P, Guglielmo F, Passalacqua G. Oral immunotherapy for egg allergy: a double-blind placebo-controlled study, with postdesensitization follow-up. J Allergy Clin Immunol Pract 2015;3(4):532-539.
50 Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a randomized controlled trial. Pediatr Allergy Immunol 2013;24(1):66-74.
51 Escudero C, Rodríguez Del Río P, Sánchez-García S, Pérez-Rangel I, Pérez-Farinós N, García-Fernández C, Ibáñez MD. Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg-allergic children. Clin Exp Allergy 2015;45(12):1833-1843.
52 Itoh-Nagato N, Inoue Y, Nagao M, Fujisawa T, Shimojo N, Iwata T. Desensitization to a whole egg by rush oral immunotherapy improves the quality of life of guardians: A multicenter, randomized, parallel-group, delayed-start design study. Allergol Int 2018;67(2):209-216.

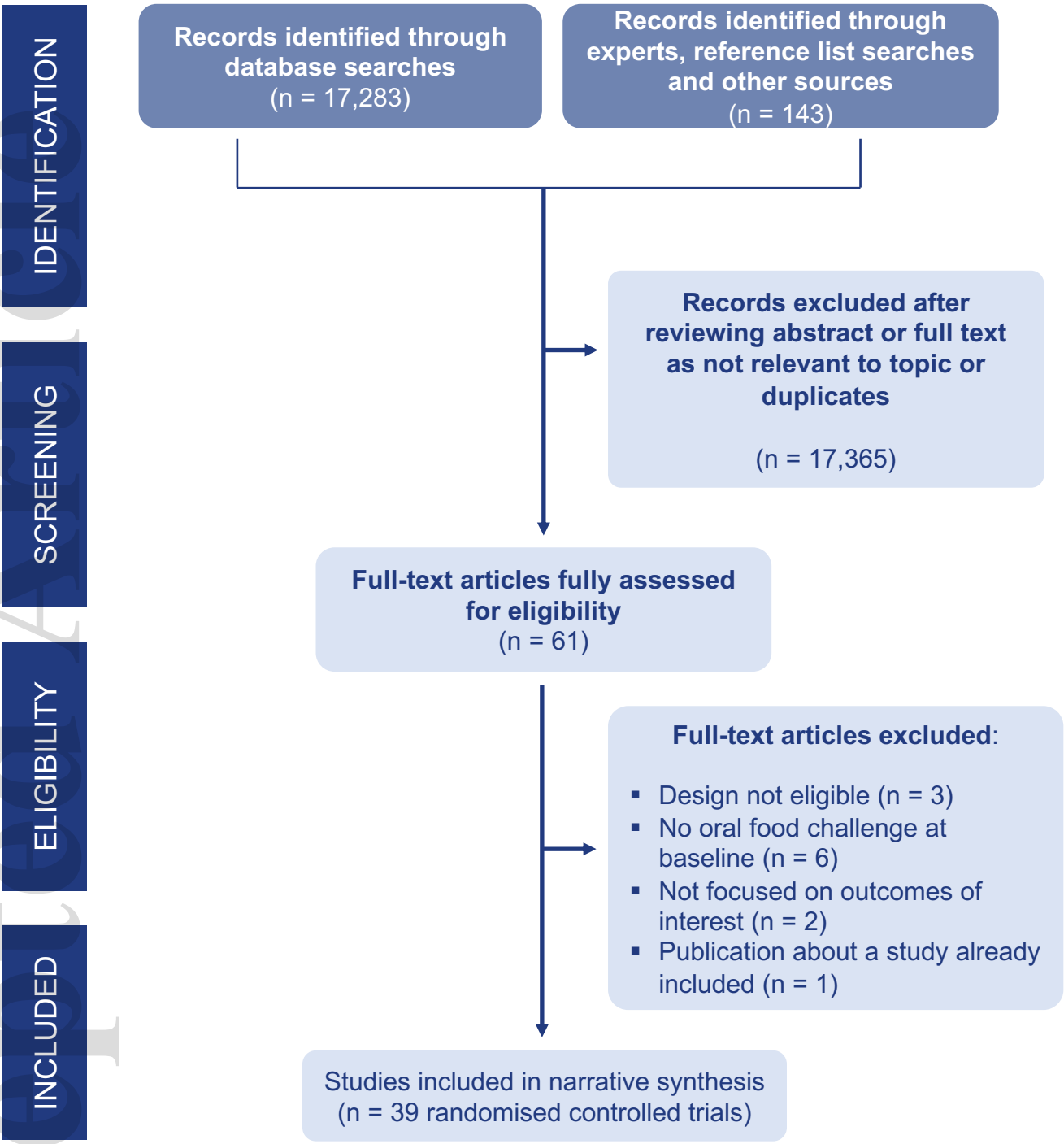
Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

53 Martín-Muñoz MF, Belver MT, Alonso Lebrero E, Zapatero Remón L, Fuentes Aparicio V, Piquer Gibert M, Plaza AM, Muñoz Román C, Martorell-Calatayud C, Martorell-Aragonés A, Blasco C, Vilá B, Gómez C, Nevot S, García Martinez JM, Madero Jarabo R, Echeverria L. Egg oral immunotherapy in children (SEICAP I): Daily or weekly desensitization pattern. Pediatr Allergy Immunol 2019;30(1):81-92.
54 Pérez-Rangel I, Rodríguez Del Río P, Escudero C, Sánchez-García S, Sánchez-Hernández JJ, Ibáñez MD. Efficacy and safety of high-dose rush oral immunotherapy in persistent egg allergic children: A randomized clinical trial. Ann Allergy Asthma Immunol 2017;118(3):356-364.e3.
55 Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. Hepatogastroenterology 1998;45(19):52-58.
56 Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy 2007;62(11):1261-1269.
57 Nowak-Węgrzyn A, Wood RA, Nadeau KC, Pongracic JA, Henning AK, Lindblad RW, Beyer K, Sampson HA. Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. J Allergy Clin Immunol 2019;143(2):651-661.e9.
58 Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R, Castelló JV, Alonso R, de Mateo JA, Cerdá-Trias T, San Miguel-Moncín Mdel M, Monzón S, García M, Palacios R, Cisteró-Bahíma A. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol 2005;116(5):1073-1079.
59 Fernández-Rivas M, Garrido Fernández S, Nadal JA, Díaz de Durana MD, García BE, González-Mancebo E, Martín S, Barber D, Rico P, Tabar AI. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy 2009;64(6):876-883.

This article is protected by copyright. All rights reserved



Accepted Article

This article is protected by copyright. All rights reserved

Online supplement S1: Search strategy

Search strategy for MEDLINE and EMBASE for immunotherapy

1. exp Food Hypersensitivity/
2. exp Milk Hypersensitivity/
3. exp Egg Hypersensitivity/
4. exp Peanut Hypersensitivity/
5. exp Tree nut Hypersensitivity/
6. exp Nut Hypersensitivity/
7. ((food or Oral Allergy Syndrome or milk or egg or peanut or arachis hypogaea or tree nut or hazelnut or brazil nut or walnut or chestnut or pistachio or almond or legumes or wheat or rice or soy or fish or seafood or shellfish or shrimp or lobster or crab or crawfish or kiwi or apple or peach or apricot or cherry or pear or plum or tomato or green pea or potato or carrot or parsley or celery or additives) adj3 (allerg* or hypersensitivit*)).mp.
8. or/1-7
9. exp Desensitization, Immunologic/
10. exp Immunotherapy/
11. Desensiti?ation.mp.
12. Hyposensitisation.mp.
13. Allergy vaccination.mp.
14. Immunotherapy.mp.
15. Oral Immunotherapy.mp.
16. Oral desensiti?ation.mp.
17. Specific oral tolerance induction.mp.
18. Oral tolerance induction.mp.
19. Sublingual immunotherapy.mp.
20. Epicutaneous immunotherapy.mp.
21. Subcutaneous immunotherapy.mp.
22. Or/9-21
23. exp Intervention Studies/
24. Intervention Studies.mp.
25. Experimental stud*.mp.
26. exp Clinical Trial/
27. Trial.mp.
28. Clinical Trial.mp.
29. Randomi?ed Controlled Trial.mp.
30. exp Placebos/
31. Placebos.mp.
32. exp Random Allocation/
33. Random Allocation.mp.
34. exp Double-Blind Method/
35. Double-Blind Method.mp.
36. Double-Blind design.mp.
37. exp Single-Blind Method/
38. Single-Blind Method.mp.
39. Single-Blind design.mp.
40. Triple-Blind Method.mp.
41. Random*.mp.
42. Cost:.mp.
43. Cost effective:.mp.
44. Cost utility:.mp.

45. Exp Health care Costs/
46. (Costs and Costs Analysis).mp.
47. Economic evaluation*.mp.
48. ((cost effective* adj1 analys*) or cost minimi?ation analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances).mp.
49. Quality of life.mp.
50. Efficacy.mp.
51. Effective*.mp.
52. Threshold.mp.
53. Biologic*.mp.
54. (omalizumab or TNX-901 or dupilumab or reslizumab or mepolizumab or benralizumab or ligelizumab or ANB020 or etokimab or tezepelumab or quilizumab or tralokinumab or nemolizumab).mp
55. Or/23-54
56. 8 and 22 and 55

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

Search strategy for CINAHL, Cochrane Library, ISI Web of Science and Scopus

(Food hypersensitivity or food allergy or Oral Allergy Syndrome or milk allergy or egg allergy or nut allergy or peanut allergy or arachis hypogaea allergy or tree nut allergy or hazelnut allergy or legumes allergy or wheat allergy or soy allergy or fish allergy or seafood allergy or shellfish allergy or kiwi allergy or apple allergy or peach allergy or additives hypersensitivity or additives allergy)

AND

(Immunologic, desensiti* or immunotherapy or hyposensitisation or oral immunotherapy or sublingual immunotherapy or subcutaneous immunotherapy or epicutaneous immunotherapy or intradermal immunotherapy or intralymphatic immunotherapy or intranasal immunotherapy or specific immunotherapy or oral desensiti* or Specific Oral Tolerance Induction or Oral Tolerance Induction or biologic* or omalizumab or TNX-901 or dupilumab or reslizumab or mepolizumab or benralizumab or ligelizumab or ANB020 or etokimab or tezepelumab or quilizumab or tralokinumab or nemolizumab)

AND

(Intervention stud* or experimental stud* or trial or clinical trial* or randomi* controlled trial or random allocation or single blind method or double blind method or triple blind method or random* or economic evaluation* or cost effective* analys* or cost analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances or quality of life or efficacy or threshold or desensiti* or sustained unresponsiveness)

Search strategy for MEDLINE and EMBASE for biological monotherapy

1. exp Food Hypersensitivity/
2. exp Milk Hypersensitivity/
3. exp Egg Hypersensitivity/
4. exp Peanut Hypersensitivity/
5. exp Tree nut Hypersensitivity/
6. exp Nut Hypersensitivity/
7. ((food or Oral Allergy Syndrome or milk or egg or peanut or arachis hypogaea or tree nut or hazelnut or brazil nut or walnut or chestnut or pistachio or almond or legumes or wheat or rice or soy or fish or seafood or shellfish or shrimp or lobster or crab or crawfish or kiwi or apple or peach or apricot or cherry or pear or plum or tomato or green pea or potato or carrot or parsley or celery or additives) adj3 (allerg* or hypersensitivit*)).mp.
8. or/1-7
9. Biologic*.mp.
10. (omalizumab or TNX-901 or dupilumab or reslizumab or mepolizumab or benralizumab or ligelizumab or ANB020 or etokimab or tezepelumab or quilizumab or tralokinumab or nemolizumab).mp.
11. Or/9-10
12. exp Intervention Studies/
13. Intervention Studies.mp.
14. Experimental stud*.mp.
15. exp Clinical Trial/
16. Trial.mp.
17. Clinical Trial.mp.
18. Randomi?ed Controlled Trial.mp.
19. exp Placebos/
20. Placebos.mp.
21. exp Random Allocation/
22. Random Allocation.mp.
23. exp Double-Blind Method/
24. Double-Blind Method.mp.
25. Double-Blind design.mp.
26. exp Single-Blind Method/
27. Single-Blind Method.mp.
28. Single-Blind design.mp.
29. Triple-Blind Method.mp.
30. Random*.mp.
31. Quasi random*.mp.
32. Controlled clinical trial.mp.
33.. Cost.mp.
34. Exp Health care Costs/
35. Economic evaluation*.mp.
36. ((cost effective* adj1 analys*) or cost minimi?ation analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances).mp.
37. Quality of life.mp.
38. Efficacy.mp.
39. Effective*.mp.
40. Or/12-39
56. 8 and 11 and 40

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

Search strategy for CINAHL, Cochrane Library, ISI Web of Science and Scopus

(Food hypersensitivity or food allergy or Oral Allergy Syndrome or milk allergy or egg allergy or nut allergy or peanut allergy or arachis hypogaea allergy or tree nut allergy or hazelnut allergy or legumes allergy or wheat allergy or soy allergy or fish allergy or seafood allergy or shellfish allergy or kiwi allergy or apple allergy or peach allergy or additives hypersensitivity or additives allergy)

AND

(biologic* or omalizumab or TNX-901 or dupilumab or reslizumab or mepolizumab or benralizumab or ligelizumab or ANB020 or etokimab or tezepelumab or quilizumab or tralokinumab or nemolizumab)

AND

(Intervention stud* or experimental stud* or trial or clinical trial* or randomi* controlled trial or random allocation or single blind method or double blind method or triple blind method or random* or quasi* or controlled clinical trial or economic evaluation* or cost effective* analys* or cost analys* or cost benefit analys* or cost utility analys* or cost consequence analys* or finances or quality of life or efficacy or desensiti* or sustained unresponsiveness)

Online supplement S2: Reasons for excluding shortlisted studies at full text review

We excluded more than 17,000 studies due to non-relevance, duplication, non-eligible study designs, not including outcomes of interest, not confirming food allergy with oral challenge or other reasons. We excluded after reading abstracts, and in some cases full text. Some studies we originally shortlisted for inclusion, but excluded after detailed full text review. These are listed below.

We acknowledge that other studies may be eligible for the review but not identified using our search criteria.

Citation	Reason for exclusion
Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, Stablein D, Henning AK, Vickery BP, Liu AH, Scurlock AM, Shreffler WG, Plaut M, Sampson HA. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med 2012;367(3):233-43.	No baseline food challenge. Eligibility determined based on clinical history of egg allergy and a serum egg-specific IgE.
Fuentes-Aparicio V, Alvarez-Perea A, Infante S, Zapatero L, D'Oleo A, Alonso-Lebrero E. Specific oral tolerance induction in paediatric patients with persistent egg allergy. Allergol Immunopathol 2013;41(3):143-50.	Baseline challenge only performed on those who had not suffered clinical episodes within the previous 3 months. In intervention group baseline open challenge performed in 27/40. In control group open challenge performed at baseline in all. No follow up challenge reported with control group. 21.8% of controls developed spontaneous tolerance to egg vs 92.5% tolerance in intervention group ($p < 0.0001$). Includes data on adverse events for intervention group, not controls.
García BE, González-Mancebo E, Barber D, Martín S, Tabar AI, Díaz de Durana AM, Garrido-Fernández S, Salcedo G, Rico P, Fernández-Rivas M. Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. J Investig Allergol Clin Immunol 2010;20(6):514-20.	Does not include outcomes of interest to the review. Explores skin reactivity using skin prick tests. No follow up food challenge
Giavi S, Vissers YM, Muraro A, Lauener R(4), Konstantinopoulos AP, Mercenier A, Wermeille A, Lazzarotto F, Frei R, Bonaguro R, Summermatter S, Nutten S, Papadopoulos NG. Oral immunotherapy with low allergenic hydrolysed egg in egg allergic children. Allergy 2016;71(11):1575-1584.	Baseline challenge not performed in all.
Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW, Martin L, Thebault C, Ruban C, Benhamou PH. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: A phase 1 study using the Viaskin patch. J Allergy Clin Immunol 2016;137(4):1258-1261.e10.	No baseline food challenge.
Leung DY, Shanahan WR Jr, Li XM, Sampson HA. New approaches for the treatment of anaphylaxis. Novartis Found Symp 2004;257:248-260.	Duplicates study already included.
MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, Heimall J, Makhija M, Robison R, Chinthrajah RS, Lee J, Lebovidge J, Dominguez T, Rooney C, Lewis MO, Koss J, Burke-Roberts E, Chin K, Logvinenko T, Pongracic JA, Umetsu DT, Spergel J, Nadeau KC, Schneider LC. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol 2017;139(3):873-881.e8.	All receive immunotherapy. Randomisation is between omalizumab and placebo.

Citation	Reason for exclusion
Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. Pediatr Allergy Immunol 2013;24(1):75-83.	Oral challenge OR convincing history were inclusion criteria. 3/20 were included based on history, not challenge.
Reier-Nilsen T, Carlsen KCL, Michelsen MM, Drottning S, Carlsen KH, Zhang C, Borres MP, Håland G. Parent and child perception of quality of life in a randomized controlled peanut oral immunotherapy trial. Pediatr Allergy Immunol 2019;30(6):638-645. AND Reier-Nilsen T, Michelsen MM, Lodrup Carlsen KC, Carlsen K-H, Mowinckel P, Nygaard UC, Namork E, Borres MP, Håland G. Feasibility of desensitizing children highly allergic to peanut by high-dose oral immunotherapy. Allergy 2019; 74: 337–48.	No outcomes in these papers relevant to the review. Measures quality of life but not with the tool listed as required in review protocol. Measured with the PedsQL 4.0. Adverse events reported for intervention group only / no control data.
Palosuo K, Karisola P, Savinko T, Fyhrquist N, Alenius H, Mäkelä MJ. A randomized, open-label trial of hen's egg oral immunotherapy: efficacy and humoral immune responses in 50 children. J Allergy Clin Immunol Pract (Published online ahead of print January 2021).	Compares 6 months of avoidance with 8 months of immunotherapy. However 8 months immunotherapy group also includes avoidance for 6 months then starting immunotherapy. No direct comparison between avoidance and immunotherapy.
Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, Hiegel A, Kamilaris J, Carlisle S, Yue X, Kulis M, Pons L, Vickery B, Burks AW. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011;127(3):654-60.	No challenge at baseline, only skin prick test.
Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, Plaut M, Sampson HA. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol 2016;137(4):1103-1110.e11.	All receive immunotherapy. Randomisation is between omalizumab and placebo.

Online supplement S3: Definitions of adverse reactions used in studies

This supplement sets out the definitions of adverse events used in the studies included in the review.

When extracting data from the studies and in the text of the review and supplements, the reviewers used the following definitions:

Life threatening reactions: presentations that that are likely to result in a fatality without medical intervention, e.g. respiratory arrest, hypotension or bradycardia.

Severe reactions: various definitions of severe reactions were used in studies (see the following pages). In general these involved marked impact on participants (e.g. symptomatic bronchospasm, hypotension) and need for medical intervention.

Adrenaline use: use of intramuscular adrenaline to treat anaphylaxis.

Anaphylaxis: as reported by authors since most studies did not provide a definition.

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Akashi 2017	Egg	Clinical report during 6-month treatment.	No definition given	No definition given	No definition given	No definition given	Yes
Anagnostou 2014	Peanut	No controlled data reported for adverse events					
Bird 2018	Peanut	Clinical report during treatment. Assessed symptom severity using protocol consistent with PRACTALL guidelines and the Consortium of Food Allergy Research's specific grading system for allergic reactions	Severity of dose-related allergic symptoms was determined per investigator judgment, using the definitions in the PRACTALL report on DBPCFC as a general guide. For assessing symptom severity, consistent with both the PRACTALL guidelines and the Consortium of Food Allergy Research's specific grading system for allergic reactions. GRADE 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalisation is possible. Symptoms may include bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, and transient hypotension among others. Parenteral medication(s) are usually indicated. medDRA dictionary also used for grading.	No definition given	No definition given	Grade 4-Life threatening: Extreme limitation in activity, significant assistance required; significant medical / therapy. Intervention is required; hospitalisation is probable. Symptoms may include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms	No

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Blumchen 2019 and Trendelenburg 2020	Peanut	During the study period adverse events were recorded daily by parents in a diary and were assessed every one to two weeks by the blinded study physician.	Severity of possible allergic reactions was determined by the investigator using a modified grading system for food-induced anaphylaxis. Severe (grade IV): wheeze, shortness of breath with wheeze/cough/decrease in peak flow or generalised hives being present simultaneously, and stridor with a simultaneous decrease in peak flow.	No definition given	No definition given	Life-threatening (grade V): respiratory arrest, bradycardia, arterial hypotension, cardiac arrest, or loss of consciousness.	No
Caminiti 2009	Milk	Unclear method. Reports worst reactions during treatment. Unclear if happened at home or in office.	No definition given	No definition given	No definition given	No definition given	Yes
Caminiti 2015	Egg	Adverse reactions were defined as the occurrence of one or more of the following: urticaria, exacerbation of eczema (>10 point increase in scoring Atopic Dermatitis), angioedema, vomiting, diarrhoea, rhinitis, wheezing, conjunctivitis, or hypotension during desensitisation and then during follow up when eating egg.	Reaction severity was evaluated according to "Grading of Food-Induced Anaphylaxis According to Severity of Clinical Symptoms" by Sampson. Criteria for anaphylaxis were those reported in EAACI position paper (Muraro 2007)	No definition given	No definition given	No definition given	Yes

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Chinthrajah 2019	Peanut	Safety outcomes were determined by Common Terminology Criteria for adverse events version 4.03 and documented per regulatory guidelines.	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care. Severe reactions are any reactions with Grade 3 symptoms	No definition given	No definition given	Life-threatening consequences; urgent intervention indicated.	Yes
Dello Iacono 2013	Egg	Adverse events documented and graded according to Sampson 2003.	Grade 4 any of Grade 1-3 plus diarrhoea, hoarseness, cough, difficulty swallowing, dyspnoea, wheezing, cyanosis, dysrhythmia and/or mild hypotension, light headiness / feeling of pending doom (Sampson 2003:).	No definition given	No definition given	Sampson grade 5: any of 1-4 plus loss of bowel control, respiratory arrest, severe bradycardia and/or hypotension or cardiac arrest, loss of consciousness.	Yes
Dupont 2010	Milk	Local reactions exceeding simple erythema, with or without local pruritus, and associating erythema, oedema, and infiltration (grade I of the International Contact Dermatitis Research Group classification) were considered local adverse events. Respiratory, ear nose throat and digestive manifestations, and generalised cutaneous disorders were considered general adverse events.	No definition given	No definition given	No definition given	No definition given	Yes

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Enrique 2005	Hazelnut	Adverse events recorded during updosing and maintenance dosing. How collected not stated.	No definition given	No definition given	No definition given	No definition given	No info provided
Escudero 2015	Egg	Measured during build-up phase and maintenance phase. Adverse reactions collected by parents / guardians in registry forms during therapy.	Severe adverse events were defined as severe respiratory distress and/or symptoms of hypotension) Clark 2003.	No definition given	No definition given	No definition given	No info provided
Fauquert 2018	Peanut	Adverse events recorded in patient's paper diary. Number of reactions per patient is presented	Classified by the severity grades of Ring and Messmer (modified) 1977. GRADE: 1,2,3a,3b or 4 Anaphylaxis was defined by Sampson in 2006 as the rapid appearance (minutes to hours) after exposure to a probable allergen of symptoms indicative of an adverse effect on two organs.	No definition given	No definition given	No definition given	Yes
Fernández-Rivas 2009	Peach	Measured during the study period; classified as local and systemic adverse events, used diary cards from patients	No definition given	No definition given	No definition given	No definition given	Yes

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Fleischer 2013	Peanut	Measured at occurrence during challenge or at home during dosing. Solicited dosing symptoms were recorded on a daily basis. Other unsolicited adverse events were separately recorded. (only blinded 44 weeks included)	No definition given	No definition given	Not given, but references Sampson 2006	No definition given	No
Fleischer 2019 and DunnGalvin 2021	Peanut	Participant diaries	Classified as moderate anaphylactic reactions without evidence of cardiovascular, neurologic, or respiratory compromise.	No definition given	Anaphylaxis is a generalised allergic reaction that is rapid in onset and may progress to death.	Severe anaphylaxis was defined by the presence of cyanosis, hypoxia, hypotension, confusion, loss of consciousness, or incontinence. Adverse events were assessed by investigators, and a serious adverse event was defined according to the International Conference on Harmonisation–Good Clinical Practice definition.	Yes
Itoh-Nagato 2018	Egg	No information	Allergic reactions were classified according to a modification of Sampson's grading system. “rhinorrhea” and the “sensation of throat pruritus or tightness, cough” were downgraded because author previous experience showed that these symptoms often occurred but did not interfere with OIT.	No definition given	No definition given	Allergic reactions were classified according to a modification of the Sampson's grading system.	Yes

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Jones 2017	Peanut	Daily diary. Adverse events assessed at telephone monthly and clinic visits.	COFAR grade 3; Marked limitation in activity. Some assistance is usually required; medical intervention/therapy required, and hospitalisation is possible. Symptoms can include bronchospasm with dyspnoea, severe abdominal pain, throat tightness with hoarseness, and transient hypotension among others. Parenteral medication(s) are usually indicated.	Not defined but taken to mean non-patch site reactions.	No definition given	COFAR grade 4; Extreme limitation in activity. Significant assistance is required; significant medical/ therapy is required. Intervention is required; hospitalisation is probable. Symptoms might include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms.	Yes
Keet 2012	Milk	During dose escalation and maintenance including with home diary.	No definition given	No definition given	No definition given	No definition given	Yes
Lee 2013	Milk	Recorded during therapy, no details about assessment approach	No definition given	No definition given	No definition given	No definition given	Yes
Longo 2008	Milk	Recorded during therapy, no details about assessment approach	Severe defined as marked dyspnoea/hypotensive symptoms (collapse/loss of consciousness) (Clark 2003)	No definition given	No definition given	No definition given	Yes

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Martín-Muñoz 2019	Egg	Reported according to rate of total dose adverse reactions and their grades, which were assessed by the study coordinator according to Sampson's grading (Grade 1, 2, 3, 4)	Adverse reactions assessed according to Sampson's grading.	No definition given	No definition given	No definition given	No info provided
Martorell 2011	Milk	No information	Severe reactions defined as severe bronchospasm, breathing difficulties with inspiratory stridor, hypotension and anaphylactic shock.	No definition given	No definition given	No definition given	Yes
Morisset 2007	Milk	No information	No definition given	No definition given	No definition given	No definition given	No info provided
Narisety 2015		No information. Only 6 months blinded therapy included.	No definition given	No definition given	No definition given	No definition given	Yes
Nowak-Węgrzyn 2019	Wheat	No information. Only first 12 months included.	No definition given	No definition given	No definition given	No definition given	No
O'B Hourihane 2020	Peanut	Treatment-emergent adverse events and serious adverse events were recorded.	The Common Toxicity Criteria for Adverse Events (CTCAE; version 4.03) was used by investigators to assess the severity of all adverse events (severe is grade 3) except for hypersensitivity events, for which the Consortium of Food Allergy Research-modified CTCAE was applied. The protocol definition of anaphylaxis was consistent with both the US National Institute of Allergy and Infectious Diseases criteria and the Food Allergy and Anaphylaxis Network criteria.	The term systemic allergic reaction was used to describe anaphylactic reaction events of any severity, and the term anaphylaxis was used to distinguish severe anaphylactic reaction events.	No definition given	The Common Toxicity Criteria for Adverse Events grade 4.	No

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Oppenheimer 1992	Peanut	During therapy using symptom scores	No definition given	No definition given	No definition given	No definition given	Yes
Pajno 2010	Milk	Measured during therapy and challenge	Not specified	No definition given	No definition given	No definition given	Yes
Patriarca 1998	Multiple	No comparative adverse event data reported					
Pérez-Rangel 2017	Egg	No comparative adverse event data reported					
Salmivesi 2013	Milk	Retrospective parental interview with an investigator.	No definition given	No definition given	Anaphylactic reaction was considered if there were symptoms from two or more organ systems treated by intramuscular adrenaline.	No definition given	Yes
Sampson 2017	Peanut	Assessed throughout study. TEAEs were defined as events that had a start time on or after dosing of the investigational product. Only phase 2b trial period included.	No definition given	No definition given	Anaphylaxis is a generalised allergic reaction that is rapid in onset and may progress to death.	No definition given	No
Skripak 2008	Milk	Patient diary	No definition given	No definition given	No definition given	No definition given	Yes
Staden 2007	Multiple	Recorded during intervention and challenge	No definition given	No definition given	No definition given	No definition given	No
Takahasi 2017	Milk	Assessed with escalation of dose	References Sampson grading	No definition given	No definition given	Sampson grade 4	Yes

Citation	Allergy type	Adverse events: when and how measured	Severe reaction definition	Systemic reaction definition	Anaphylaxis definition	Life threatening reaction definition	Identified reactions from intervention?
Vickery 2018	Peanut	Recorded during treatment. Only 4-17 year group reported.	Used National Cancer Institute Common Toxicity Criteria (NCI-CTC) with the modification previously used by the Consortium of Food Allergy Research (CoFAR) for hypersensitivity events and with the use of the NCI-CTC for all other events.	Clinically important systemic allergic reactions that were not classified as anaphylaxis according to this definition, consistent with guidance from the Food and Drug Administration.	Anaphylaxis was defined in the protocol according to National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network criteria.	COFAR grade 4; Extreme limitation in activity. Significant assistance is required; significant medical/therapy is required. Intervention is required; hospitalisation is probable. Symptoms might include persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms.	No

Online supplement S4: Wording conventions used to summarise evidence (GRADE)

Certainty of evidence	Size of effect			
	None / minor / not clinically meaningful (0% to 10% absolute difference)	Small (10% to 25% absolute difference)	Medium (26% to 50% absolute difference)	Large (51%+ absolute difference)
High	X does not reduce / increase outcome	X reduces / increases outcome slightly	X reduces / increases outcome	X results in a large reduction / increase in outcome
Moderate	X probably does not reduce / increase outcome	X probably reduces / increases outcome slightly	X probably reduces / increases outcome	X probably results in a large reduction / increase in outcome
Low	X may not reduce / increase outcome	X may reduce / increase outcome slightly	X may reduce / increase outcome	X may result in a large reduction / increase in outcome
Very low	It is unclear whether [intervention] has any impact because the certainty of the evidence is very low			

Online supplement S5: Characteristics of included studies and risk of bias assessment

Characteristics of included studies - immunotherapy

Further details about risk of bias are on other pages

Study	Allergy type	Admin route	Overall risk of bias	Region	Industry sponsored	Total participants began	Main population	Allergy severity	Raw or cooked	Duration in weeks, inc maintenance	Comparator
Akashi 2017	Egg	Oral	Moderate	Asia	Yes	36	Children	Mild / moderate	Raw	27	Elimination
Anagnostou 2014	Peanut	Oral	Moderate	Europe	No	99	Children	Mixed	Roasted	27	Elimination
Bird 2018	Peanut	Oral	Low	USA	Yes	55	Mixed	Moderate	Roasted	24	Placebo
Blumchen 2019 / Trendelenburg 2020	Peanut	Oral	Low	Europe	No	62	Children	Mixed	Roasted	68	Placebo
Caminiti 2009	Milk	Oral	High	Europe	No	6	Children	Severe	Raw	18	Placebo
Caminiti 2015	Egg	Oral	Low	Europe	No	31	Children	Mild / moderate	Raw	16	Placebo
Chinthrajah 2019	Peanut	Oral	Low	USA	No	120	Children	Mixed	Roasted	156	Placebo
Dello Iacono 2013	Egg	Oral	Moderate	Europe	No	20	Children	Severe	Raw	27	Elimination
Dupont 2010	Milk	Epicutaneous	Moderate	Europe	Yes	19	Mixed	Mixed	Raw	12	Placebo
Enrique 2005	Hazelnut	Sublingual	Moderate	Europe	No	23	Adults	Mixed	Raw	11	Placebo
Escudero 2015	Egg	Oral	Moderate	Europe	No	61	Children	Mixed	Raw	13	Elimination
Fauquert 2018	Peanut	Oral	Moderate	Europe	No	30	Children	Mixed	Roasted	24	Placebo
Fernández-Rivas 2009	Peach	Sublingual	Moderate	Europe	Yes	55	Adults	Mixed	Raw	29	Placebo
Fleischer 2013	Peanut	Sublingual	Low	USA	No	40	Adults	Mild / moderate	Raw	44	Placebo
Fleischer 2019 / DunnGalvin 2021	Peanut	Epicutaneous	Low	Multiple	Yes	356	Children	Mild / moderate	Raw	52	Placebo
Itoh-Nagato 2018	Egg	Oral	Moderate	Asia	No	45	Children	Mixed	Roasted	13	Elimination
Jones 2017	Peanut	Epicutaneous	Low	USA	Yes	74	Mixed	Mild / moderate	Raw	52	Placebo
Keet 2012	Milk	OIT vs SLIT	Moderate	USA	No	30	Children	Mixed	Raw	80	OIT vs SLIT
Lee 2013	Milk	Oral	High	Asia	No	31	Infants	Mixed	Raw	27	Elimination
Longo 2008	Milk	Oral	Moderate	Europe	Not reported	60	Children	Severe	Raw	52	Elimination
Martín-Muñoz 2019	Egg	Oral	Moderate	Europe	No	101	Children	Mixed	Raw	52	Elimination
Martorell 2011	Milk	Oral	High	Europe	Not reported	60	Infants	Mild / moderate	Raw	52	Elimination
Morisset 2007	Milk	Oral	High	Europe	Not reported	42	Mixed	Mild / moderate	Raw	13	Elimination
Narisety 2015	Peanut	OIT vs SLIT	Moderate	USA	No	21	Mixed	Mild / moderate	Raw	52	OIT vs SLIT

Study	Allergy type	Admin route	Overall risk of bias	Region	Industry sponsored	Total participants began	Main population	Allergy severity	Raw or cooked	Duration in weeks, inc maintenance	Comparator
Nowak-Węgrzyn 2019	Wheat	Oral	Moderate	USA	Yes	46	Mixed	Mild / moderate	Raw	52	Placebo
O'B Hourihane 2020	Peanut	Oral	Low	Europe	Yes	175	Children	Mixed	Raw	40	Placebo
Oppenheimer 1992	Peanut	Subcutaneous	High	USA	No	8	Mixed	Severe	Raw	5	Placebo
Pajno 2010	Milk	Oral	Moderate	Europe	No	30	Children	Mixed	Raw	18	Placebo
Patriarca 1998	Multiple	Oral	High	Europe	Not reported	24	Children	Mixed	Raw	27	Elimination
Pérez-Rangel 2017	Egg	Oral	High	Europe	Yes	33	Children	Mild / moderate	Raw	23	Elimination
Salmivesi 2013	Milk	Oral	High	Europe	No	28	Children	Mixed	Raw	23	Placebo
Sampson 2017	Peanut	Epicutaneous	Low	Multiple	Yes	221	Mixed	Mixed	Raw	52	Placebo
Skripak 2008	Milk	Oral	Moderate	USA	No	20	Children	Mild / moderate	Raw	23	Placebo
Staden 2007	Multiple	Oral	Moderate	Europe	No	45	Children	Mild / moderate	Raw	72	Elimination
Takahasi 2017	Milk	Oral + omalizumab	High	Japan	No	16	Children	Severe	Cooked	8 weeks omalizumab first then 16 weeks	Elimination
Vickery 2018	Peanut	Oral	Low	Multiple	Yes	555	Children	Mixed	Roasted	52	Placebo

Further details about peanut oral immunotherapy studies

	SPT mm Wheal DM	sIgE KU/L	Age	Inclusion criterion challenge	Average tolerance threshold at inclusion Median (IQR) MDT mean (range)
Anagnostou	Mean(SD) 8.92 mm (3.02)	Mean SD 202.9 (539)	Mean, SD 12.4 (2.42)		To be calculated from change in NOAELS
Bird	Median (range) 14 mm (5-30)	Median (range) 64.3 (0.8-≥100.0)	Median (range) 7 (4-21)	≤ 100 mg (143 mg cumulative) dose of peanut protein	13 mg (3-43)
Blumchen	Median (IQR) 8 mm (6.5-9.5)	Median (IQR) 347 kU/L (193-766.5)	median (IQR) 6.6 (4.8-9.8)	< 300 mg reaction	30 (10-300) mg
Chinthrajah	O gr 13.3 mm (8.5-18.1) 300 gr11.5 mm (8.5-15.5)	0 gr75.7 kU/L (13.1-282.5) 300 gr 99.3 kU/L (15.3-132.5)	0 group: 10 (9-13) 300 gr 11 (7-17) total :11 (8-15)	≤ 500 mg of peanut protein!	25 mg for each arm.
Fauquert	12.4 mm (6.7)	162 ku/L (200) Ara h 2 79 (85)	Mean (SD) 14.5 (1.8)	over 20 mg and below 400 mg (pp)	(CUM) 122 mg pp (122-400)
Hourihane	9.5 mm (7.50- 103.00)	Median kU/L 43.50 (5.20- 147.000)	9.1 (4-17) 73%: 4-11 27%:12-17	Over 3 mg and Below 300 mg pp	10 (3-10) mg
Vickery	mm (IQR) 11 (9-14)	Median kUA/L 69 (19-194)	Mean unknown 64% 4-11 36% 12-17	Below 100 mg pp	10 (3-30) mg
Mean	**11.1 mm**	**132.9 KU/L**		**100-400 mg**	**33.6 mg**

Risk of bias assessment - peanut

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, Palmer C, Deighton J, Ewan P, Clark A. 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(9925):1297-1304.	Low Used audited online system, 1:1. Group allocation not masked but this risk is covered in other criteria for assessment. Minimisation was used to reduce imbalance of baseline covariates, with a random element using a weighting.	Low Most received allocated intervention (3/50 controls did not want control intervention and withdrew); all 49 intervention group received intervention	Moderate/High >20% in intervention group did not have double blind challenge. In intervention group 5 withdrew and 1 discontinued / 49. 49 analysed but 10 excluded from primary analysis since no follow up challenge. Power calculations showed 49 needed in each group, so not powered to extent expected. Did per protocol analysis.	Moderate Double blind challenges. All study personnel were masked to the challenge assignment except the scientist who prepared the challenge material; they had no interaction with the participant or study team. However compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Crossover element of trial not included in extraction for this review. Single centre.	Low Analysed according to pre-specified plan (available online)	Moderate
Bird JA, Spergel JM, Jones SM et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of arc001, a Randomised, double-blind, placebo-controlled phase 2 clinical trial. J Allergy Clin Immunol Pract 2018;6(2):476-485.e3.	Low 1:1 ratio. Central randomization schedule of randomly permuted blocks that was prepared by an independent unblinded statistician and accessed by the investigational sites via an automated system.	Low All received allocated intervention.	Low Little missing data. 6 who discontinued treatment before exit challenge were considered non-responders	Low Double blind challenges. Multicentre (8 USA). Power calculation was low (80%), used for sample size estimate.	Low Analysed according to pre-specified plan (online). However difficult to extract safety data	Low

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Blumchen K, Trendelenburg V, Ahrens F et al. Efficacy, safety, and quality of life in a multicentre, Randomised, placebo-controlled trial of low-dose peanut oral immunotherapy in children with peanut allergy. J Allergy Clin Immunol Pract 2019;7(2):479-491.e10. AND Trendelenburg V, Blumchen K, Bellach J, Ahrens F, Gruebl A, Hamelmann E, Hansen G, Heinzmann A, Nemat K, Holzhauser T, Röder M, Niggemann B, Beyer K. Peanut oral immunotherapy protects patients from accidental allergic reactions to peanut. J Allergy Clin Immunol Pract 2020;8(7):2437-2441.	Low Recruited consecutively from clinics. Participants assigned via block randomization with size of 4 using computerised system, 1:1 stratification for age (over or under 6 years) and peanut specific IgE performed by independent statistician	Low Received allocated intervention. Researchers and participants blinded	Low Little missing data. All Randomised were included for the analysis of the primary endpoint as the intention to treat population. For the robustness of the statistical analysis of the primary endpoint a worst case analysis was also conducted where all drop outs of the placebo group were considered to reach the primary endpoint and all drop outs of active group were considered to fail the primary endpoint.	Low All participants were assessed in the same way. Multicentre (7 German sites)	Low Analysed according to pre-specified plan.	Low

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Chinthrajah RS, Purington N, Andorf S, Long A, O'Laughlin KL, Lyu SC, Manohar M, Boyd SD, Tibshirani R, Maecker H, Plaut M, Mukai K, Tsai M, Desai M, Galli SJ, Nadeau KC. Sustained outcomes in oral immunotherapy for peanut allergy (POISED study): a large, randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2019;394(10207):1437-1449.	Low Randomly assigned (2.4: 1.4: 1) in a two-by-two block design via a computerised system. Blinded. Original protocol amended. Prespecified randomisation list was generated by a statistician who had no further involvement with the trial. The unblinded investigational pharmacist used the randomisation list to assign treatment allocation. Participants were enrolled by a separate clinical team. A master randomisation assignment list was kept by the investigational pharmacist in a locked cabinet. Allocation concealed via secure communication.	Low As intended. Pharmacist assigned treatment on the basis of a randomised computer list. Peanut or placebo (oat) flour was administered orally and participants and the study team were masked throughout by use of oat flour that was similar in look and feel to the peanut flour and nose clips, as tolerated, to mask taste	Low 16/120 (13%) lost to follow up but ITT analysis used	Low Measured in same way. Double blind challenges. Order random. But single centre. Multiple comparisons undertaken and may not be powered for all. Only objective allergic reactions were used for eligibility and for endpoint testing. In the discontinuation phase, masking was ensured through protocol-regulated procedures in which each participant received the same volume of dry weight flour (peanut flour for peanut protein vs oat flour for placebo) and the study team and participants remained masked.	Low Appears analysed according to pre-specified plan. Intention to treat analysis. Sustained unresponsiveness reporting may introduce some interpretation issues as not clearly differentiating 52 week period	Low
Fauquert JL, Michaud E, Pereira B et al. Peanut gastrointestinal delivery oral immunotherapy in adolescents: Results of the build-up phase of a Randomised, double-blind, placebo-controlled trial (PITA study). Clin Exp Allergy 2018;48(7):862-874.	Low A central randomisation centre used computer-generated tables to allocate treatments. 2:1 ratio. The random allocation process was performed with a computer software program (Stata) that generates a sequence of blocks of different sizes.	Low Assigned as planned. Double blind	Low 2 people from intervention group withdrew due to adverse effects but used intention to treat analysis.	Moderate risk All assessed in the same way. Blinded. Multicentre (3). Power required 60 participants. Planned blinded interim analysis as the primary outcome was reached, so stopped randomisation after the 30th patient and unblinded the study. This means study did not recruit as expected.	Low Analysed in line with pre-specified plan, intention to treat analysis.	Moderate

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, Sicherer SH, Liu AH, Stablein D, Henning AK, Mayer L, Lindblad R, Plaut M, Sampson HA. Sublingual immunotherapy for peanut allergy: a Randomised, double-blind, placebo-controlled multicentre trial. J Allergy Clin Immunol 2013;131(1):119-27.e1-7.	Low 1:1 random assignments were centrally prepared, stratified by site, and sequentially provided to unblinded site pharmacists. Primary investigators, clinical and laboratory staff, subjects, and families remained blind A cohort of subjects aged 18 to 40 years was enrolled initially; after 20 weeks of therapy and Data Safety Monitoring Board review, subjects aged 12 to 40 years were enrolled.	Low Almost all received as expected	Low Focusing on blinded part for outcomes of interest in this review. 2 intervention and 1 placebo withdrew but treated as non responders	Low Blinded for first part. Second part was open, but not focus of this review. Multicentre (5)	Unclear Planned analysis uncertain. Number / proportion of participants in each group experiencing adverse events unclear	Low

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Fleischer DM, Greenhawt M, Sussman G et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: The PEPITES Randomised clinical trial. JAMA 2019;321(10):946-955. AND DunnGalvin A, Fleischer DM, Campbell DE, O'B Hourihane J, Green TD, Sampson HA, Greenhawt M. Improvements in Quality of Life in Children Following Epicutaneous Immunotherapy (EPIT) for Peanut Allergy in the PEPITES and PEOPLE Studies. J Allergy Clin Immunol Pract 2021;9(1):216-224.e1.	Low Participants were Randomised 2:1, stratified by screening eliciting dose. Randomisation was determined using a computer-generated random number; there was a blocking schema for each stratification criterion (screening eliciting dose stratum), and the block size was 6	Low Double-blind. Participants received allocated treatment. 98.5% adherence	Low 90% of participants completed the trial. 36/356 did not complete but were treated as non-responders (intention to treat analysis)	Low Blinded challenges. All assessed in prespecified standardised way. Participants with missing food challenge values at 12 months were counted as non-responders in this analysis. Multicentre (31 sites across 5 countries)	Low Analysed in line with pre-specified plan.	Low

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, Henning AK, Berin MC, Chiang D, Vickery BP, Pesek RD, Cho CB, Davidson WF, Plaut M, Sampson HA, Wood RA. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017;139(4):1242-1252.e9.	Low Randomisation appears Computerised. 1:1:1 assignment. Stratified by site. Enrolment and randomisation of younger participants (ages 4-<6 years) was paused after the first 10 participants were enrolled for a predetermined interim safety review after 35 days of dosing	Low All received expected intervention	Low 6/74 discontinued (3 placebo, 3 intervention). All considered non-responders, intention to treat analysis	Low Double blind challenges. Multicentre (5). Slightly underpowered according to author's own calculations	Low Undertook some post hoc analyses, but data from these not used for this review.	Low
O'B Hourihane J, Beyer K, Abbas A et al. Efficacy and safety of oral immunotherapy with AR101 in European children with a peanut allergy (ARTEMIS): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. Lancet Child Adolesc Health 2020;4(10):728-739.	Low Randomised 3:1, masked. Participants were randomly assigned in blocks of eight by a interactive web response system, using a computerised random number generator.	Low All received expected intervention. Masked tasting placebo. All participants, investigators, and care providers were masked to treatment allocation throughout.	Low Used intention to treat analysis but a lot of dropouts: 26 intervention; 3 controls. Other elements of methods low risk of bias so have not listed higher risk for this element.	Low All participants assessed in the same way. Multicentre (18).	Low Analysed in line with pre-specified plan (available in detail online)	Low

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol 1992;90(2):256-62.	Low Researchers and participants blind to randomisation code. Generation method not described	High Study terminated and unblinded after death of one patient due to accidental administration of maintenance dose to placebo participant. Investigators blinded to group assignment.	High Only 4/8 underwent second challenge. 11 originally enrolled	High Limited measurement due to early termination	High Early termination influenced what could be reported. No statistical analysis could be performed. However reporting focuses on symptom scores and 'positive' results, even though very small numbers and not statistically powered or significant	High
Sampson HA, Shreffler WG, Yang WH et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a Randomised clinical trial. JAMA 2017;318(18):1798-1809.	Low Randomisation concealed. Assigned equally to 4 groups. Randomisation was stratified by site and age group using a web system.	Low Received expected intervention. Product cannot be accessed outside of research trial.	Low 12/221 missing. All assumed to be non-responders in intention to treat analysis.	Low Double blind challenges. Multicentre (22). Power calculation provided	Low Analysed in line with pre-specified plan. Notes 4 additional secondary end points in protocol not presented in this report.	Low

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO et al. AR101 oral immunotherapy for peanut allergy. N Engl J Med 2018;379(21):1991-2001.	Low Researchers and participants blinded to randomisation code, 3:1 randomisation. Randomisation was performed according to a central randomisation schedule of randomly permuted blocks, with the use of an interactive online system. An unbalanced randomisation was chosen in order to maximize the number of observations of participants receiving active treatment and to minimize the number of participants who were randomly assigned to an inactive regimen for 1 year	Low Blind allocation; allocated as planned	Low Among participants 4 to 17 years of age, 294 of 372 (79.0%) in the active-drug group and 115 of 124 (92.7%) in the placebo group completed the trial. Hi dropout in intervention group, but used intention to treat analysis	Low Multicentre (66 sites in 10 countries)	Low Analysed in line with pre-specified plan (online). Enrolled people up to 55 years, but prespecified primary analysis was 4-17 year olds	Low

Risk of bias assessment - cow's milk

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, Ruggeri P, Guglielmo F, Passalacqua G. Oral immunotherapy for egg allergy: a double-blind placebo-controlled study, with postdesensitisation follow-up. J Allergy Clin Immunol Pract 2015;3(4):532-9.	Low Randomisation by computer generated list. Concealment uncertain	Low Received allocated intervention. Follow up open label where dietary interventions may not have been consistent.	Low 1 withdrawal from each group, but small numbers overall so any withdrawal is important	Low Measured in same way. Double blind challenges. 2 centres. However small numbers, no power calculation. Intention to treat analysis.	Low Results appear reported as planned but some reporting issues e.g. baseline challenges, inclusion and exclusion criteria and adverse events measurement not clearly reported.	Low
Dupont C, Kalach N, Soulaines P, Legoué-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol 2010;125(5):1165-7.	Unclear 1:1 allocation. Randomisation method not described	Low All received the intervention	Low Intention to treat analysis. Three patients were excluded from the per protocol population (1 lost to follow-up and 2 enrolled despite baseline CTD >67.1 mL)	Moderate All assessed in the same way, but open challenges. 2 centres. Small sample.	Low Analysed in line with pre-specified plan. Patients with at least 1 treatment dose were included in the intention-to-treat analysis. The per protocol analysis included patients not lost to follow-up who completed the study without major protocol deviation.	Moderate

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Lee JH, Kim WS, Kim H, Hahn YS. Increased cow's milk protein-specific IgG4 levels after oral desensitisation in 7- to 12-month-old infants. Ann Allergy Asthma Immunol 2013;111(6):523-8.	Unclear Randomisation method not described	Moderate All began allocated treatment but open-label study and 5/31 dropouts	Moderate 3 dropouts in control group, 2 in treatment group so 5/31 dropouts. Able to use intention to treat analysis but not reported this way by authors. The 2 withdrawals in treatment group were die to adverse reactions	High Different ways of measuring outcomes: intervention group were not challenged, looked at tolerance to 200ml cow's milk as part of therapy schedule. Controls had oral food challenge. Cannot rule out spontaneous desensitisation in infants who underwent oral desensitisation. Compared intervention versus elimination diet rather than placebo. Single centre. No details of how adverse events were recorded or categorised. Numbers small. Power uncertain.	Unclear Planned analysis uncertain. Reports outcomes and analysis approach but does not refer to pre-set endpoints or pre-specified plan	High
Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, Ventura A. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol 2008;121(2):343-7.	Low Computerised randomisation. Blinding was ensured by using sequentially numbered, opaque, sealed envelopes.	Moderate Open-label study. All began assigned treatment, however not always implemented as planned. At the end of the in-hospital phase, 9/30 in intervention group had reached the single dose of 20 mL of whole milk, as expected by the protocol. The remainder stabilised at lower doses because of frequent allergic reactions.	Low No missing data	Moderate Different ways of measuring outcomes: intervention group were not challenged, looked at tolerance to 200ml cow's milk. Controls had oral food challenge. However, tolerating open administration is gold standard so assessed as moderate rather than high risk taking into account gold standard. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Single centre. Powered for primary outcome.	Unclear Planned analysis uncertain. No reference made to pre-specified plan. Outcomes listed in methods section are reported on and power calculation was undertaken on primary outcome. However does state that to simplify presentation only some data are reported (not related to outcomes of interest for this review)	Moderate

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Martorell A, De la Hoz B, Ibáñez MD, Bone J, Terrados MS, Michavila A, Plaza AM, Alonso E, Garde J, Nevot S, Echeverria L, Santana C, Cerdá JC, Escudero C, Guallar I, Piquer M, Zapatero L, Ferré L, Bracamonte T, Muriel A, Martínez MI, Félix R. Oral desensitisation as a useful treatment in 2-year-old children with cow's milk allergy. Clin Exp Allergy. 2011 Sep;41(9):1297-304.	Low Centralized randomisation using random numbers table, but not concealed	Moderate Most received allocated treatment but open-label study	Low 4 withdrawals in control group, 1 withdrawal in intervention group, but able to analyse intention to treat. Some challenge measures seem not to be done, but have accounted for this in bias assessment for outcome measurement	High Different ways of measuring outcomes (maximum tolerated dose vs challenge). Double blind challenge for those not tolerating daily milk. However blind challenge after 1 year not reported in 2/30 of the intervention group and was not done in 7/30 of the control group. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Multicentre.	Moderate Planned analysis uncertain. Not listed in registration document. Reporting of adverse events limited and not fully aligned to methods section.	High
Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, Hanss Ch, Beaudouin E, Petit N, Kanny G. Oral desensitisation in children with milk and egg allergies obtains recovery in a significant proportion of cases. A Randomised study in 60 children with cow's milk allergy and 90 children with egg allergy. Eur Ann Allergy Clin Immunol 2007;39(1):12-9.	Low Randomised using a random numbers table, but difference in sample size between groups not explained by procedure. Odd numbers used for controls, even numbers for intervention. Numbers in hens' egg group were 39 controls vs 51 intervention (whole sample). However, for this review ONLY using data about IgE-mediated milk where numbers are similar between groups (20 vs 22) so have marked as low risk.	High Open-label study. Not all foods quantified in protocol from month 2 onwards so people could have been consuming different quantities. Some foods not allowed as contain raw egg but similar to allowed foods so family adherence uncertain	Moderate < 10% missing data overall (3/60 in milk and 6/80 for egg). Statistical analysis can be done per protocol not intention to treat. Authors report per protocol analysis. For review only using IgE mediated milk allergy data.	Moderate Single blind. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Numbers small when just looking at IgE-mediated data so may not be powered.	Moderate Planned analysis uncertain. No reference made to pre-specified plan. Limited information in methods section. Presents IgE-mediated analysis for milk but not for egg.	High

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, Passalacqua G. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a Randomised single-blind controlled study. Ann Allergy Asthma Immunol 2010;105(5):376-81.	Low Online randomisation, concealed	Moderate Investigators blinded when administering. People may have been able to distinguish soy placebo by taste	Low 3 out of 30 people dropped out (10%), 3 had therapy stopped; significant with small numbers. Able to analyse intention to treat	Moderate Single blind study, double blind tests. Multicentre (2). No power calculation in advance.	Moderate Tables report by individual rather than comparing groups. Results reported positively even when participants did not achieve tolerance	Moderate
Salmivesi S, Korppi M, Mäkelä MJ, Paassilta M. Milk oral immunotherapy is effective in school-aged children. Acta Paediatr 2013;102(2):172-6.	Unclear 2:1 block randomisation performed by head pharmacist. No information about system used. Allocation concealed.	Low All received expected intervention	Moderate 86% completed protocol. Discontinuations due to adverse effects in intervention group (2). 2 controls also withdrew.	High No efficacy outcome measured in placebo group. Proceeded directly to open-label immunotherapy without testing whether desensitisation outcome had been achieved in placebo group. Unclear how conclusions were made about treatment effectiveness. No sample size determination. Open challenges, except for those with recent systemic reactions. Single centre.	Unclear No description of analysis plan. No primary outcome identified.	High

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, Matsui EC, Burks AW, Wood RA. A Randomised, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol 2008;122(6):1154-60.	Unclear Randomisation method not described	Low All began expected intervention	Moderate 1 dropout. Reported per protocol	Moderate Double blind. 2 centres. Low numbers. May be under powered.	Unclear Predefined statistical analysis plan not described. Outcomes not reported in terms of % reaching desensitisation level	Moderate

Risk of bias assessment - hen's egg

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Akashi M, Yasudo H, Narita M, Nomura I, Akasawa A, Ebisawa M, Takahashi T, Ohya Y. Randomised controlled trial of oral immunotherapy for egg allergy in Japanese patients. Pediatr Int 2017;59(5):534-539.	Low Randomly assigned by computerised algorithm. Concealment unknown. No significant differences between groups in most baseline characteristics, but small numbers.	Low Received allocated intervention.	Moderate 3/18 people from intervention group withdrew due to treatment effects (0 controls), but not before second challenge. >20% missing data from intervention group, important as small sample and there was a difference in cumulative tolerated doses before intervention.	Moderate Double blind challenges. However authors note compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Observed for only 6 months. Small, single centre study. Adverse effects measurement not highly detailed.	Low Analysed according to pre-specified plan (available online). Extra analysis based on differences in baseline cumulative tolerated doses.	Moderate
Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R, Pajno GB. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. Allergy Asthma Proc 2009;30(4):443-8.	Unclear Only 6 Randomised, 7 open label. Randomisation details unclear.	Low All received the intervention. Blinded	High 1/3 in intervention group needed to withdraw due to adverse events	High All assessed in the same way. 2 participants did not undergo baseline challenge due to the severity of past reactions (anaphylaxis). Small numbers due to ethics committee approving only 6 for RCT. Study combined open and Randomised participants but only Randomised extracted for this review. Soy milk may taste different	Moderate Appears analysed to plan, however reporting in tables etc combined open and Randomised participants which may introduce interpretation bias. Issues with reporting of adverse events	High

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a Randomised controlled trial. Pediatr Allergy Immunol 2013;24(1):66-74.	Low Computerised randomisation 1:1. A computer scientist not involved in the study was responsible for the Computerised randomisation of the children to each group. Healthcare staff and parents were aware of the treatment.	Moderate Participants knew they were ingesting raw hen's egg but blind to dose increases. Parents measured the pre-specified amount to be administered so could have differed in dosage. All received intervention. Researcher bias minimised by double blind challenge. Dose customised for each patient based on frequency and severity of side effects and asthma worsening. If saw mild symptoms maintained dosage programme but if saw Grade 2,3,4 symptoms then gave previous dose. This was protocol but does introduce deviations	Low Data on all participants presented. No loss to follow up.	Moderate Double blind challenges, but limited doses for intervention group. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Small sample, 80% power. Single centre.	Low Analysed in line with pre-specified plan.	Moderate

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Escudero C, Rodríguez Del Río P, Sánchez-García S, Pérez-Rangel I, Pérez-Farinós N, García-Fernández C, Ibáñez MD. Early sustained unresponsiveness after short-course egg oral immunotherapy: a Randomised controlled study in egg-allergic children. Clin Exp Allergy 2015;45(12):1833-43.	Low Participants were assigned to groups in a 1:1 ratio using a computer-generated randomisation table.	Low Almost all received as expected	Low Loss to follow up in control group more than accounted for in power calculations however used intention to treat analysis	Moderate Blinded challenges, but missing data for control group adverse events. No challenge for desensitisation, Children receiving intervention came to the office and those in the control group did not. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Single centre. Ten percent (3/30) of OIT needed more than 3 months to be desensitised (mean 121 days, SD 16.8 days) due to adverse reactions. These patients did not perform an elimination diet or DBPCFC at 4 months and were included in the group of children who did not pass the DBPCFC at 4 months for the statistical analysis. Seven percent of OITG children (2/30) were withdrawn from the study for non-severe repeated allergic reactions.	Unclear Planned analysis uncertain	Moderate

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Itoh-Nagato N, Inoue Y, Nagao M, Fujisawa T, Shimojo N, Iwata T. Desensitisation to a whole egg by rush oral immunotherapy improves the quality of life of guardians: A multicentre, Randomised, parallel-group, delayed-start design study. Allergol Int 2018;67(2):209-216.	Low Recruited through advertisements displayed in hospitals. Randomisation with computer-based 1:1 allocation stratified by age, gender, specific IgE levels. Randomisation done by independent centre.	Moderate On days not ingesting maintenance dose patients consumed egg dishes at home/school but levels of egg ingestion were not fixed. Could have confounded due to different eating customs. However all participants received correct allocation	Low 4/45 missing data but intention to treat analysis. Quality of life data for parents not shown in detail	Moderate Double blind challenges. Multicentre (9). However compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Challenged with raw egg but protocol used cooked egg.	Moderate Analysed in line with pre-specified plan (trial registration), however some issues due to first 3 months of data only	Moderate
Martín-Muñoz MF, Belver MT, Alonso Lebrero E et al. Egg oral immunotherapy in children (SEICAP I): Daily or weekly desensitisation pattern. Pediatr Allergy Immunol 2019;30(1):81-92.	Low Centralized computer algorithm	Low Most received allocated treatment	Moderate 15 did not complete in intervention group and 3 in control group. Used intention to treat analysis for desensitisation but 18% withdrawl rate may impact adverse event outcomes. Some outcomes used per protocol analysis.	Moderate Double blind challenges. However compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Boiled egg in challenges but pasteurized egg white used for immunotherapy. Intervention group and controls who passed blind challenge had additional raw egg open challenge. Power calculation reported. Multicentre (9). Children in intervention group older on average than controls which may affect outcome.	Moderate Planned analysis uncertain. Outcomes reported appear to be in line with planned approach and list of primary and secondary outcomes provided in methods section. Adverse events comparing control and intervention not well reported.	Moderate

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Pérez-Rangel I, Rodríguez Del Río P, Escudero C, Sánchez-García S, Sánchez-Hernández JJ, Ibáñez MD. Efficacy and safety of high-dose rush oral immunotherapy in persistent egg allergic children: A Randomised clinical trial. Ann Allergy Asthma Immunol 2017;118(3):356-364.e3.	Low Computer generated randomisation table	Moderate Comparator is untreated people so open to confounding / not blind. Allocated as planned. Study included second phase where controls received treatment, Not used for this review.	Low Few missing data, 3 withdrawals	High Outcomes measured in different ways. Intervention patients did not have an exit challenge. This is gold standard but differences in measurement approach could introduce bias. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Adverse events not broken down by phase. Single centre. Power calculation performed.	Low Analysed in line with pre-specified plan.	High

Risk of bias assessment - other allergens

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R, Castelló JV, Alonso R, de Mateo JA, Cerdá-Trias T, San Miguel-Moncín Mdel M, Monzón S, García M, Palacios R, Cisteró-Bahíma A. Sublingual immunotherapy for hazelnut food allergy: a Randomised, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol 2005;116(5):1073-9.	Unclear Randomisation method not described	Low Almost all received as expected. Single blind. All patients were first challenged with a placebo pudding (so as to eliminate possible placebo reactors). If no symptoms were reported, blinding proceeded	Low Little missing data	Moderate Double blind challenges. But included oral allergy syndrome symptoms at the challenge for inclusion in the study. Some participants may only be birch sensitised and Cor a 1 positive. Patients who had systemic reactions or anaphylaxis were challenged, but they were started with a modified schedule (but double blind). Multicentre (3), all using single protocol. Small sample.	Unclear Planned analysis uncertain. Limited p-value comparisons between groups	Moderate
Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitisation. Hepatogastroenterology 1998;45(19):52-8.	Moderate Generation method not reported. 22 people eligible but not allocated equally between groups and rationale not provided. Matched controls slightly different allergy profile	High Comparator is untreated people so open to confounding / not blind. Allocated as planned, but person received 3 therapies. Treatment took different number of months for different participants. Unclear whether there was maintenance treatment or gap between when some people were challenged at follow up	Low Primary outcome of desensitisation reported in all participants so low risk of bias	High One person had 3 allergies and was treated with 3 different therapies, and reported as 3 separate cases. No blinding. Unclear methods about follow up challenge. Detailed results about controls after treatment period not provided. Data on thresholds missing. High risk for safety outcomes which are not detailed well and include self report data. Compared intervention versus elimination diet rather than placebo. Single centre. No power calculation.	Moderate Single efficacy outcome is prespecified and reported. However tabulations based on individuals, not group comparisons	High

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. Allergy 2007;62(11):1261-9.	Unclear Randomisation method not described	Moderate Received allocated treatment but open-label study	Moderate 9 did not complete induction phase due to side effects (non-responders). 2 drop outs	Moderate Participants challenged and assessed the same way, but unblinded. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. 2 centres	Low Analysed in line with pre-specified plan.	Moderate
Fernández-Rivas M, Garrido Fernández S, Nadal JA, Díaz de Durana MD, García BE, González-Mancebo E, Martín S, Barber D, Rico P, Tabar AI. Randomised double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy 2009;64(6):876-83.	Low Stratified block randomisation, 2:1 ratio	Low All received expected intervention	Moderate 4 dropouts in intervention group and 3 in placebo i.e. 7/56 original. Used data for completers only	Moderate Double blind. All participants assessed in the same way. States focus is desensitisation but does not provide clear numbers (log tests only). Multicentre (2)	Moderate Used per protocol analysis and did not report % reaching desensitisation even though stated as a key outcome. The originally planned statistical analysis was the survival analysis (Log Rank test), but on the basis of another publication also added discrete-time survival analysis as viewed as better suited to these data	Moderate
Nowak-Węgrzyn A, Wood RA, Nadeau KC, Pongracic JA, Henning AK, Lindblad RW, Beyer K, Sampson HA. Multicentre, Randomised, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. J Allergy Clin Immunol 2019;143(2):651-661.e9.	Unclear Randomised 1:1	Low All began expected intervention. There was a change in vehicle for active treatment (capsules first, then flour)	Low 6/46 withdrawals (4 intervention, 2 control) before year 1 challenge. Able to analyse intention to treat	Moderate All participants assessed in the same way at year 1, but introduction of active treatment to controls after year 1 meant no comparison possible for sustained unresponsiveness. So low risk for desensitisation outcome and high for sustained unresponsiveness. Multicentre (4).	Low Appears analysed in line with pre-specified plan.	Moderate

Risk of bias assessment - direct comparison of administration routes

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, Steele P, Driggers S, Burks AW, Wood RA. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012;129(2):448-55, 455.e1-5.	Low Randomisation with Computerised block-stratified program using a block size of 6	Moderate Received allocated treatment but open-label study	Low No missing data	Low All participants assessed in the same way. Double blind challenges. Multicentre (2)	Unclear Planned analysis uncertain. Protocol endpoints described	Moderate
Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, Wood RA. A Randomised, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol 2015;135(5):1275-82.e1-6.	Unclear Randomisation approach not reported. But no significant differences between groups in key characteristics	Low All received expected intervention	Low 5/21 withdrew, some due to adverse events. Outcomes were analysed by using both a per-protocol analysis, which did not include dropouts, and an intent-to-treat model, which considered dropouts to have the same OFC result on subsequent challenges as at baseline.	Moderate All participants assessed in the same way. Single centre. Numbers were not sufficient to allow assessment of sustained unresponsiveness. Overall numbers low. Power not stated.	Moderate Analysed in line with pre-specified plan. However for some outcomes, presented data for per protocol analysis only, when per protocol found a significant difference and intention to treat analysis found none (e.g. increase in median challenge dose at 6 months). Some reporting conflates results from original blinded and add on phase. Non combined results are available, but not emphasised.	Moderate

Risk of bias assessment - immunotherapy plus biological

Citation	Randomisation process risk of bias	Risk of bias due to assignment	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selective reporting	Overall risk of bias
Takahashi M, Soejima K, Taniuchi S, Hatano Y, Yamanouchi S, Ishikawa H, Irahara M, Sasaki Y, Kido H, Kaneko K. Oral immunotherapy combined with omalizumab for high-risk cow's milk allergy: a Randomised controlled trial. Sci Rep 2017;7(1):17453.	Low Simple Computerised randomisation was carried out and allocation was by sequentially numbered, opaque sealed envelops by a hospital nurse.	Moderate Received allocated treatment but open-label study	Low No missing data	High Both groups challenged at the same time using the same protocol. 90% of the intervention group had other allergies so could be confounding. This study initially aimed to recruit 50 patients but then stopped after 16 patients due to all 6 children in the control group failing the food challenge and all of the intervention group passing the challenge. Compared intervention versus elimination diet rather than placebo, so this may have affected outcomes. Used fresh milk for challenges but reports microwaved milk for therapy	Moderate Analysis was pre-specified, but the study stopped prematurely due to challenge outcome. The reporting of sustained unresponsiveness does not provide pre-specified endpoint.	High

Characteristics of included studies – biological monotherapy

Citation	Country	Funding source	Total participants	Intervention group no.	Age	Allergy type	Severity of allergy	Biological tested	Biological dose and duration	Comparator
Chinthrajah et al. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight 2019 ;4(22):e131347.	USA	US National Institutes for Health, AnaptysBio, Hartman Vaccine Fund, Stanford University Sean N. Parker Center for Allergy and Asthma Research	20	15	Adults. Median age (range): intervention 27 years (19 to 54); placebo 22 years (18 to 50)	Peanut	Not specified Appears moderate.	Etokimab	Single dose of etokimab, 300mg/100 mL i.v.	Placebo
Leung et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 2003;348:986-93.	USA	Tanox, US Peanut Board, US Peanut Foundation, US Institutes of Health National Center of Research, Mount Sinai School of Medicine, Mayo Foundation. Sponsor did not limit the investigators' right to publish the results.	84	61 150mg = 19 300mg = 19 450mg = 21	13+ years Eligible: 12 to 60 years, included 13 to 59	Peanut	Moderate to severe	TNX-901 (humanized IgG1 monoclonal antibody against IgE)	150mg, 300mg, or 450mg of TNX-901 subcutaneously every 4 weeks for 4 doses.	Placebo
Sampson et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol 2011 ;127(5):1309-10.e1.	USA	Genentech	14	9	Mixed 5 to 12 (50%) and 13+ years (50%) Range 6 to 75 years	Peanut	Not specified	Omalizumab	Dose based on total IgE levels and body weight. Treatment was 20 to 22 weeks every 2 to 4 weeks. Dose was a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks. Those requiring more than a 300mg dose had the dose divided and given every 2 weeks.	Placebo

Risk of bias assessment – biological monotherapy

Citation	Randomisation process risk of bias	Risk of bias due to assignment / deviations from intended intervention	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selection of reported result	Overall risk of bias
Chinthrajah S, Cao S, Liu C, Lyu SC, Sindher SB, Long A, Sampath V, Petroni D, Londei M, Nadeau KC. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. JCI Insight 2019 ;4(22):e131347.	Unclear Randomisation process not described apart from 3:1 ratio. Some participant characteristics may be unbalanced e.g. gender (47% female in intervention group vs 60% controls); peanut specific IgE at baseline; median cumulative tolerated dose at baseline. Lack of balance not through fault in randomisation process, but small numbers likely contributed so results may be at high risk of bias due to different characteristics of each group.	Low All participants received planned treatment. Multicentre study. All standardised oral food challenge results were reviewed by an independent, blinded expert reviewer (though uncertain whether rest of study team were blinded). States all work done in research facilities with independent review, but two food challenges were open food challenges rather than double-blind placebo-controlled food challenges.	Moderate Some loss to follow up at 45 day follow up. Follow up was convenience sample based on people's ability to visit the clinic in their work schedules for challenge. Convenience sample has risk of bias.	Moderate Blinded outcome assessment, however two food challenges were open, which could make a difference when sample size is small. Authors do not specify which group(s) had open challenges. Oral food challenge results were reviewed by an independent, blinded expert reviewer. Adverse effect data mostly based on participant self-reports, which can be variable and may not measure events of interest.	Moderate Analyses conducted based on pre-defined analysis plan. All planned safety analyses appear to be presented. However, P-values not reported for adverse events analysis even though safety was a key focus of the study.	**Moderate**
Leung DYM, Sampson HA, Yunginger JW, Burks Jr AW., Schneider LC, Wortel CH, Davis FM, Hyun JD, Shanahan WR. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med 2003;348:986-93.	Low Patients were randomly assigned in groups of 28 and in a 3:1 ratio to receive 150 mg, 300 mg, or 450 mg of TNX-901 or placebo. Central randomisation performed in blocks of four per site. Enrolment at each dose level was completed before enrolment at the next level began. No information provided about generation or concealment methods.	Low Double-blind study with patients randomly assigned in a 3:1 ratio with three different doses or placebo. A pharmacist reconstituted with 1 ml of sterile water in an unblinded fashion and placed the solution in a syringe, which was masked to prevent study personnel from identifying the contents, for subcutaneous injection.	Low Little missing data with 81 of 84 patients completing study. What is missing unlikely to have an impact on trial result.	Low Double-blind study. Efficacy was assessed in all patients with a double-blind, placebo-controlled oral food challenge.	Low Data from all participating centres were sent to independent group. All data were entered and locked before analysis began. Data analysed by separate team.	**Low**

Citation	Randomisation process risk of bias	Risk of bias due to assignment / deviations from intended intervention	Risk of bias due to missing outcome data	Risk of bias due to outcome measurement	Risk of bias due to selection of reported result	Overall risk of bias
Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, Wong DA. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol 2011 ;127(5):1309-10.e1.	Unclear Randomisation process not described. Randomized 2:1 (omalizumab: placebo) to double-blind treatment. Generation and allocation concealment unknown. However, process meant thee were 5 in control group and 9 in intervention group, with differences between groups in baseline characteristics: average age (27 vs 16 placebo), gender (f=20% vs 56% placebo) and proportion age 6-12 years (40% vs 56% placebo)	Low Assignment was double blind.	High Study intended to randomize 150 people but was stopped early due to recommendation of the Data Safety Monitoring Committee because of the severity of 2 anaphylactic reactions that occurred during oral food challenges before the administration of the study drug. This meant that only 14 people reached the study's primary endpoint before the trial was discontinued. The trial appears to have been implemented well in those 14 people, but there is still a high risk of bias due to missing outcome data / limited sample size / early closure.	Low All participants were assessed in the same way. Approach appears appropriate. Not influenced by prior knowledge of allocation.	Low Analyses conducted based on pre-defined analysis plan.	**Moderate**

Online supplement S6: Summary of findings and evidence profiles

Peanut allergy - oral immunotherapy

Summary of findings

Oral immunotherapy for peanut allergy				
People: Children and adults with peanut allergy ranging from mild to severe **Settings:** Hospital and home; Australasia, Europe and North America **Intervention:** Oral immunotherapy, usually with roasted peanut for between 1 month and 3 years **Comparison:** Placebo (elimination diet in one case)				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Desensitisation: % able to tolerate defined dose during therapy	Oral immunotherapy results in a large increase in the proportion of children with peanut allergy able to tolerate peanut during therapy. 7 out of 7 RCTs about oral immunotherapy found a benefit compared to placebo or elimination diet (68% immunotherapy vs 6% control, absolute difference 62%, RR 9.9, CI 4.5 to 21.4, NNT 2).	High	7 RCTs (total n = 1023)	One RCT found that a higher proportion of children with mild to severe peanut allergy who had 6 months of oral immunotherapy with roasted peanut could tolerate 1400mg peanut protein compared to those on an elimination diet (62% vs 0%, p<0.001, per protocol analysis) (Anagnostou 2014). One RCT found that a higher proportion of children and adults with moderate peanut allergy who had a mean 24 weeks of oral immunotherapy with roasted peanut could tolerate 443mg cumulative peanut protein compared to those having placebo (79% vs 19%, p<0.0001). 62% tolerated 1043mg compared with 0% placebo (p<0.001) (Bird 2018). One RCT found that an increased proportion of children with mild to severe peanut allergy who had 16 months of oral immunotherapy with roasted peanut could tolerate a single dose of 300mg of peanut protein compared to those who had placebo (74.2% vs 16.1%, p<0.01) (Blumchen 2019). One RCT found an increased proportion of children with mild to severe peanut allergy who had 2 years of oral immunotherapy with roasted peanut could tolerate 4g peanut protein compared to those who had placebo (85% vs 4%, p<0.0001) (Chinthrajah 2019). One RCT of 24 weeks of gastrointestinal delivery oral immunotherapy with roasted peanuts in children (adolescents) with mild to severe peanut allergy found an increased proportion tolerated 400mg cumulative dose of peanut protein compared to placebo (80.9% vs 11.1%, p<0.001) (Fauquert 2018). One RCT of 9 months of oral immunotherapy with raw peanut for children with mild to severe peanut allergy found an increase in the proportion who could tolerate a cumulative dose of 2043mg compared to placebo (58% vs 2%, p<0.0001) (O'B Hourihane 2020).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
				One RCT found that 1 year of oral immunotherapy with roasted peanut increased the proportion of children with moderate/severe allergy who could ingest 600mg peanut protein compared to placebo (67.2% vs 4% for 4-17 year olds, p<0.001). Results were only significant for children, not adolescents/adults (Vickery 2018).
Sustained unresponsiveness: % able to tolerate defined dose after ending therapy	Oral immunotherapy may increase children's ability to tolerate peanut 3 months after ending therapy, but the certainty of evidence is low and based on 1 RCT.	Low	1 RCT (n = 85)	One RCT found that an increased proportion of children with mild to severe peanut allergy who had 2 years of oral immunotherapy with roasted peanut could tolerate 4g peanut protein 3 months after ending therapy compared to placebo (35% vs 4%, p<0.05) (Chinthrajah 2019).
Quality of life	The effect of immunotherapy on quality of life is unclear because the certainty of evidence is very low. 2 out of 3 RCTs found improved quality of life in children compared to placebo. 2 found no improvement in parental quality of life compared to placebo.	Very low	3 RCTs (total n = 336)	One RCT with children with mild to severe peanut allergy found that 6 months of oral immunotherapy with roasted peanut did not improve parental reports of children's quality of life compared to an elimination diet (Anagnostou 2014). One RCT with children with mild to severe peanut allergy found that about 16 months of oral immunotherapy with roasted peanut was associated with improved changes in food allergy related quality of life in children compared to placebo. There was no significant overall difference for the quality of life of caregivers (Blumchen 2019 and Trendelenburg 2020). One RCT of 9 months of oral immunotherapy with raw peanut for children with mild to severe peanut allergy found improved food allergy quality of life compared to placebo (O'B Hourihane 2020).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
% of people experiencing adverse reactions	Immunotherapy may not alter the likelihood of adverse reactions compared with placebo amongst children and adults with peanut allergy, the certainty of evidence is low. Adverse events tend to be mild/moderate. 2 out of 6 RCTs about oral immunotherapy found that an increased proportion of people with peanut allergy experienced adverse reactions compared to placebo. 4 RCTs found no difference. Pooled data found no difference overall (98% immunotherapy vs 89% control, absolute difference 9%, RR 1.1, CI 0.99 to 1.2, p>0.05).	Low	6 RCTs 7 comparisons (n = 953)	One RCT found a trend towards a higher proportion of adverse reactions in children and adults with moderate peanut allergy who had an average of 24 weeks of oral immunotherapy with roasted peanut compared to placebo (96.6% vs 84.6%, p not reported) (Bird 2018). One RCT found no difference in adverse reactions in children with mild to severe peanut allergy who had 16 months of oral immunotherapy with roasted peanut compared to placebo (100% vs 100%, p>0.05) (Blumchen 2019). One RCT found an increased proportion of adverse reactions in children with mild to severe peanut allergy who had 2 years of oral immunotherapy compared to placebo (Year 1: 93.6% vs 64%, Year 2: 69.8% vs 26% p<0.05). (Chinthrajah 2019). One RCT of 24 weeks of gastrointestinal delivery oral immunotherapy with roasted peanuts in children (adolescents) with mild to severe peanut allergy found no difference in the proportion experiencing adverse reactions compared to placebo (90.5% vs 88.9%, p>0.05) (Fauquert 2018). One RCT of 9 months of oral immunotherapy with raw peanut for children with mild to severe peanut allergy found no difference in the proportion experiencing adverse reactions compared to placebo (98% vs 99%, p>0.05) (O'B Hourihane 2020). One RCT of 1 year of oral immunotherapy with roasted peanut for children with moderate/severe peanut allergy found no difference in the proportion experiencing adverse reactions compared to placebo (98.7% vs 95.2%, p not reported) (Vickery 2018).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
% of people experiencing severe adverse reactions	There may be no difference in severe reactions between oral immunotherapy and placebo, but the certainty of evidence is low. Studies defined and measured severe adverse reactions in different ways. Overall there was no significant difference. The number of severe reactions was small (4% immunotherapy vs 2% control, absolute difference 2%, RR 1.6, CI 0.7 to 3.5, p>0.05).	Low	6 comparisons (n=950)	One RCT with children and adults with moderate peanut allergy found no significant difference in the proportion of those who had an average of 24 weeks of oral immunotherapy with roasted peanut experiencing anaphylaxis or severe adverse reactions compared to placebo (3.44% vs 0% for anaphylaxis, 0% vs 0% severe events, p not reported) (Bird 2018). One RCT found no difference in severe adverse reactions in children with mild to severe peanut allergy who had 16 months of oral immunotherapy with roasted peanut compared to placebo (10.7% vs 20.8%, p>0.05) (Blumchen 2019). One RCT found an increase in the proportion who needed adrenaline for adverse reactions in children with mild to severe peanut allergy who had 2 years of oral immunotherapy compared to placebo (Year 1: 19% vs 0%, Year 2: 13% vs 0% p<0.05). (Chinthrajah 2019). One RCT of 24 weeks of gastrointestinal delivery oral immunotherapy with roasted peanuts in children (adolescents) with mild to severe peanut allergy found an increased proportion experience severe multisystem reactions compared to placebo (19.1% vs 0%, p not reported) (Fauquert 2018). One RCT of 9 months of oral immunotherapy with raw peanut for children with mild to severe peanut allergy found no difference in the proportion experiencing severe adverse reactions compared to placebo (12% vs 2%, p not reported) (O'B Hourihane 2020). One RCT of 1 year of oral immunotherapy with roasted peanut for children with moderate/severe peanut allergy found a trend towards increased systemic adverse reactions compared to placebo (14.2% vs 3.2%, p not reported) (Vickery 2018).
% of doses with severe adverse reactions	The effect of immunotherapy for adults and children with peanut allergy on the % of doses associated with severe adverse reactions in unclear because the certainty of evidence is very low. 1 RCT about found no difference to placebo.	Very low	1 RCT (n = 62)	One RCT found no difference in the proportion of doses associated with systemic adverse reactions in children with mild to severe peanut allergy who had 16 months of oral immunotherapy with roasted peanut compared to placebo (0.59% vs 0.74%, p not reported) (Blumchen 2019).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % able to tolerate defined dose during therapy						
7 RCTs (total n = 1023)	Reduced grade by one level as not all studies at low risk.	No grade change. Studies had consistent trends.	No grade change. Studies from range of countries and include variety of severity levels. Varied types of therapy but likely to be generalizable to populations of interest.	No grade change. Lack of reporting of p-values in some cases and small number of events, but offset against larger studies.	No grade change. Bias uncertain but studies published from a range of countries with and without industry sponsorship. Funnel plot inconclusive.	**High** Graded up one level due to large effect size.
Sustained unresponsiveness: % able to tolerate defined dose after ending therapy						
1 RCT (n = 85)	No change to grade level Single study at low risk of bias.	No grade change. Single study only so not able to comment on consistency of results.	Reduced grade by one level. Single study in single country so may impact on generalisability.	No change to grade level.	Reduced grade level by one. Publication bias possible given many other studies published but do not report follow up data. No industry sponsorship.	**Low** No reason to grade up based on effect size, dose response or potential effect of confounders
Quality of life						
3 RCTs (total n = 336)	Reduced grade by one level due to 1 study at moderate risk of bias.	Reduced grade level by one level due to some inconsistency in trends between studies.	No change to grade level. Studies from variety of countries and covered measurement in children and caregivers.	Reduced grade by one level due to small sample sizes in some studies and difficulty comparing outcomes due to variations in reporting approach.	No grade change, but publication bias uncertain. Other studies may have measured quality of life and not reported it.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
% of people experiencing adverse reactions						
7 comparisons (n=953)	No change to grade level. 1 Most studies at low risk of bias.	Reduced by one grade level due to some inconsistency in findings across studies.	No grade change. Studies focused on different therapy and had varied inclusion criteria, but likely to have some generalisability.	Reduced grade by one level due to small sample sizes in some cases and lack of reporting of p-values so precision unclear in some studies. Varied measurement approaches.	No grade change. Bias uncertain but studies published from a range of countries, with and without industry sponsorship.	**Low** No reason to grade up based on effect size, dose response or potential effect of confounders.
% of people experiencing severe adverse reactions						
6 comparisons (n=950)	No change to grade level. Most studies at low risk of bias.	No change to grade level. Consistent trends.	Reduced by one grade. Different definitions and measurement approaches make difficult to apply.	Reduced grade by one level due to lack of reporting of p-values in some cases.	No change. Multiple countries and with and without industry sponsorship.	**Low** No reason to grade up.

Peanut allergy – epicutaneous immunotherapy

Summary of findings

Immunotherapy for peanut allergy				
People: Children and adults with peanut allergy ranging from mild to severe **Settings:** Hospital and home; Australasia, Europe and North America **Intervention:** Oral immunotherapy, usually with roasted peanut for between 1 month and 3 years **Comparison:** Placebo (elimination diet in one case)				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Desensitisation: % able to tolerate defined dose during therapy	Epicutaneous immunotherapy may increase the proportion of people with peanut allergy who tolerate peanut during therapy (46% immunotherapy vs 17% controls, absolute difference 29%, RR 2.6, CI 1.8 to 3.8, NNT 3).	Moderate	3 RCTs (n=651)	One RCT of 1 year of epicutaneous immunotherapy with raw peanut for children with mild/moderate peanut allergy found an increased proportion tolerated a single eliciting dose of 300mg or 1000mg peanut (depending on baseline tolerance) compared to placebo (35.5% vs 13.6%, p<0.001) (Fleischer 2019). One RCT of 1 year of epicutaneous immunotherapy with raw peanut for adults and children with mild/moderate peanut allergy found an increased proportion tolerated 5044mg peanut or 10-fold increase from baseline compared to placebo (45.8% 100ug group vs 48% 250ug group vs 12%, p both <0.05) (Jones 2017). One RCT of 1 year of epicutaneous immunotherapy with raw peanut for adults and children with mild to severe peanut allergy found an increased proportion tolerated 1000mg peanut or 10-fold increase from baseline compared to placebo, but only for the 250mcg dose (45.3% 50mcg vs 41.1% 100mcg vs 50% 250mcg vs 25% placebo, p = 0.01 for 250mcg vs placebo) (Sampson 2017).
Quality of life	Epicutaneous immunotherapy may improve quality of life but the certainty of evidence is low. 1 RCT found improved quality of life in children and caregivers compared to placebo.	Low	1 RCT (n = 356)	One RCT of 12 months of epicutaneous immunotherapy with raw peanut for children with mild/moderate peanut allergy found an improvement in food allergy quality of life in children and their caregivers compared to placebo (Fleischer 2019 and DunnGalvin 2021).
% of people experiencing adverse reactions	Epicutaneous immunotherapy may have no impact on adverse reactions compared to placebo (78% vs 61%, absolute difference 17%, RR 1.2, CI 0.95 to 1.6, p>0.05).	Low	4 comparisons (n=676)	One RCT of 1 year of epicutaneous immunotherapy with raw peanut for children with mild/moderate peanut allergy found no difference in adverse events compared to placebo (95.4% vs 89%, p not reported) (Fleischer 2019). One RCT of 1 year of epicutaneous immunotherapy with raw peanut for adults and children with mild to severe peanut allergy found no difference in adverse events compared to placebo (99.4% vs 92.9%, p not reported) (Sampson 2017).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
% of doses with adverse reactions	The effect on doses with adverse reactions is unclear as the certainty of evidence is very low.	Very low	1 RCT (n = 74)	One RCT of 1 year of epicutaneous immunotherapy with raw peanut for adults and children with mild/moderate peanut allergy found an increased proportion of doses resulted in a reaction compared to placebo (79.8% vs 14.4%, p<0.05) (Jones 2017).
% of people experiencing severe reactions	Epicutaneous immunotherapy may have no impact on severe adverse reactions compared to placebo (6% vs 2%, absolute difference 4%, RR 2.0.2, CI 0.8 to 5.1, p>0.05).	Low	4 comparisons (n=676)	One RCT of 12 months of epicutaneous immunotherapy with raw peanut for children with mild/moderate peanut allergy found no significant difference in the proportion of severe adverse events compared to placebo (5.1% vs 4.2%, p not reported) (Fleischer 2019). One RCT of 1 year of epicutaneous immunotherapy with raw peanut for adults and children with mild/moderate peanut allergy found no difference in the proportion with severe or systemic adverse events compared to placebo (2.2% vs 0%, p>0.05) (Jones 2017). One RCT of 1 year of epicutaneous immunotherapy with raw peanut for adults and children with mild to severe peanut allergy found no difference in severe adverse events compared to placebo (12% vs 7%, p not reported) (Sampson 2017).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % able to tolerate defined dose during therapy						
3 RCTs (total n = 651)	Reduced grade by one level as not all studies at low risk.	No grade change. Studies had consistent trends.	No grade change. Varied therapy but likely to be generalizable to populations of interest.	No grade change.	No grade change. Bias uncertain but studies published from a range of countries with and without industry sponsorship. Funnel plot inconclusive.	**Moderate**
Adverse reactions and severe reactions and quality of life						
4 comparisons (n = 676)	Reduced grade by one level as not all studies at low risk.	No grade change. Consistent results.	Reduced grade by one level due to limited variation in contexts.	Reduced grade by one level due to small numbers of events and some multiple comparisons drawn from single study.	No grade change. Bias uncertain.	**Low** No reason to grade up based on effect size, dose response or potential effect of confounders

Peanut allergy – sublingual immunotherapy

Summary of findings

Sublingual immunotherapy for peanut allergy				
People: Adults with mild/moderate peanut allergy **Settings:** USA **Intervention:** Sublingual immunotherapy **Comparison:** Placebo				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Desensitisation: % with 10-fold increase in threshold at 12 months compared to baseline	The effect of sublingual immunotherapy on desensitisation in peanut allergy is unclear because the certainty of evidence is very low. 1 small RCT found no increased tolerance with immunotherapy.	Very low	1 RCT (n = 40)	One RCT of 44 weeks of sublingual immunotherapy with raw peanut in adults with mild/moderate peanut allergy found an increased proportion tolerated 2.5g of peanut protein compared to placebo (70% vs 15%, p<0.001) (Fleischer 2013).
% of doses with adverse reactions	The effect of sublingual immunotherapy on the proportion of doses with adverse reactions in peanut allergy is unclear because the certainty of evidence is very low. 1 small RCT found increased adverse reactions with immunotherapy.	Very low	1 RCT (n = 40)	One RCT of 44 weeks of sublingual immunotherapy with raw peanut in adults with mild/moderate peanut allergy found a higher proportion of doses with adverse events compared to placebo (40.1% vs 0.6%, p not reported) (Fleischer 2013).
% of doses with severe reactions	The effect of sublingual immunotherapy on the proportion of doses with adverse reactions in peanut allergy is unclear because the certainty of evidence is very low. 1 small RCT found no difference between groups	Very low	1 RCT (n = 40)	One RCT found no severe adverse events in either group (Fleischer 2013).

Evidence profile – all outcomes

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
1 RCT (n = 40)	No change to grade level. Low risk of bias.	No grade change. Not possible to examine consistency as one study only.	Reduced grade by one level as single study in single country so may impact generalisability.	Reduced grade by two levels. Small study so small number of events affects proportions significantly.	No grade change. Bias uncertain. Only single study published.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Peanut allergy – subcutaneous immunotherapy

Summary of findings

Subcutaneous immunotherapy for peanut allergy				
People: Mixed aged groups with severe peanut allergy **Settings:** USA **Intervention:** Subcutaneous immunotherapy **Comparison:** Placebo				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Desensitisation: % with 10-fold increase in threshold at 12 months compared to baseline	The effect of subcutaneous immunotherapy on desensitisation in peanut allergy is unclear because the certainty of evidence is very low. 1 small RCT found no significant difference between groups.	Very low	1 RCT (n = 8)	One RCT of 4 weeks of subcutaneous immunotherapy with raw peanut for adults and children with severe peanut allergy found a trend towards an increased proportion that tolerated 8g compared to placebo, but this was not significant, perhaps due to small sample size (33% vs 0%, p not reported) (Oppenheimer 1992).
% of doses with severe reactions	The effect of subcutaneous immunotherapy on the proportion of doses with severe reactions in peanut allergy is unclear because the certainty of evidence is very low. 1 small RCT found no significant difference between groups.	Very low	1 RCT (n = 8)	One RCT of 4 weeks of subcutaneous immunotherapy with raw peanut for adults and children with severe peanut allergy found no difference in doses with severe reactions compared to placebo (13.3% vs 0%, p not reported) (Oppenheimer 1992).

Evidence profile – all outcomes

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
1 RCT (n = 8)	Reduced grade by two levels as high risk of bias	No grade change. Not possible to examine consistency as one study only.	Reduced grade by one level as single study in single country so may impact generalisability.	Reduced grade by one level. Small study so small number of events affects proportions significantly.	No grade change. Bias uncertain. Only single study published.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Oral versus sublingual immunotherapy for peanut allergy

Summary of findings

Oral versus sublingual immunotherapy for peanut allergy				
People: Children and adults with mild/moderate peanut allergy **Settings:** USA **Intervention:** Oral immunotherapy with raw peanut for 1 year **Comparison:** Sublingual immunotherapy with raw peanut for 1 year				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Desensitisation: % with 10-fold increase in threshold at 12 months compared to baseline	It is not possible to compare the effect on Desensitisation of oral versus sublingual immunotherapy for adults and children with mild/moderate peanut allergy because the certainty of evidence is very low. 1 small RCT found no significant difference between administration methods.	Very low	1 RCT (n = 21)	One RCT found no significant difference between oral and sublingual therapy in the proportion of adults and children with mild/moderate peanut allergy who could tolerate 10-times the baseline threshold after 12 months (63.6% oral vs 70% sublingual, p = 0.76). The quantity of the increased threshold was significantly greater in the oral immunotherapy group (141 vs 22-fold increase, p = 0.01) (Narisety 2015)
Sustained unresponsiveness: after 4 weeks off therapy	It is not possible to compare the effect on sustained unresponsiveness of oral versus sublingual immunotherapy for adults and children with mild/moderate peanut allergy because the certainty of evidence is very low. 1 small RCT found no significant difference between administration methods.	Very low	1 RCT (n = 21)	One RCT found no significant difference between oral and sublingual therapy in the proportion of adults and children with mild/moderate peanut allergy who sustained unresponsiveness at a 10-fold increase in threshold from baseline 4 weeks after they ended treatment (27.3% oral vs 10% sublingual, p = 0.59). (Narisety 2015)
% of people experiencing adverse reactions	It is not possible to compare the proportion of adults and children with mild/moderate peanut allergy experiencing adverse reactions from oral versus sublingual immunotherapy because the certainty of evidence is very low. 1 small RCT found no significant difference between administration methods.	Very low	1 RCT (n = 21)	One RCT found no significant difference between oral and sublingual immunotherapy in the proportion of adults and children with mild/moderate peanut allergy who experienced adverse reactions over the course of 1 year (100% oral vs 90% sublingual, p = 0.10). (Narisety 2015)

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
% of doses with adverse reactions	It is not possible to compare the proportion of doses of oral versus sublingual immunotherapy resulting in adverse reactions because the certainty of evidence is very low. 1 small RCT found a higher proportion adverse reactions in doses of oral immunotherapy for children and adults with mild/moderate peanut allergy.	Very low	1 RCT (n = 21)	One RCT found a significantly higher proportion of doses of oral immunotherapy resulted in adverse reactions compared to sublingual immunotherapy over 1 year (42.8% oral vs 9% sublingual, p<0.001). Most adverse reactions were mild/moderate (Narisety 2015).
% people with systemic reactions needing adrenaline	It is not possible to compare whether oral versus sublingual immunotherapy is more likely to result in systemic reactions needing adrenaline because the certainty of evidence is very low. 1 RCT found increased systemic events requiring adrenaline with oral immunotherapy.	Very low	1 RCT (n = 21)	One RCT found a higher proportion of people receiving oral immunotherapy had systemic events requiring adrenaline compared to sublingual immunotherapy over 1 year (40% oral vs 0% sublingual, p not reported) (Narisety 2015).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % with 10-fold increase in threshold tolerated at 12 months						
1 RCT (n = 21)	Reduced grade by one level as moderate risk of bias	No grade change. Not possible to examine consistency as one study only.	Reduced grade by one level as single study in single country so may impact generalisability.	Reduced grade by one level. Small study so small number of events affects proportions significantly.	No grade change. Bias uncertain. Only single study published. No industry sponsorship.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
Sustained unresponsiveness: % maintaining 10-fold increase in tolerance 4 weeks after ending therapy						
1 RCT (n = 21)	Reduced grade by one level as moderate risk of bias	No grade change. Not possible to examine consistency as one study only.	Reduced grade by one level as single study in single country so may impact generalisability.	Reduced grade by one level. Small study so small number of events affects proportions significantly.	No grade change. Bias uncertain. Only single study published. No industry sponsorship.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
% of people experiencing adverse reactions and % with systemic events requiring adrenaline						
1 RCT (n = 21)	Reduced grade by one level as moderate risk of bias	No grade change. Not possible to examine consistency as one study only.	Reduced grade by one level as single study in single country so may impact generalisability.	Reduced grade by one level. Small study so small number of events affects proportions significantly.	No grade change. Bias uncertain. Only single study published. No industry sponsorship.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
% of doses with adverse reactions						
1 RCT (n = 21)	Reduced grade by one level as moderate risk of bias	No grade change. Not possible to examine consistency as one study only.	Reduced grade by one level as single study in single country so may impact generalisability.	Reduced grade by one level. Small study so small number of events affects proportions significantly. Incomplete reporting.	No grade change. Bias uncertain. Only single study published. No industry sponsorship.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Cow's milk protein allergy – oral immunotherapy

Summary of findings

Immunotherapy for children and infants with cow's milk allergy				
People: Children and infants with allergy to cow's milk protein ranging from mild to severe **Settings:** Hospital and home, Asia, Europe, USA **Intervention:** Oral immunotherapy with raw allergen **Comparison:** Placebo or elimination diet				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
% able to tolerate specific dose (Desensitisation)	Oral immunotherapy probably increases the proportion of children and infants able to tolerate cow's milk during treatment compared to placebo or elimination diet by a large amount. 7 out of 7 RCTs found an increase in the proportion able to tolerate a dose of around 150-200ml during treatment (68% immunotherapy vs 15% control, absolute difference 53%, RR 5.7, CI 1.9 to 16.7, p<0.05, NNT 2)	Moderate	7 RCTs (total n = 249) (n = 6 and 31 and 60 and 60 and 42 and 30 and 20)	One RCT of oral immunotherapy versus placebo in children with severe cow's milk allergy found a trend towards an increased proportion able to tolerate 200ml after 18 weeks (66% vs 0%, p not reported) (Caminiti 2009). One RCT of oral immunotherapy versus elimination diet in infants with mild to severe cow's milk allergy found an increased proportion able to tolerate 200ml at 6 months (88% vs 0%, p not reported) (Lee 2013). One RCT of oral immunotherapy versus elimination diet in children with severe cow's milk allergy found an increased proportion able to tolerate 150ml at 1 year (36% vs 0%, p<0.001) (Longo 2008). One RCT of oral immunotherapy versus elimination diet in children with mild/moderate cow's milk allergy found an increased proportion able to tolerate 200ml at 1 year (90% vs 23.3%, p<0.05) (Martorell 2011). One RCT of oral immunotherapy versus elimination diet in children and infants with moderate cow's milk allergy found an increased proportion able to tolerate 200-250ml at 6 months (90% vs 54.5%, p<0.05) (Morisset 2011). One RCT of oral immunotherapy versus placebo in children with mild to severe cow's milk allergy found an increased proportion able to tolerate 200ml at 4.5 months (75% vs 0%, p<0.05) (Pajno 2010). One RCT of oral immunotherapy versus placebo in children with mild/moderate cow's milk allergy found an increased proportion able to tolerate 8140mg cow's milk protein at 23 weeks (33% vs 0%, p<0.05) (Skripak 2008).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
% of people experiencing adverse reactions	Oral immunotherapy may increase the proportion of infants and children with cow's milk allergy experiencing adverse reactions by a large amount. 6 out of 6 RCTs found increased adverse reactions compared to placebo or elimination diet (85% immunotherapy vs 17% control, absolute difference 67%, RR 3.9, CI 2.1 to 7.5, NNH 2). Adverse reactions were largely mild.	Low	6 RCTs (total n = 215, 210 evaluable) 6 RCTs oral (n = 6 and 31 and 60 and 60 and 30 and 28)	One RCT of oral immunotherapy versus placebo in children with severe cow's milk allergy found a trend towards an increased proportion experiencing adverse reactions (66% vs 0%, p not reported) (Caminiti 2009). One RCT of oral immunotherapy versus elimination diet in infants with mild to severe cow's milk allergy found an increased proportion experienced adverse reactions (87.5% vs 25%, p not reported) (Lee 2013) One RCT of oral immunotherapy versus elimination diet in children with severe cow's milk allergy found an increased proportion experienced adverse reactions (100% vs 20%, p<0.05) (Longo 2008). One RCT of oral immunotherapy versus elimination diet in children with mild/moderate cow's milk allergy found an increased proportion with mild/moderate adverse reactions (80% vs 10%, p<0.05) (Martorell 2011). One RCT of oral immunotherapy versus placebo in children with mild to severe cow's milk allergy found an increased proportion of adverse reactions (76% vs 0%, p<0.05) (Pajno 2010). One RCT of oral immunotherapy versus placebo in children with mild to severe cow's milk allergy found an increased proportion of adverse reactions (100% vs 62.5%, p<0.05) (Salmivesi 2013).
% of people experiencing severe adverse reactions	The effect of oral immunotherapy on the proportion of people experiencing severe reactions is unclear because the certainty of evidence is very low. 3 out of 4 RCTs found a trend towards increased severe adverse reactions compared to placebo, but the numbers were too small to draw conclusions. Meta-analysis found no significant difference between groups (3% immunotherapy vs 0% controls, RR 7.0, CI 0.4 to 124.8, p>0.05).	Very low	4 RCTs (total n = 204 evaluable)	One RCT of oral immunotherapy versus placebo in children with severe cow's milk allergy found a trend towards an increased proportion experiencing severe adverse reactions (33% vs 0%, p not reported) (Caminiti 2009). One RCT of oral immunotherapy versus elimination diet in infants with mild to severe cow's milk allergy found none had severe adverse reactions (0% vs 0%, p>0.05) (Lee 2013) One RCT of oral immunotherapy versus elimination diet in children with severe cow's milk allergy found a trend towards an increased proportion experiencing an event that required emergency department treatment during home maintenance (10% vs 0%, p not reported). 90% of the oral immunotherapy group required nebulized adrenaline during the rush build-up phase (Longo 2008). One RCT of oral immunotherapy versus placebo in children with mild to severe cow's milk allergy found an increased proportion of severe adverse reactions requiring treatment to be stopped (20% vs 0%, p not reported) (Pajno 2010).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % tolerating specific dose during treatment						
7 RCTs (total n = 249)	Reduced grade by two levels due to 3 studies at moderate risk of bias and 4 at high risk.	No change in grade level. All studies found consistent result.	No change in grade level. There are variations in individual studies including severity and inclusion criteria, but studies cover range of countries, levels of severity and treatment regimes.	No change in grade level. Small studies and some p-values not reported, but large effect sizes	No change in grade level	**Moderate** Graded up one level due to consistent and large effect size.
Adverse reactions						
6 RCTs (total n = 210)	Reduced grade by one level due to 4 studies at moderate and high risk of bias.	No change in grade level. Studies have consistent trends for overall adverse reactions.	Reduced grade by one level due to variations in individual studies including severity and inclusion criteria, which may impact on ability to generalise.	Reduced grade by one level. Small sample sizes and numbers of events. P-values not always reported.	No change in grade level. Appears studies with various findings published. Funnel plot does not show clear trend.	**Low** for % experience adverse reactions Increased grade level based on effect sizes.
Severe adverse reactions						
4 RCTs (total n = 204)	Reduced grade by one level due to 4 studies at moderate risk of bias and 4 at high risk.	Some inconsistencies for severe adverse reactions, but accounted for in imprecision factor.	Reduced grade by one level due to variations in individual studies including severity and inclusion criteria, which may impact on ability to generalise.	Reduced grade by one level. Small sample sizes and numbers of severe events. P-values not always reported.	No change in grade level. Appears studies with various findings published.	**Very low**

Cow's milk protein allergy – epicutaneous immunotherapy

Summary of findings

Immunotherapy for children and infants with cow's milk allergy				
People: Children and infants with allergy to cow's milk protein ranging from mild to severe **Settings:** Hospital and home, Europe **Intervention:** Epicutaneous immunotherapy with raw allergen **Comparison:** Placebo				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Increase in mean tolerated dose during treatment	The effect of epicutaneous immunotherapy on tolerated dose is unclear because the certainty of evidence is very low. 1 RCT found no difference from placebo.	Very low	1 RCT (n = 19)	One RCT of epicutaneous immunotherapy versus placebo in infants and children with cow's milk allergy found no difference in the mean increase in cumulative tolerated dose after about 13 weeks (p>0.05) (Dupont 2010).
% doses resulting in adverse reactions	The effect of immunotherapy on the proportion of doses resulting in adverse reactions is unclear because the certainty of evidence is very low. 1 RCT found an increase of epicutaneous immunotherapy compared to placebo.	Very low	1 RCT (n = 19)	One RCT of epicutaneous immunotherapy in infants and children with cow's milk allergy found an increased proportion of doses resulting in adverse reactions compared to placebo (25% of 470 doses vs 16.5% of 316 doses placebo, p<0.05) (Dupont 2010).
% doses resulting in severe adverse reactions	The effect of epicutaneous immunotherapy on the proportion of doses resulting in severe events is unclear because the certainty of evidence is very low. 1 RCT found no difference compared to placebo.	Very low	1 RCT epicutaneous (n = 19)	One RCT of epicutaneous immunotherapy in infants and children with cow's milk allergy found no significant difference in the proportion of doses resulting in severe adverse reactions compared to placebo (5% of 470 doses vs 2.5% of 316 doses placebo, p>0.05) (Dupont 2010).

Evidence profile – all outcomes

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
1 RCT (n = 19)	Reduced grade by one level due to moderate risk of bias.	No change in grade level. Not possible to examine consistency as 1 study only.	Reduced grade by one level due to single study in single country which may impact on ability to generalize.	Reduced grade by one level. Single small study.	Uncertain.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Oral versus sublingual immunotherapy for cow's milk allergy

Summary of findings

Oral versus sublingual immunotherapy for children and infants with cow's milk allergy				
People: Children with mild to severe allergy to cow's milk protein **Settings:** USA **Intervention:** Oral immunotherapy with raw allergen to 1000mg or 2000mg (following sublingual to 7mg) **Comparison:** Sublingual immunotherapy with raw allergen to 7mg				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
% able to tolerate 8g cow's milk protein (Desensitisation)	Oral immunotherapy may increase the proportion of children able to tolerate 8g cow's milk protein at 12 and 60 weeks compared to sublingual immunotherapy, but the certainty of evidence is low and based on 1 RCT.	Low	1 RCT (n = 30)	One RCT found that a higher proportion of children receiving oral immunotherapy could tolerate 8g cow's milk protein compared to those receiving sublingual therapy (12 weeks: 60% 1000mg oral vs 80% 2000mg oral vs 10% sublingual; 60 weeks: 70% 1000mg oral vs 90% 2000mg oral vs 10% sublingual, p oral versus sublingual = 0.002) (Keet 2012).
Sustained unresponsiveness: % tolerating specific dose after treatment ended	The effect of oral vs sublingual immunotherapy on sustained unresponsiveness in children with cow's milk allergy is unclear because the certainty of evidence is very low. 1 RCT found no significant difference between groups 6 weeks after ending treatment.	Very low	1 RCT (n = 30)	One RCT found there was a trend towards a higher proportion of children receiving oral immunotherapy could tolerate 8g cow's milk protein 6 weeks after ending treatment compared to those receiving sublingual therapy, but this did not reach statistical significance (40% vs 10% p = 0.09) (Keet 2012).
% doses resulting in adverse reactions	Oral immunotherapy and sublingual immunotherapy may result in a similar proportion of doses with adverse reactions during build up and maintenance, mostly mild/moderate, but the certainty of evidence is low and based on 1 RCT.	Low	1 RCT (n = 30)	One RCT found no differences in the proportion of oral immunotherapy doses associated with adverse reactions versus sublingual doses (23% of 10,645 doses vs 29% of 6246 doses, p>0.05) (Keet 2012).
% doses resulting in severe adverse reactions	Oral immunotherapy may be associated with more doses with multisystem adverse reactions compared to sublingual immunotherapy but the certainty of evidence is low and based on 1 RCT.	Low	1 RCT (n = 30)	One RCT found significantly more multisystem adverse reactions associated with oral immunotherapy doses compared to sublingual doses (relative risk 11.5, p<0.001) (Keet 2012).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % tolerating specific dose during treatment						
1 RCT (n = 30)	Reduced grade by one level due to moderate risk of bias.	No change in grade level. Single study so not able to assess consistency, but consistent results across different doses of oral immunotherapy.	Reduced grade by one level due single study in single country so may be difficult to generalize. Open label study.	Reduced grade by one level. Small sample size so minor changes may appear significant. P-values reported consistently.	Uncertain. Only one study published. No industry sponsorship reported.	**Low** Graded up one level based on effect size, dose response and consistency at multiple time points.
Sustained unresponsiveness: % tolerating specific dose after treatment ended						
1 RCT (n = 30)	Reduced grade by one level due to moderate risk of bias.	No change in grade level. Single study so not able to assess consistency, but consistent results across different doses of oral immunotherapy.	Reduced grade by one level due single study in single country so may be difficult to generalize. Open label study.	Reduced grade by one level. Small sample size.	Uncertain. Only one study published. Industry sponsorship reported.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders.
% doses resulting in adverse reactions or systemic or severe adverse reactions						
1 RCT (n = 30)	Reduced grade by one level due to moderate risk of bias.	No change in grade level. Single study so not able to assess consistency, but consistent results across different doses of oral immunotherapy.	Reduced grade by one level due single study in single country so may be difficult to generalize. Open label study.	No change in grade level. Small sample size but large number of doses so more precise measure.	Uncertain. Only one study published. No industry sponsorship reported.	**Low** No reason to grade up based on effect size, dose response or potential effect of confounders.

Hen's egg allergy – oral immunotherapy

Summary of findings

Oral immunotherapy for hen's egg allergy				
People: Children with hen's egg allergy ranging from mild to severe **Settings:** Asia and Europe **Intervention:** Oral immunotherapy with raw or cooked allergen for 3-12 months **Comparison:** Elimination diet (or placebo in one case)				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Desensitisation: % able to tolerate defined dose during therapy	Oral immunotherapy with raw or cooked egg probably results in a large increase the proportion of children with hen's egg allergy able to tolerate hen's egg during treatment. 6 out of 6 RCTs found that oral immunotherapy was more effective than an elimination diet (or placebo in one case). (84% immunotherapy vs 5% control, absolute difference 79%, RR 8.9, 95% CI 4.4 to 18.0, p<0.05, NNT 2).	Moderate	6 RCTs (total n = 266 of which 259 available for meta-analysis) (n = 36 and 31 and 20 and 45 and 101 and 33)	1 RCT with children with mild/moderate hen's egg allergy found that an increased proportion of those receiving oral immunotherapy with raw egg tolerated 4g dry egg powder after 6 months compared to an elimination diet (57% vs 0%, p<0.01) (Akashi 2017). 1 RCT with children with mild/moderate hen's egg allergy found that an increased proportion of those receiving oral immunotherapy with raw egg tolerated 4g egg white after 4 months compared to placebo (94% vs 7%, p not reported) (Caminiti 2017). 1 RCT with children with severe hen's egg allergy found that a higher proportion of those receiving oral immunotherapy with raw egg tolerated 10-39ml raw egg emulsion after 6 months compared to an elimination diet (90% vs 0%, p<0.01) (Dello Iacono 2017). 1 RCT with children with mild to severe hen's egg allergy found that an increased proportion of those receiving oral immunotherapy with cooked egg for 3 months were able to tolerate a dose of 1000mg egg powder compared to those on an elimination diet (87% vs 0%, p<0.05). 87% of the immunotherapy group and 22.7% of controls increased the tolerated dose (p<0.001) (Itoh-Nagato 2018). 1 RCT with children with mild to severe hen's egg allergy found that an increased proportion of those receiving oral immunotherapy with raw egg for 1 year tolerated 3.9g egg protein compared to an elimination diet (84.2% vs 18.2%, p<0.01) (Martín-Muñoz 2019). 1 RCT with children with mild/moderate hen's egg allergy found that an increased proportion of those receiving oral immunotherapy with raw egg tolerated 2808mg egg white protein after 5 months compared to an elimination diet (89.5% vs 0%, p<0.05) (Pérez-Rangel 2017).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
Sustained unresponsiveness: % able to tolerate defined dose after ending therapy	Oral immunotherapy may increase the proportion of children with hen's egg allergy able to tolerate hen's egg after treatment ends, but the certainty of evidence is low. 2 out of 2 RCTs found increases sustained responsiveness compared with an elimination diet (35% immunotherapy vs 4% control, absolute difference 30%, RR 7.1, CI 1.7 to 29.4, NNT 4).	Low	2 RCTs (total n = 92 of which 91 available for analysis) (n = 31 and 61)	1 RCT found a trend towards increased sustained unresponsiveness in children with mild/moderate hen's egg allergy receiving oral immunotherapy with raw egg compared to placebo (31% vs 7% tolerated 3.7g egg white 9 months after therapy finished and 3 months after total egg elimination diet, p not reported) (Caminiti 2017). 1 RCT found increased sustained unresponsiveness in children with mild to severe hen's egg allergy receiving oral immunotherapy with raw and then cooked egg compared to elimination diet (37% vs 3% tolerated cumulative dose of 2808mg egg white protein 1 month after therapy ended, p = 0.003) (Escudero 2015).
Quality of life	The impact of oral immunotherapy on the quality of life of children with hen's egg allergy is unclear as the certainty of evidence is very low. 1 RCT found an improvement compared to an elimination diet.	Very low	1 RCT (n = 45)	1 RCT with children with mild to severe hen's egg allergy found that an increased proportion of those receiving oral immunotherapy with cooked egg for 3 months improved their Quality of Life score more than 10 points from baseline compared to those on an elimination diet (65.2% vs 31.8%, p=0.04). There was no significant difference in the proportion improving more than one point on the Food Allergy Quality of Life survey (65.2% vs 54.6%, p = 0.55) (Itoh-Nagato 2018).
% of people experiencing adverse reactions	Oral immunotherapy with raw or cooked egg is probably linked to a large increase in the proportion of children with hen's egg allergy who experience adverse reactions compared to an elimination diet (or placebo in one case). (79% immunotherapy vs 8% control, absolute difference 71%, RR 7.0, CI 2.4 to 19.8, NNH 2).	Moderate	6 RCTs (total n = 291)	Adverse reactions were not necessarily linked to therapy. Few studies recorded the number of adverse reactions linked to therapy. Most adverse reactions were mild/moderate. They were mainly gastrointestinal.
% of people experiencing severe reactions	The effect of oral immunotherapy on severe adverse reactions in children with hen's egg allergy is unclear because the certainty of evidence is very low. (6% immunotherapy vs 0% control, absolute difference 6%, RR 3.4, CI 0.6 to 19.6, p>0.05).	Very low	4 RCTs (total n = 211)	Severe events were uncommon. The studies defined and measured severe events in different ways, so it is difficult to draw conclusions. In addition, studies also explored life-threatening reactions, anaphylaxis and use of adrenaline. There were no significant differences between groups but the certainty of evidence was very low.

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % able to tolerate defined dose during therapy						
6 RCTs (total n = 266)	Reduced grade by two levels as 4 studies at moderate risk of bias and 1 at high risk. 1 study was at low risk.	No grade change. Studies had consistent trends.	No grade change. Studies from range of countries and include variety of severity levels. Varied types of therapy but likely to be generalizable to population of interest.	No grade change. Lack of reporting of p-values in some cases and small number of events, but no heterogeneity in meta-analysis.	No grade change. Studies from a range of countries with and without sponsorship. Funnel plot suggests potential for bias.	**Moderate** Graded up one level due to large effect size.
Sustained unresponsiveness: % able to tolerate defined dose after ending therapy						
2 RCTs (total n = 92)	Reduced grade by one level as 1 study at moderate risk of bias. 1 study was at low risk.	No grade change. Both studies found consistent result.	No grade change. Studies from different countries but each focused on different therapy and had varied inclusion criteria. May impact on generalisability but not enough to reduce by grade level.	Reduced grade by one level due to small sample sizes and resulting wide confidence intervals and lack of reporting of p-values in some cases.	No grade change. Publication bias possible given small number of studies. No industry sponsorship.	**Low** No reason to grade up based on effect size, dose response or potential effect of confounders
Quality of life						
1 RCT (n = 45)	Reduced grade by one level due to moderate risk of bias.	No grade change. Not possible to draw conclusions about consistency as only one study.	Reduced grade by one level. Single study from single country so may not be generalizable.	Reduced grade by one level due to small sample size and manner in which data are reported.	No grade change. Bias possible given only one study. Other studies may have measured quality of life and not reported it.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
% of people experiencing adverse reactions						
6 RCTs for adverse reactions (total n = 291)	Reduced grade by one level as 3 studies had moderate risk of bias. 1 study was at low risk.	No grade change. Consistent findings across studies for adverse reactions.	No grade change. Studies focused on different therapy and had varied inclusion criteria, but likely to have some generalisability.	Reduced grade by one level due to small sample sizes and lack of reporting of p-values in some cases. Heterogeneity in meta-analysis	No grade change. Studies published from a range of countries. Funnel plot suggests issues.	**Moderate** Graded up one level due to large effect size.
% of people experiencing systemic or severe adverse reactions						
4 RCTs for severe events (total n = 211)	Reduced grade by one level as 4 studies had moderate risk of bias. 1 study was at low risk.	Reduced by grade by one level due to inconsistent findings (likely due to different measurement and focus).	No grade change. Likely to have some generalisability, but measurement differences make difficult to apply.	Reduced grade by one level due to small sample sizes and lack of reporting of p-values in some cases.	No grade change. Bias uncertain. Studies published with and without sponsorship.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders.

Immunotherapy for people with other food allergies – overall summary of findings

Summary of findings

Immunotherapy for adults and children with other types of food allergy				
People: Adults and children with various food allergy (peach, wheat, hazelnut, mixed) **Settings:** Europe, USA **Intervention:** Oral or sublingual immunotherapy with raw allergen **Comparison:** Placebo or elimination diet				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Ability to consume food allergen: % tolerating specific dose (Desensitisation)	The impact of oral or sublingual immunotherapy on sustained unresponsiveness in children with various food allergies is unclear because the certainty of evidence is very low. 2 out of 2 RCTs about oral immunotherapy found improved Desensitisation and 1 out of 2 RCTs about sublingual immunotherapy found trends towards improved Desensitisation, but the samples were small, measures imprecise and there may be issues with generalisability.	Very low	4 RCTs (total n = 148) 1 RCT wheat (n = 46) 1 RCT hazelnut (n = 23) 1 RCT peach (n = 55) 1 RCT mixed (n = 24)	One RCT comparing oral immunotherapy versus placebo in adults and children found improved ability to tolerate 4443mg wheat after 1 year (52.2% vs 0%, p<0.0001) (Nowak-Węgrzyn 2019). One RCT comparing sublingual immunotherapy versus placebo in adults found a trend towards improved ability to tolerate 20g hazelnut after 2-3 months (45% vs 9%, p not reported) (Enrique 2005). One RCT comparing sublingual peach immunotherapy versus placebo found no significant difference in changes in the threshold of peach tolerated by adults at 6 months (p>0.05, numbers not reported) (Fernández-Rivas 2009). One RCT comparing oral immunotherapy versus elimination diet in children with milk, egg, fish or apple allergy found improved ability to tolerate a specific dose at 6 months (85.7% vs 0%, p not reported) (Patriarca 1998).
Sustained unresponsiveness: % tolerating specific dose after treatment ended	The impact of oral immunotherapy on sustained unresponsiveness in children with various food allergies is unclear because the certainty of evidence is very low. One RCT found no significant difference in sustained unresponsiveness at a median of 21 months after beginning treatment.	Very low	1 RCT (n = 45)	One RCT comparing oral immunotherapy versus elimination diet in children with milk or egg allergy found no significant difference in the ability to tolerate a specific dose 2 months after finishing therapy (36% vs 35%, p>0.05) (Staden 2007).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
Adverse events: % of people experiencing adverse reactions	Immunotherapy may increase the proportion of people with various food allergies experiencing (mild/moderate) adverse reactions. 2 RCTs about oral immunotherapy and 2 about sublingual immunotherapy found increased overall adverse reactions compared to placebo or elimination diet. The increase was in mild/moderate events.	Moderate	4 RCTs (total n = 169) 1 RCT wheat (n = 46) 1 RCT hazelnut (n = 23) 1 RCT peach (n = 55) 1 RCT mixed (n = 45)	One RCT comparing oral immunotherapy versus placebo in adults and children with wheat allergy found a trend towards increased adverse reactions over a 1 year period (100% vs 78.3%, p not reported). The events were mainly mild/moderate (Nowak-Węgrzyn 2019). One RCT comparing sublingual immunotherapy versus placebo in adults with hazelnut allergy found a trend towards increased adverse reactions over a 2-3 month period (45% vs 9%, p not reported). The events were mainly mild/moderate. (Enrique 2005) One RCT in adults with peach allergy found that a greater proportion of people suffered (mild local) adverse reactions with sublingual immunotherapy compared to placebo for 6 months (Fernández-Rivas 2009). One RCT comparing oral immunotherapy versus elimination diet in children with milk or egg allergy found increased adverse reactions (100% of 25 vs 30% of 20 placebo, p not reported). All were mild to moderate events, except for 1 in the control group due to accidental exposure (Staden 2007).
% of people experience systemic or severe adverse reactions	Immunotherapy may not increase the proportion of people with various food allergies experiencing severe adverse reactions. 2 RCTs about oral immunotherapy and 2 about sublingual immunotherapy found no difference in severe events compared with placebo or elimination diet.	Moderate	4 RCTs (total n = 169) 1 RCT wheat (n = 46) 1 RCT hazelnut (n = 23) 1 RCT peach (n = 55) 1 RCT mixed (n = 45)	One RCT comparing oral immunotherapy versus placebo for 1 year found no significant difference in the number of adults and children with wheat allergy experiencing severe adverse reactions or the proportion of doses where there was a severe event (Nowak-Węgrzyn 2019). One RCT comparing sublingual immunotherapy versus placebo in adults with hazelnut allergy found no significant difference in systemic adverse reactions over a 2-3 month period (9% vs 9%, p>0.05) (Enrique 2005). One RCT in adults with peach allergy found no difference in systemic or severe adverse reactions at 6 months between sublingual immunotherapy and placebo (Fernández-Rivas 2009). One RCT comparing oral immunotherapy versus elimination diet in children with milk or egg allergy found no difference in severe adverse reactions (Staden 2007).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Ability to consume allergen: % tolerating specific dose						
4 RCTs (total n = 148) 1 RCT wheat (n = 46) 1 RCT hazelnut (n = 23) 1 RCT peach (n = 55) 1 RCT mixed (n = 24)	Reduced grade by one level due to 3 studies at moderate risk of bias and 1 at high risk.	No change in grade level. 3 out of 4 studies found improvement.	Reduced grade by one level due to variations in individual studies including allergy types, severity and inclusion criteria, which may impact on ability to generalize.	Reduced grade by one level. Limited precision in individual studies and half do not report p-values.	Uncertain. 4 studies available but unknown whether others have been conducted and not published, especially given wide range of allergens.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
Sustained unresponsiveness: % tolerating set dose 2 months after treatment ended						
1 RCT (n = 45)	Reduced grade by one level due to moderate risk of bias.	No change in grade level. One study only so not able to compare consistency of findings.	Reduced grade by one level due to single study in one country so may not be generalizable. Not able to differentiate results for children with different types of allergies.	Reduced grade by one level. Small sample size impacts on precision. P-values not reported.	No change in grade level. Only single study is available, but other studies published examining milk and egg allergies alone.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders.
Adverse events and systemic or severe adverse reactions						
4 RCTs (total n = 169) 1 RCT wheat (n = 46) 1 RCT hazelnut (n = 23) 1 RCT peach (n = 55) 1 RCT mixed (n = 45)	Reduced grade by one level due to all 4 studies being at moderate risk of bias.	No change in grade level. All studies have consistent trends for overall adverse reactions and severe adverse reactions.	Reduced grade by one level due to variations in individual studies including allergy types, severity and inclusion criteria, which may impact on ability to generalise.	No change in grade level. Reporting not always precise and small sample sizes, but consistent approach.	Uncertain. 4 studies available but unknown whether others have been conducted and not published, especially given wide range of allergens.	**Moderate** Increased grade level based on effect sizes (for mild/moderate events).

Wheat immunotherapy

Summary of findings

Wheat oral immunotherapy				
People: Adults and children with mild/moderate wheat allergy **Settings:** USA **Intervention:** Oral immunotherapy with raw wheat gluten for 1 year **Comparison:** Placebo				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
% able to consume 4443mg wheat protein at 1 year	Oral immunotherapy for 1 year may increase the proportion of adults and children with wheat allergy able to tolerate the equivalent of about 1 slice of bread, but the certainty of evidence is low.	Low	1 RCT (n = 46)	One RCT comparing oral immunotherapy versus placebo in adults and children found improved ability to tolerate 4443mg wheat after 1 year (52.2% vs 0%, p<0.0001) (Nowak-Węgrzyn 2019).
Adverse events measured up to 1 year: % of people experiencing any event And % of doses	The impact of oral immunotherapy on adverse reactions in adults and children with wheat allergy is unclear because the certainty of evidence is very low. One RCT found a trend towards increased (mild/moderate) adverse reactions with oral immunotherapy.	Very low	1 RCT (n = 46)	One RCT comparing oral immunotherapy versus placebo in adults and children found a trend towards an increased proportion of people experiencing adverse reactions over 1 year (100% of 23 vs 78.3% of 23 placebo, p not reported) and the proportion of doses where there was an adverse event (15.4% of 7822 doses vs 5.8% 921 placebo doses, p not reported). The events were mainly mild/moderate (Nowak-Węgrzyn 2019).
Adverse events measured up to 1 year: % of people experiencing severe events And % of doses	The impact of oral immunotherapy on severe adverse reactions in adults and children with wheat allergy is unclear because the certainty of evidence is very low. One RCT found no increase in severe adverse reactions with oral immunotherapy.	Very low	1 RCT (n = 46)	One RCT comparing oral immunotherapy versus placebo in adults and children found no significant difference in the number of people experiencing severe adverse reactions over 1 year (13% of 23 vs 0% of 23 placebo, p<0.05) or the proportion of doses where there was a severe event (0.04% of 7822 doses vs 0% 921 placebo doses, p<0.05) (Nowak-Węgrzyn 2019).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Ability to consume wheat: % tolerating 4443mg						
1 RCT (n = 46)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings but appears to be internally consistent in trends related to Desensitisation.	Reduced grade by one level due to single study in one country so may not be generalizable.	Reduced grade by one level. Small sample size impacts on precision.	Uncertain. Only single study is available. Sponsored by industry. Unknown whether other studies conducted but not published.	**Low** Increased grade one level based on effect size.
Adverse events and severe adverse reactions						
1 RCT (n = 46)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings but appears to be internally consistent in trends related to adverse reactions.	Reduced grade by one level due to single study in one country so may not be generalizable.	Reduced grade by one level. Small sample size impacts on precision. P-values not reported.	Uncertain. Only single study is available. Sponsored by industry. Unknown whether other studies conducted but not published.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Hazelnut immunotherapy

Summary of findings

Hazelnut sublingual immunotherapy				
People: Adults with moderate to severe hazelnut allergy **Settings:** Spain **Intervention:** Sublingual immunotherapy with raw hazelnut (build up 4 days, maintenance 2-3 months) **Comparison:** Placebo				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
% able to consume 20g cumulative total dose of hazelnut after 2-3 months	The impact of sublingual immunotherapy on Desensitisation in adults with hazelnut allergy is unclear because the certainty of evidence is very low. One RCT found a trend towards improved ability to tolerate hazelnut after 2-3 months compared to placebo.	Very low	1 RCT (n = 23)	One RCT comparing sublingual immunotherapy versus placebo in adults found a trend towards improved ability to tolerate 20g hazelnut after 2-3 months (45% vs 9%, p not reported) (Enrique 2005).
Adverse events measured up to 2-3 month: % of people experiencing any event	The impact of sublingual immunotherapy on adverse reactions in adults with hazelnut allergy is unclear because the certainty of evidence is very low. One RCT found a trend towards increased (mild/moderate) adverse reactions with sublingual immunotherapy.	Very low	1 RCT (n = 23)	One RCT comparing sublingual immunotherapy versus placebo in adults found a trend towards increased adverse reactions over a 2-3 month period (45% vs 9%, p not reported) (Enrique 2005). The events were mainly mild/moderate.
Adverse events measured up to 2-3 months: % of people experiencing systemic events	The impact of sublingual immunotherapy on systemic adverse reactions in adults with hazelnut allergy is unclear because the certainty of evidence is very low. One RCT found no increase in systemic adverse reactions with sublingual immunotherapy.	Very low	1 RCT (n = 23)	One RCT comparing sublingual immunotherapy versus placebo in adults found no significant difference in systemic adverse reactions over a 2-3 month period (9% vs 9%, p>0.05) (Enrique 2005).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Ability to consume hazelnut: % tolerating 20g cumulative total dose						
1 RCT (n = 23)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings but appears to be internally consistent in trends related to Desensitisation.	Reduced grade by one level due to single study in one country so may not be representative. Included oral allergy syndrome symptoms at the challenge for inclusion in the study so not all may have hazelnut allergy.	Reduced grade by one level. Small sample size impacts on precision. P-values not reported.	No grade change. Only single study is available. Not sponsored by industry.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
Adverse events and systemic adverse reactions						
1 RCT (n = 23)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings but appears to be internally consistent in trends related to adverse reactions.	Reduced grade by one level due to single study in one country so may not be representative. Included oral allergy syndrome symptoms at the challenge for inclusion in the study so not all may have hazelnut allergy.	Reduced grade by one level. Small sample size impacts on precision. P-values not reported.	No grade change. Only single study is available. Not sponsored by industry.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Peach immunotherapy

Summary of findings

Peach sublingual immunotherapy				
People: Adults with mild to severe peach allergy **Settings:** Hospital and home, Spain **Intervention:** Sublingual immunotherapy with raw peach (2 weeks build up in hospital and 6 months maintenance at home) **Comparison:** Placebo (dried coconut)				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Ability to consume peach after 6 months (threshold tolerated)	The impact of sublingual immunotherapy on Desensitisation in adults with peach allergy is unclear because the certainty of evidence is very low. One RCT found no improvement in adults' ability to tolerate peach after six months compared to placebo.	Very low	1 RCT (n = 55)	One RCT comparing sublingual peach immunotherapy versus placebo found no significant difference in changes in the threshold of peach tolerated by adults at 6 months (p>0.05, numbers not reported) (Fernández-Rivas 2009).
Adverse events measured up to 6 months: % of administered doses	Sublingual immunotherapy may be associated with an increased rate of adverse reactions compared to placebo for adults with peach allergy, but these events may be mild and mainly related to the oral administration method.	Low	1 RCT (n = 55)	One RCT found that a higher proportion of sublingual peach immunotherapy doses were associated with adverse reactions compared to placebo (difference between groups 27.9%, p<0.0001). These were mainly mild and related to the oral cavity (Fernández-Rivas 2009).
Adverse events measured up to 6 months: % of people experiencing local events	Sublingual immunotherapy may increase the proportion of adults with peach allergy experiencing local adverse reactions compared to placebo. Events may be mild and mainly related to the oral administration method.	Low	1 RCT (n = 55)	One RCT found that 89.2% of adults receiving peach immunotherapy had local adverse reactions compared to 13.5% placebo (p<0.05). 1344/1356 adverse reactions related to immunotherapy were in the intervention group. 12/1356 events were in the placebo group. No adverse reactions were serious. (Fernández-Rivas 2009).
Adverse events measured up to 6 months: % of people experiencing systemic events	Sublingual immunotherapy may not increase systemic events compared to placebo for adults with peach allergy.	Low	1 RCT (n = 55)	One RCT found no significant difference in systemic adverse reactions between the proportion of adults receiving peach immunotherapy versus placebo (13.5% vs 16.7%, p>0.05). All systemic reactions were mild (Fernández-Rivas 2009).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Ability to consume peach at 6 months: threshold tolerated						
1 RCT (n = 55)	Reduced grade by one level due to moderate risk of bias	Uncertain. One study only so not able to compare consistency of findings and not able to examine internal consistency as single measures used.	Reduced grade by one level due to single study in one country so may not be representative.	Reduced grade by one level due to small sample size and lack of reporting of numbers.	Reduced grade by one level due to not reporting key predefined outcomes. Only single study is available and sponsored by industry.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
Adverse events and systemic adverse reactions						
1 RCT (n = 55)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings but appears to be internally consistent in trends related to adverse reactions.	Reduced grade by one level due to single study in one country so may not be representative.	No change in grade level. Small sample size impacts on precision but confidence intervals not overly wide for adverse reactions.	Uncertain. Only single study is available and sponsored by industry, but unsure whether other studies have been undertaken and not published.	**Low** No reason to grade up based on effect size, dose response or potential effect of confounders

Immunotherapy for mixed groups with food allergies

Summary of findings

Oral immunotherapy for groups with different food allergies				
People: Children with mild/moderate allergy to either milk, egg, fish or apple **Settings:** Hospital and home, Europe (Italy and Germany) **Intervention:** Oral immunotherapy with raw allergen; duration of treatment varied by child **Comparison:** Elimination diet				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
% able to consume specified dose at 6 months (Desensitisation)	The impact of oral immunotherapy on Desensitisation in children with various food allergies is unclear because the certainty of evidence is very low. One RCT found a trend towards increased Desensitisation with oral immunotherapy.	Very low	1 RCT (n = 24)	One RCT comparing oral immunotherapy versus elimination diet in children with milk, egg, fish or apple allergy found improved ability to tolerate a specific dose at 6 months (85.7% vs 0%, p not reported) (Patriarca 1998).
Sustained unresponsiveness: % able to consume specified dose 2 months after treatment ended	The impact of oral immunotherapy on sustained unresponsiveness in children with various food allergies is unclear because the certainty of evidence is very low. One RCT found no significant difference in sustained unresponsiveness at a median of 21 months after beginning treatment.	Very low	1 RCT (n = 45)	One RCT comparing oral immunotherapy versus elimination diet in children with milk or egg allergy found no significant difference in the ability to tolerate a specific dose 2 months after finishing therapy (36% vs 35%, p>0.05) (Staden 2007).
% of people experiencing any adverse event	The impact of oral immunotherapy on adverse reactions in children with various food allergies is unclear because the certainty of evidence is very low. One RCT found a trend towards increased (mild/moderate) adverse reactions with oral immunotherapy.	Very low	1 RCT (n = 45)	One RCT comparing oral immunotherapy versus elimination diet in children with milk or egg allergy found increased adverse reactions (100% of 25 vs 30% of 20 placebo, p not reported). All were mild to moderate events, except for 1 in the control group due to accidental exposure (Staden 2007).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Desensitisation: % tolerating set dose						
1 RCT (n = 24)	Reduced grade by two levels due to high risk of bias	No change in grade level. One study only so not able to compare consistency of findings.	Reduced grade by one level due to single study in one country so may not be generalizable. Not able to differentiate results for children with different types of allergies.	Reduced grade by one level. Small sample size impacts on precision. P values not reported.	No change in grade level. Only single study is available, but other studies published examining milk and egg allergies alone.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
Sustained unresponsiveness: % tolerating set dose 2 months after treatment ended						
1 RCT (n = 45)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings.	Reduced grade by one level due to single study in one country so may not be generalizable. Not able to differentiate results for children with different types of allergies.	Reduced grade by one level. Small sample size impacts on precision. P-values not reported.	No change in grade level. Only single study is available, but other studies published examining milk and egg allergies alone.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders.
Adverse events						
1 RCT (n = 45)	Reduced grade by one level due to moderate risk of bias	No change in grade level. One study only so not able to compare consistency of findings. Trends consistent internally related to adverse reactions.	Reduced grade by one level due to single study in one country so may not be generalizable. Not able to differentiate results for children with different types of allergies.	Reduced grade by one level. Small sample size impacts on precision. P-values not reported.	No change in grade level. Only single study is available, but other studies published examining milk and egg allergies alone.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders.

Immunotherapy plus biological for cow's milk allergy

Summary of findings

Immunotherapy plus biological for children with cow's milk allergy				
People: Children with severe allergy to cow's milk protein **Settings:** Japan **Intervention:** Omalizumab plus oral immunotherapy with baked cow's milk (microwave heated) (24 weeks, with omalizumab alone for first 8 weeks) **Comparison:** Elimination diet				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Sustained unresponsiveness: % able to tolerate 200ml cow's milk 8 weeks after treatment ended	The effect of oral immunotherapy plus omalizumab is unclear because the certainty of evidence is very low. 1 RCT found a trend towards better sustained unresponsiveness compared to an elimination diet.	Very low	1 RCT (n = 16)	One RCT of omalizumab plus oral immunotherapy versus elimination diet found a higher proportion of children with severe cow's milk allergy could tolerate 200ml 8 weeks after ending treatment compared to placebo (70% vs 0%, p not reported) (Takahashi 2017).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Sustained unresponsiveness: % tolerating specific dose after treatment ended						
1 RCT (n = 16)	Reduced grade by two levels due to high risk of bias.	No change in grade level. Single study so not able to assess consistency.	Reduced grade by one level due single study in single country so may be difficult to generalize. Open label study.	Reduced grade by one level. Small sample size and no p-values reported.	Uncertain. Only one study published. No industry sponsorship reported.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders.

Biological monotherapy – peanut allergy

Summary of findings

Any biological monotherapy				
People: Children and adults with peanut allergy **Settings:** Hospital (outpatient), USA **Intervention:** Single dose intravenous etokimab (300mg/100 mL) OR omalizumab for 20-22 weeks every 2-4 weeks OR 150mg, 300mg, or 450mg of TNX-901 subcutaneously every 4 weeks for 4 doses **Comparison:** Placebo				
Outcomes	**Summary**	**Certainty of evidence**	**Number of studies (participants)**	**Findings of individual studies**
Ability to consume peanut: % able to tolerate defined dose	There is low certainty of evidence about the effect of monotherapy with biological medicines on the ability to tolerate peanut. Two out of three RCTs found no change in the proportion able to tolerate a defined dose. One RCT found that a single dose of intravenous etokimab increased the proportion able to tolerate a low dose of peanut (275mg) (Chinthrajah 2019). Two other RCTs found no significant differences after omalizumab (Sampson 2011) or TNX-901 (Leung 2003).	Very low	3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	One small RCT found 73% of adults taking a single dose of intravenous etokimab tolerated 275mg peanut protein at 15 days compared to 0% of placebo (p<0.01) (Chinthrajah 2019). One very small RCT found that omalizumab did not increase the proportion of children and adults able to tolerate 1000mg peanut protein at 24 weeks (44% omalizumab vs 20% placebo, p>0.05) (Sampson 2011). One RCT found that TNX-901 did not increase the proportion of adults able to tolerate 8000mg peanut protein at 14-16 weeks (0% 150mg TNX-901 vs 21% 300mg TNX-901 vs 24% 450mg TNX-901 vs 4% placebo, p>0.05) (Leung 2003).
Median or mean cumulative tolerated dose of peanut protein compared to baseline	The impact of biological medicines on the dose of peanut tolerated is unclear because the certainty of evidence is very low. One RCT found an improvement with etokimab and another with 450mg TNS-901. Another RCT found no significant difference with omalizumab.	Very low	3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	One small RCT found that adults receiving a single dose of intravenous etokimab were able to tolerate a higher median dose of peanut protein at 15 days compared to those receiving placebo (increase in median dose compared to baseline: etokimab 100mg vs placebo 50mg, p<0.05) (Chinthrajah 2019). One very small RCT found no statistically significant improvement from omalizumab in the maximum dose of peanut tolerated by children and adults compared to baseline, but there were positive trends (p>0.05) (Sampson 2011). One RCT found that a 450mg dose of TNX-901 increased adult's threshold of sensitivity to peanut from about half a peanut at baseline (178mg) to almost nine peanuts by 18-20 weeks (2805mg). This was statistically significant compared to placebo (p<0.001). Lower doses of TNX-901 did not have a statistically significant effect. (Leung 2003).

Outcomes	Summary	Certainty of evidence	Number of studies (participants)	Findings of individual studies
Adverse events	The impact of biological medicines on adverse events is unclear because the certainty of evidence is very low. Three RCTs suggested that biologicals were generally well tolerated.	Very low	3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	One small RCT found that 20% of adults receiving a single dose of intravenous etokimab had mild adverse events compared with 40% of placebo. 60% of the etokimab group had moderate events versus 100% of placebo (p not reported) (Chinthrajah 2019). One very small RCT found no difference in mild to moderate adverse events reported in children and adults taking omalizumab versus placebo (77% vs 89% placebo, p>0.05) (Sampson 2011). One RCT found no difference in the incidence and type of adverse events between 150mg, 300mg or 450mg subcutaneous TNX-901 versus placebo (Leung 2003).
Severe or systemic adverse events	The impact of biological medicines on severe or systemic adverse events is unclear because the certainty of evidence is very low. Three RCTs found that biologicals were not associated with significantly more severe adverse events than placebo.	Very low	3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	One small RCT found no severe or systemic adverse events in adults taking a single dose of etokimab or placebo (p>0.05) (Chinthrajah 2019). One very small RCT found no systemic adverse events in children and adults taking omalizumab or placebo (Sampson 2011). One RCT found no difference in the incidence and type of systemic adverse events was similar between 150mg, 300mg or 450mg subcutaneous TNX-901 vs placebo (Leung 2003).

Evidence profile

Studies (participants)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty
Ability to consume peanut: % able to tolerate defined dose						
3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	Reduced grade by one level as two out of three studies are at moderate risk of bias	No grade change. Two out of three studies found consistent result, but number of studies too small to draw conclusions about consistency.	Reduced grade by one level. Studies all from one country. Studies each focused on different therapy. Varied inclusion criteria.	Reduced grade by one level due to small sample sizes, lack of reporting of p-values in some cases and wide confidence intervals.	No grade change, but publication bias possible given small number of studies and all industry sponsored.	**Very low** One study found large effect and dose response relationship but not consistent enough to grade up one level.
Ability to tolerate peanut: mean or median cumulative tolerated dose						
3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	Reduced grade by one level as two out of three studies are at moderate risk of bias	No grade change. Two out of three studies found consistent result, but number of studies too small to draw conclusions about consistency.	Reduced grade by one level. Studies all from one country. Studies each focused on different therapy. Varied inclusion criteria.	Reduced grade by one level due to small sample sizes, lack of reporting of p-values in some cases and wide confidence intervals.	No grade change, but publication bias possible given small number of studies and all industry sponsored.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders
Adverse events and systemic/severe adverse events						
3 RCTs (total n = 118) Etokimab: 1 RCT (n = 20) Omalizumab: 1 RCT (n = 14) TNX-901: 1 RCT (n = 84)	Reduced grade by one level as two out of three studies are at moderate risk of bias	No grade change. Consistent findings across three studies.	Reduced grade by one level. Studies all from one country. Studies each focused on different therapy. Varied inclusion criteria.	Reduced grade by one level due to small sample sizes, lack of reporting of p-values in some cases and wide confidence intervals.	No grade change, but publication bias possible given small number of studies and all industry sponsored.	**Very low** No reason to grade up based on effect size, dose response or potential effect of confounders

Online supplement S7: Pooled estimates of effects

Analysis	Page
Peanut allergy	
Oral immunotherapy – desensitisation and thresholds tolerated	2
Oral immunotherapy – sustained unresponsiveness	4
Oral immunotherapy – adverse reactions	4
Oral immunotherapy – severe reactions	5
Oral immunotherapy – life-threatening reactions	5
Oral immunotherapy – anaphylaxis	6
Oral immunotherapy – use of adrenaline	6
Epicutaneous immunotherapy – desensitisation and thresholds tolerated	7
Epicutaneous immunotherapy – adverse reactions	7
Epicutaneous immunotherapy – severe reactions	7
Sublingual immunotherapy	8
Subcutaneous immunotherapy	8
Duration of treatment	9
Cow's milk protein allergy – oral immunotherapy	
Desensitisation	10
Adverse reactions	12
Severe reactions	14
Use of adrenaline	15
Life-threatening reactions	16
Anaphylaxis	17
Hen's egg allergy – oral immunotherapy	
Desensitisation	18
Sustained unresponsiveness	19
Adverse reactions	20
Severe reactions	21
Life-threatening reactions	22
Anaphylaxis	23
Use of adrenaline	24
All studies combined	
Desensitisation	25
Sustained unresponsiveness	30
Number experiencing any adverse reaction	31
People with adverse reactions related to therapy	32
Doses associated with any adverse reaction	33
Doses with adverse events related to therapy	36
Number experiencing severe reactions	37
People with severe reactions related to therapy	39
Doses associated with severe reactions	40
Number experiencing life-threatening events	41
Doses associated with life-threatening events	43
People who received adrenaline	44
People with anaphylaxis	46
Duration of treatment	48
Direct comparison studies of oral versus sublingual immunotherapy	49

See Supplement S3 for the definitions of severe adverse reactions, life-threatening reactions, anaphylaxis and use of adrenaline. S5 contains study characteristics.

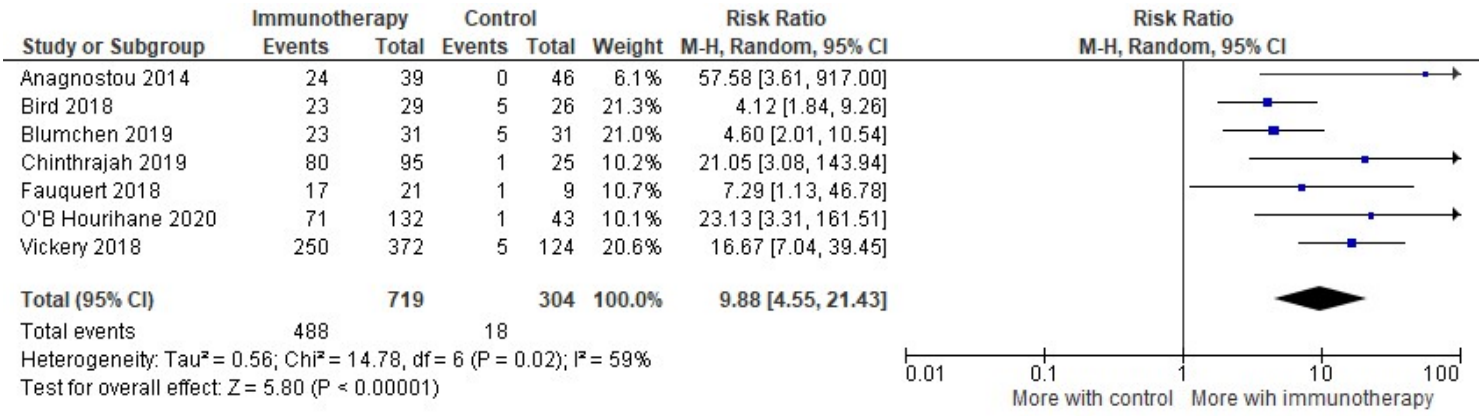
Peanut allergy

Oral immunotherapy

Desensitisation

Pooled data from 7 studies suggested increased desensitisation with oral immunotherapy. However the results were heterogeneous. This was not explained by age or allergy severity.

All but one study was in children with mixed levels of allergy severity (RR 12.17, 95% CI 5.43 to 27.32). The other study had mixed age groups and moderate level of severity (RR 4.1, 95% CI 1.8 to 9.3).

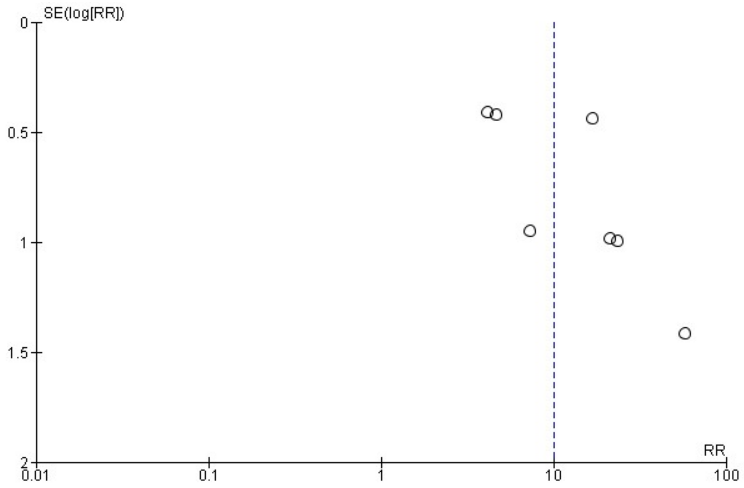


Study or Subgroup	Immunotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Anagnostou 2014	24	39	0	46	6.1%	57.58 [3.61, 917.00]
Bird 2018	23	29	5	26	21.3%	4.12 [1.84, 9.26]
Blumchen 2019	23	31	5	31	21.0%	4.60 [2.01, 10.54]
Chinthrajah 2019	80	95	1	25	10.2%	21.05 [3.08, 143.94]
Fauquert 2018	17	21	1	9	10.7%	7.29 [1.13, 46.78]
O'B Hourihane 2020	71	132	1	43	10.1%	23.13 [3.31, 161.51]
Vickery 2018	250	372	5	124	20.6%	16.67 [7.04, 39.45]
Total (95% CI)		**719**		**304**	**100.0%**	**9.88 [4.55, 21.43]**
Total events	488		18			

Heterogeneity: Tau² = 0.56; Chi² = 14.78, df = 6 (P = 0.02); I² = 59%
Test for overall effect: Z = 5.80 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100
More with control More wih immunotherapy



All of the studies were at low or moderate risk of bias. Excluding studies at moderate risk of bias, the trend was maintained in pooled data from 6 studies at low risk (RR 9.09, CI 3.80 to 21.73).

Tolerated 300mg single dose of peanut protein

Pooled data from 5 studies found that oral immunotherapy was associated with an increased likelihood of being able to tolerate a dose of 300mg at study exit. 4 of these studies were in children with mixed levels of allergy severity and 1 in mixed age groups with moderate level severity. 4 of the studies included exact data for the proportion tolerating a 300mg dose. We extracted data in the range 300 to 600mg from 1 study.



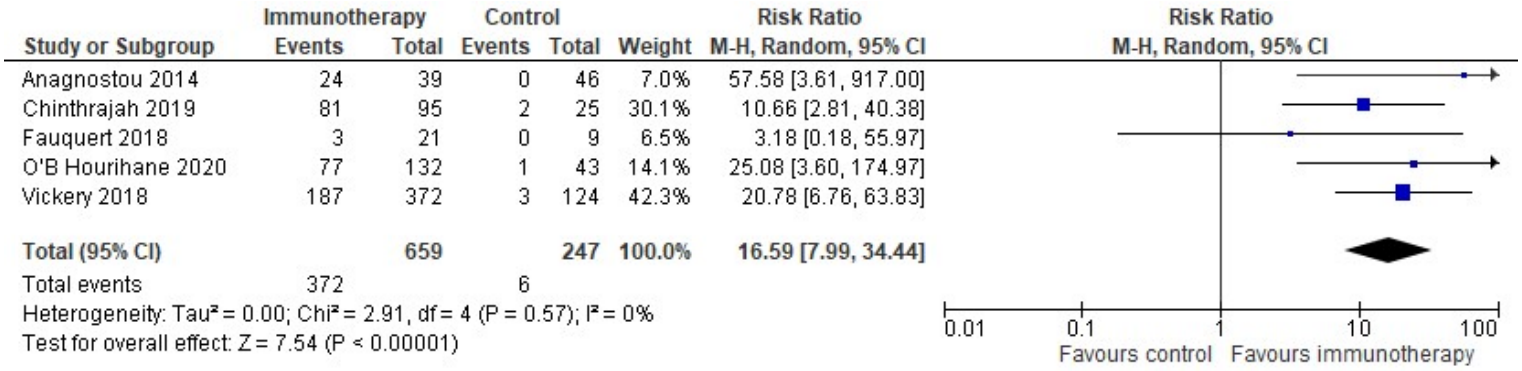
Tolerated cumulative dose of 300mg peanut protein

Pooled data from the same 5 studies found that oral immunotherapy was associated with an increased likelihood of being able to tolerate a cumulative dose of 300mg at study exit. 1 of the studies included exact data for the proportion tolerating a cumulative 300mg dose. We extracted data in the range 300 to 600mg from the other 4 studies.



Tolerated single dose of 1000mg peanut protein at exit

Pooled data from 5 studies found that oral immunotherapy was associated with an increased likelihood of being able to tolerate a dose of 1000mg at study exit. All studies included exact data about the proportion tolerating a 1000mg dose.



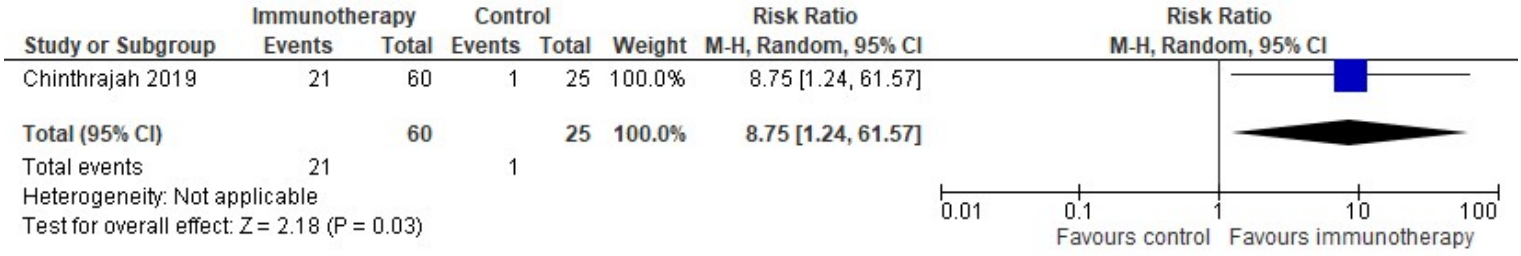
Tolerated cumulative dose of 1000mg peanut protein at exit

Pooled data from 6 studies found that oral immunotherapy was associated with an increased likelihood of being able to tolerate a cumulative dose of 1000mg at study exit. 3 of these studies included exact data about the proportion tolerating a 1000mg cumulative dose. We extracted data in the range 1000 to 2000mg from the other 3 studies.



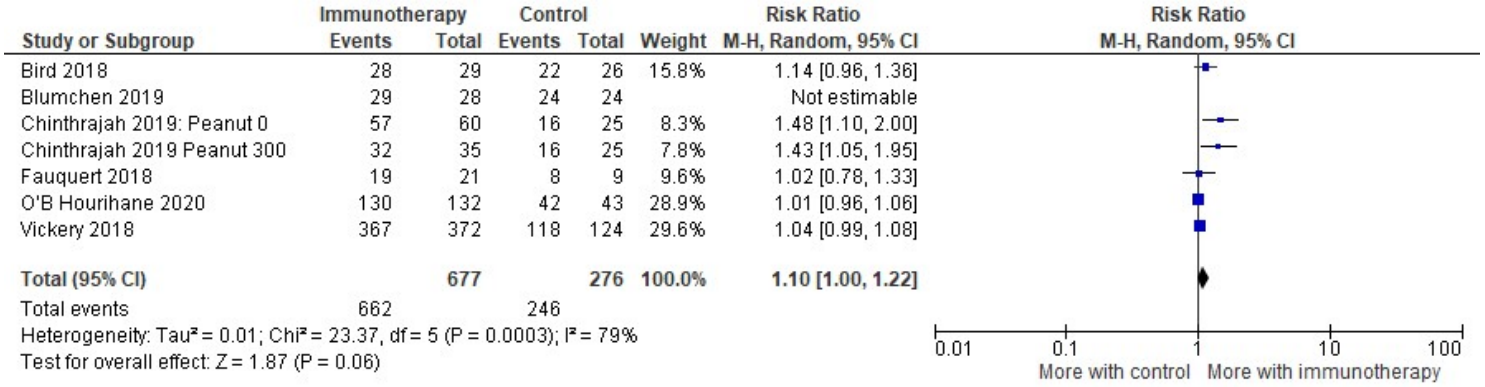
Sustained unresponsiveness

1 study in children found an increased proportion of sustained responsiveness in the oral immunotherapy group. This study was at low risk of bias. The children had mixed levels of allergy severity.



Any adverse reactions

7 comparisons examined the number of people experiencing adverse events of any type, not necessarily linked to therapy. Oral immunotherapy was not associated with an increased number of people experiencing adverse events compared to control (placebo), but the data were heterogeneous. The trend was also borderline, with P=0.06.



6 of the comparisons were in children (figure below) and 1 in mixed age groups.

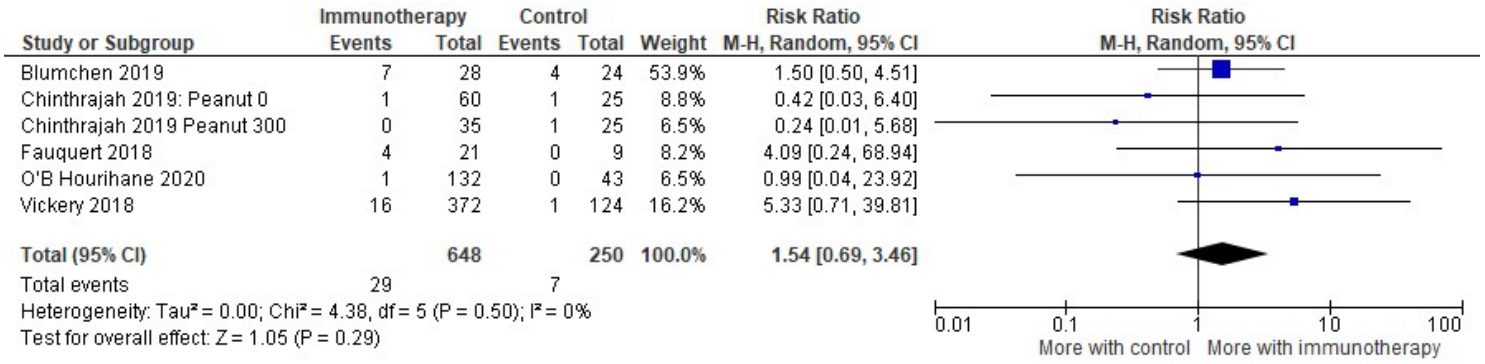


Only 2 studies explicitly focused on drug-related adverse events. Here again, there was no significant difference between groups but the data were heterogeneous. These studies were both at low risk of bias. One was in children and 1 in mixed age groups.

There were too few studies to pool with data about the number of doses associated with any adverse event or events linked to therapy.

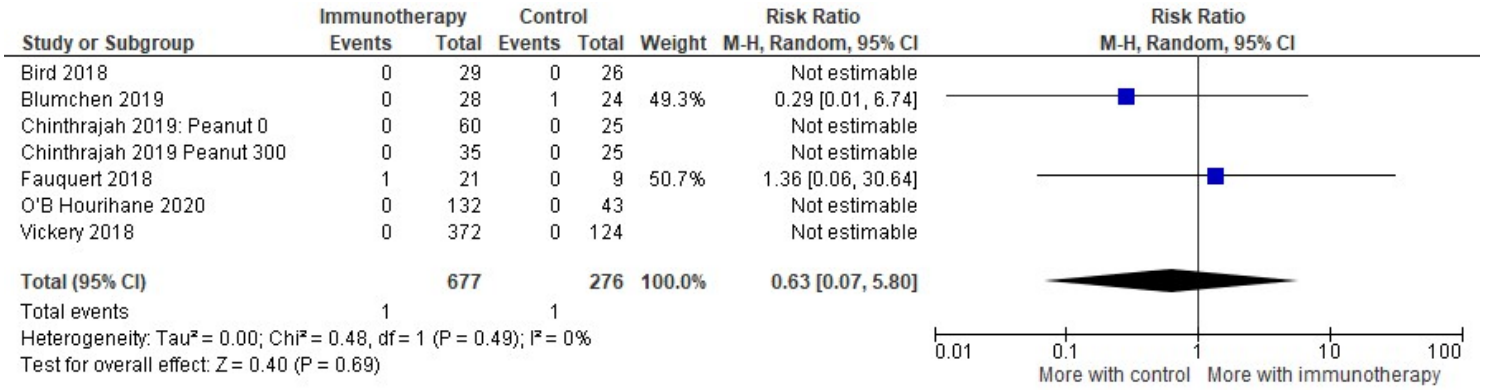
Severe reactions

6 comparisons explored the number of people experiencing severe reactions, whether related to the intervention or not. There was no significant difference between oral immunotherapy and placebo. All of the studies were in children and participants had mixed levels of allergy severity.



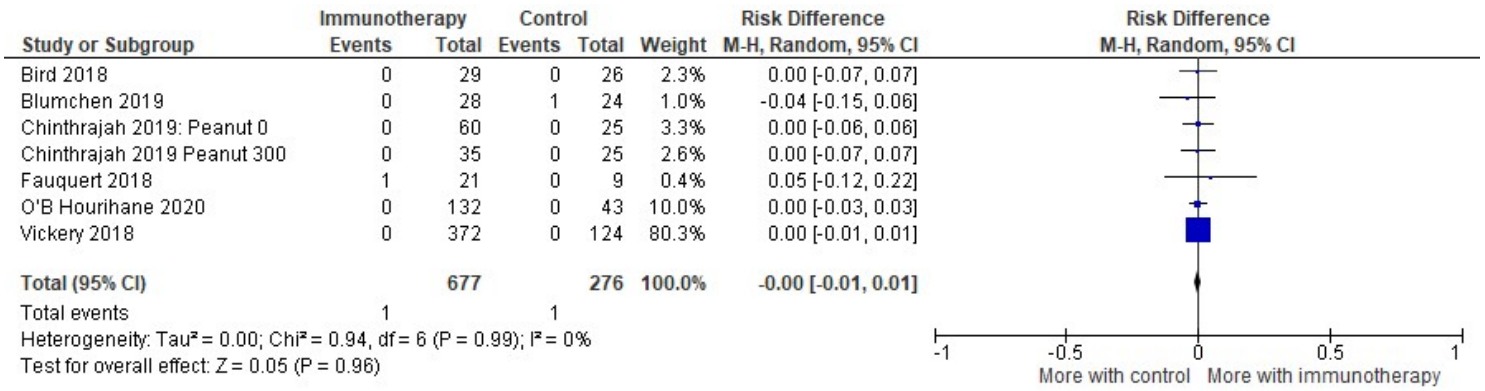
Life-threatening reactions

7 comparisons collected data about the number of people experiencing life-threatening reactions. Most had no events. There was no difference between oral immunotherapy and controls. Continuity correction did not affect this conclusion. 6 of the comparisons were in groups of children with mixed allergy severity. 1 was in mixed age groups with moderate severity.



Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.



Anaphylaxis

3 studies collected data about anaphylaxis, as defined by the included studies. There was no difference between immunotherapy and control groups in the number of people who had anaphylaxis. Continuity correction did not affect this conclusion.



Adrenaline

5 studies included data about the number of people given intravenous adrenaline for anaphylaxis during the study period. Continuity correction did not affect this conclusion. People receiving oral immunotherapy were 2.5 times more likely to be given adrenaline for anaphylaxis. Continuity correction did not affect this conclusion. However, it is difficult to interpret these findings because studies found that immunotherapy was not associated with a great risk of anaphylaxis so findings about adrenaline may be linked to variations in how this is used in different countries.



Epicutaneous immunotherapy

Desensitisation
Pooled data from 3 studies suggested increased rates of desensitisation with epicutaneous immunotherapy compared to controls. There were too few studies to examine subgroups. 1 study was in children and two in mixed age groups. 2 studies focused on people with mild/moderate allergy and 1 with mixed levels of severity.



Tolerated 300mg peanut protein single dose (and same figures for cumulative dose)
Pooled data from 3 comparisons from 1 study found an increased proportion of those receiving epicutaneous immunotherapy had a last tolerated dose of 300mg. The same is true for cumulative doses of 300mg. We used data in the range 300 to 600mg from this study for both single and cumulative doses.



Tolerated cumulative dose of 1000mg peanut protein at exit
2 comparisons from 1 study found no difference in the proportion of epicutaneous and control participants who tolerated a cumulative dose of 1000mg peanut protein at study exit. We used data in the range 1000 to 2000mg from this study.



Any adverse reactions
4 comparisons explored any adverse reactions, not necessarily related to therapy. Epicutaneous immunotherapy was not associated with an increased proportion of people experiencing adverse reactions compared to placebo. However the data were heterogeneous. This was not explained by age. 1 of the studies was in children and the other 4 comparisons in mixed age groups.



Only 1 study explicitly focused on drug-related adverse events. Here again, there was no significant difference between groups. There were too few studies to pool with data about the number of doses associated with any adverse event or events linked to therapy.

Severe reactions
4 comparisons explored the number of people experiencing severe reactions. There was no significant difference between epicutaneous immunotherapy and placebo. There were too few studies to pool data for the number of doses associated with severe reactions. There was no difference between groups in life-threatening events, use of adrenaline or anaphylaxis.



Sublingual immunotherapy

Desensitisation

We included only 1 study of sublingual immunotherapy for people with peanut allergy. This study found increased desensitisation. The study was in adults with mild/moderate peanut allergy.



Tolerated 300mg peanut protein single dose

The 1 study of sublingual immunotherapy for people with peanut allergy found no increase in the proportion able to tolerate a last dose of 300mg peanut protein: RR 1.67 (0.46, 6.06). We extracted data about last tolerated dose in the range 300 to 600mg from this study.

Tolerated cumulative dose of 1000mg peanut protein at exit

The 1 study of sublingual immunotherapy for people with peanut allergy found no increase in the proportion able to tolerate a cumulative dose of 1000mg peanut protein: RR 1.50 (0.28, 8.04). We extracted cumulative data in the range 1000 to 2000mg from this study.

Severe reactions

The study examined severe reactions, but there were 0 events in each arm.

Subcutaneous immunotherapy

Desensitisation

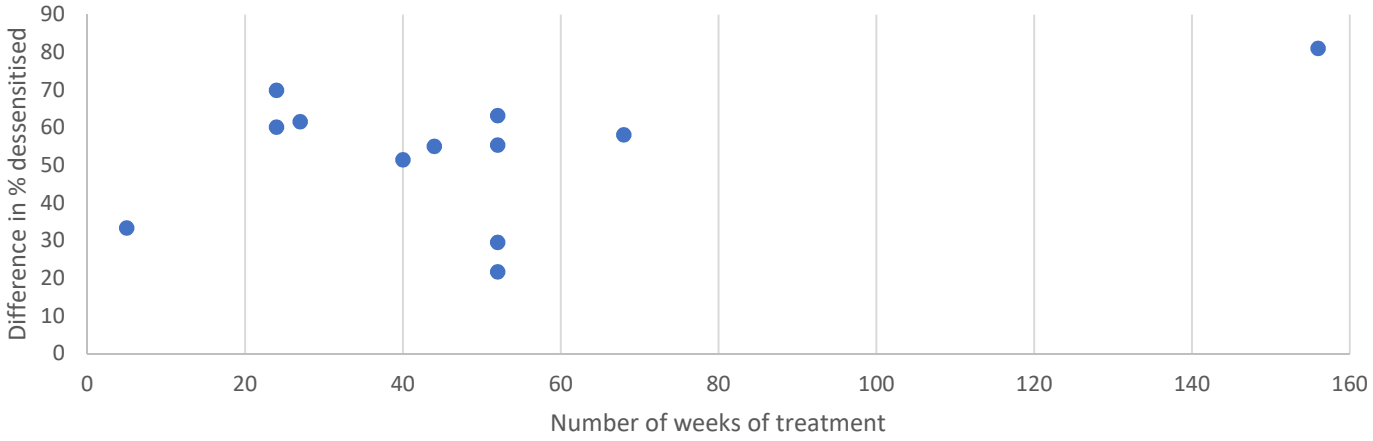
We included only 1 study of subcutaneous immunotherapy for people with peanut allergy. This was in mixed age groups with severe allergy. In this study subcutaneous immunotherapy had no significant impact on desensitisation compared to control. It did not explore other outcomes of interest to the review.



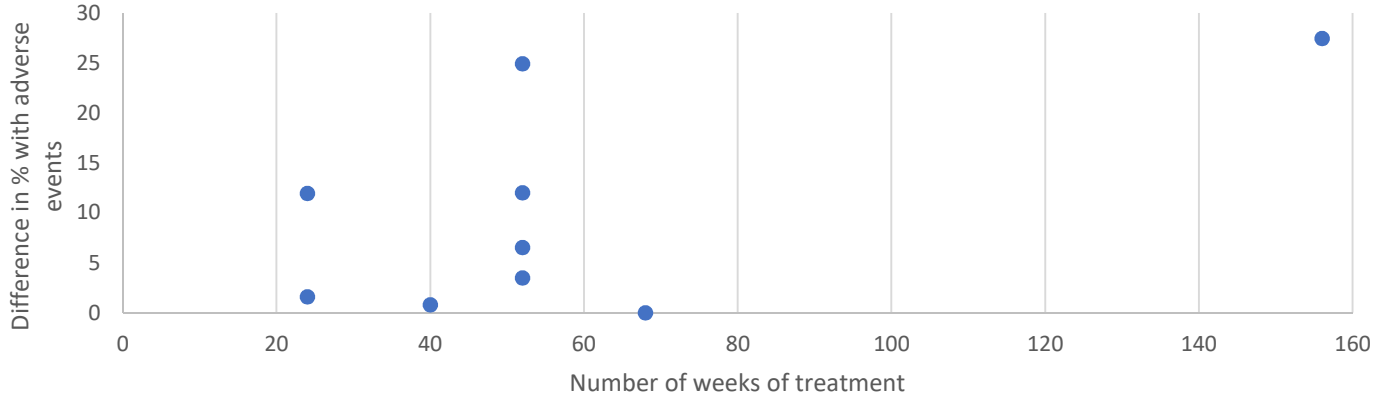
Duration of treatment

We found no clear relationship between the total duration of treatment (build up and maintenance) and outcomes of immunotherapy for people with peanut allergy.

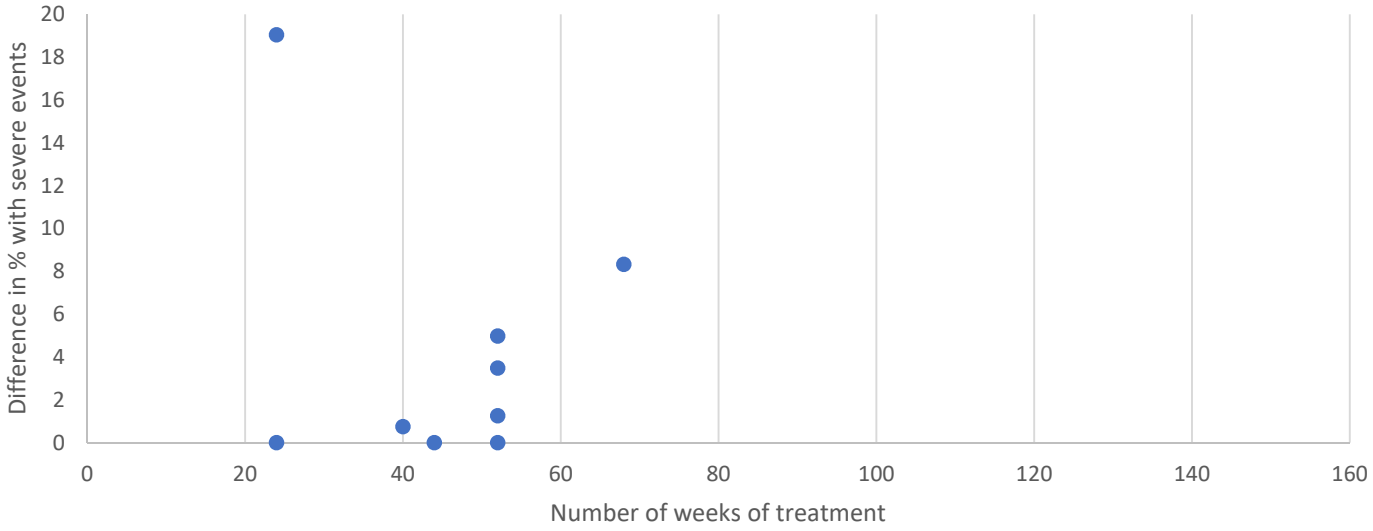
Total number of weeks therapy vs absolute difference in % desensitised (intervention minus placebo)



Total number of weeks therapy vs absolute difference in % with adverse events (intervention - placebo)



Total number of weeks therapy vs absolute difference in % with severe adverse events (intervention - placebo)

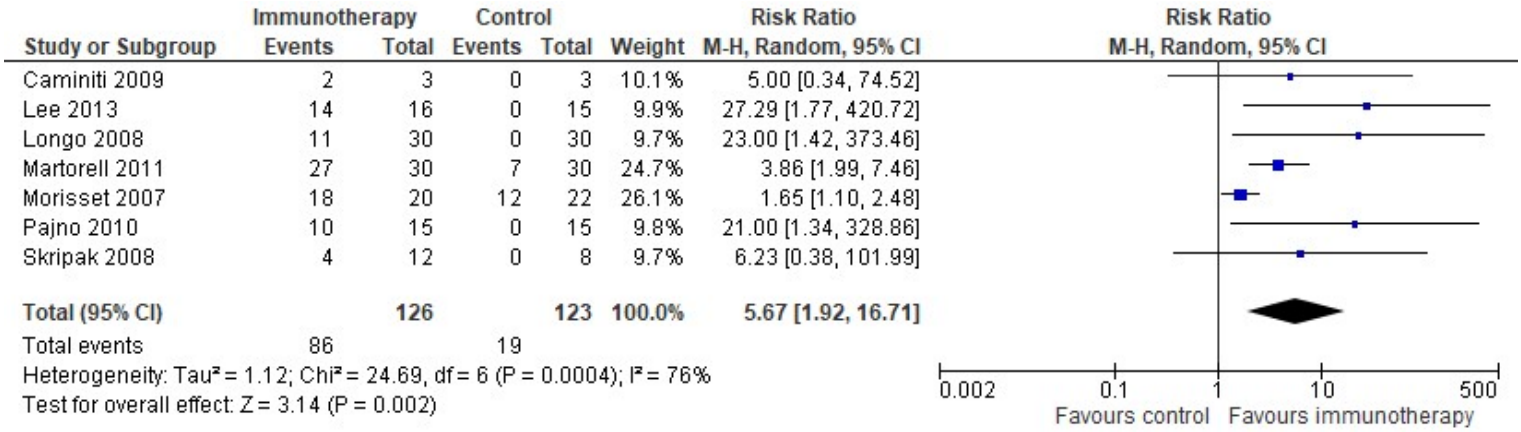


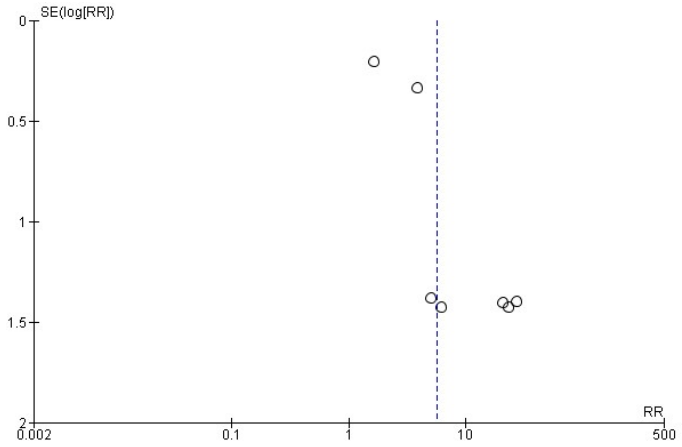
Oral immunotherapy

All of the data available for pooling about cow's milk protein allergy was about oral immunotherapy, apart from rare events such as life-threatening events, people who experienced anaphylaxis and people given adrenaline. Here there was one additional study about epicutaneous immunotherapy focused on safety. Those data were pooled with oral immunotherapy safety data as there were 0 events and this did not affect the conclusions.

Desensitisation

Pooled data from 7 studies of oral immunotherapy in cow's milk found increased likelihood of desensitisation but the data were heterogeneous. We performed subgroup analysis and found that heterogeneity decreased once studies at high risk of bias were removed.





Risk of bias

3 studies were at moderate risk of bias (below). No studies were at low risk.



Desensitisation by comparator

Heterogeneity was high in the 4 studies which compared oral immunotherapy with an elimination diet.



Heterogeneity was lower when oral immunotherapy was compared to placebo in 3 studies, though the confidence interval was wider.



Desensitisation by age

Pooled data from 2 studies in infants found no statistically significant improvement in desensitisation, but the data were heterogeneous. The trend was positive, but it did not reach significance.



Pooled data from 4 studies in children found a significant improvement in desensitisation and low heterogeneity.



1 study was in mixed age groups.



Desensitisation by severity of allergy

Oral immunotherapy was associated with a significant improvement in desensitisation using pooled data from the 3 studies of mild/moderate cow's milk protein allergy. However heterogeneity remained.



The trend was stronger in pooled data from 2 studies in people with severe allergy.

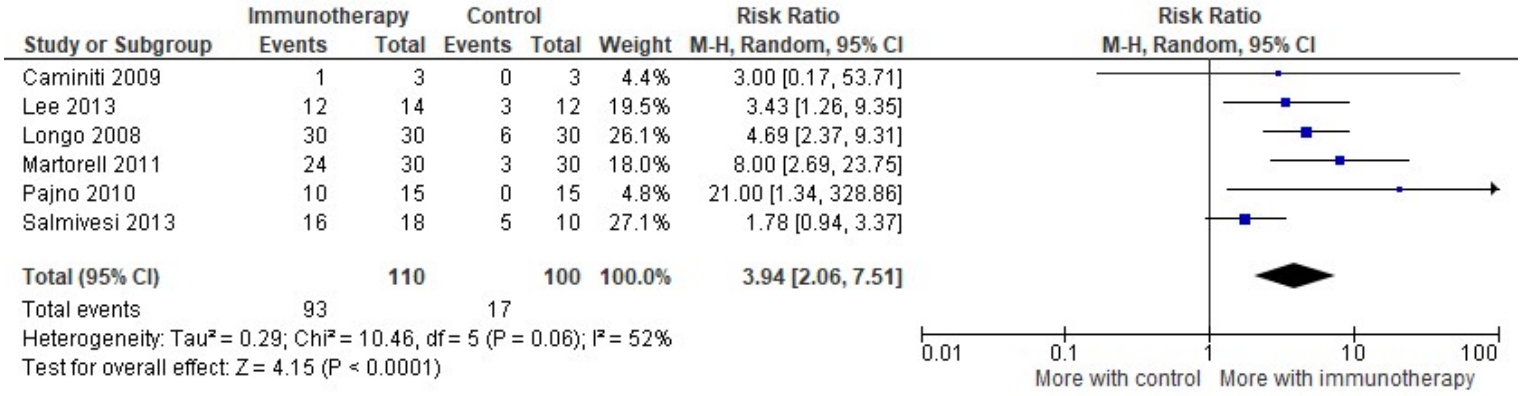


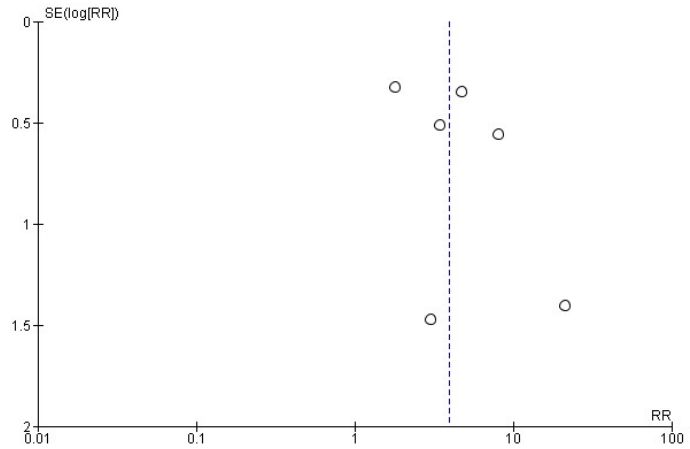
2 studies had mixed age groups.



Adverse reactions

6 studies explored any adverse reactions, regardless of whether linked to therapy. Oral immunotherapy was associated with increased proportion of people with cow's milk protein allergy experiencing adverse reactions, but the data were heterogeneous.





<u>Risk of bias</u>

Excluding studies at high risk of bias reduced the heterogeneity, but widened the confidence interval. Two studies were at moderate risk of bias (below). No studies were at low risk.



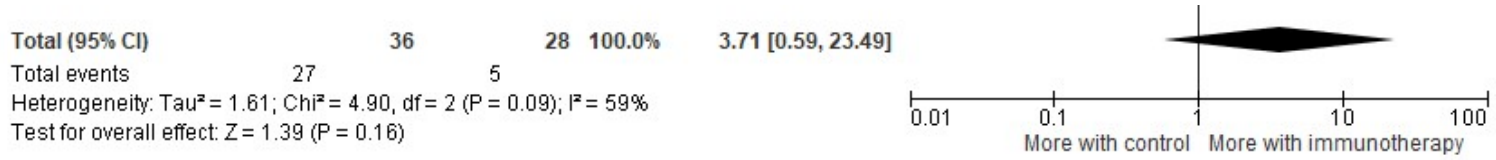
Adverse reactions by comparator

The trend towards increased proportion of people with adverse reactions held if oral immunotherapy was compared with an elimination diet (3 studies). However there was no significant difference between groups in adverse events when oral immunotherapy was compared with placebo (3 studies), though these data were heterogeneous.

Elimination diet



Placebo



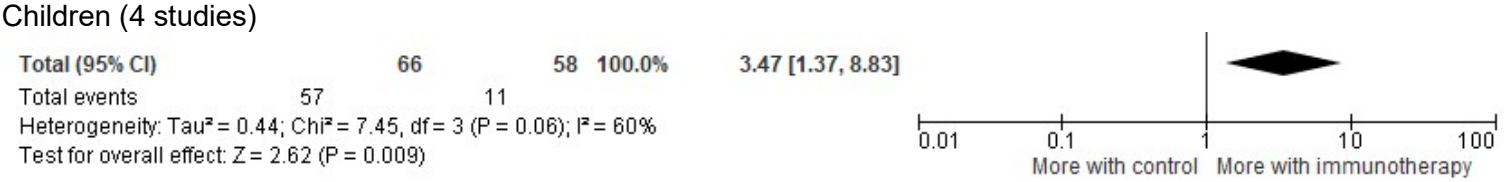
Adverse reactions by age

The trend of increased proportion with adverse reactions remained regardless of whether children or infants.

Infants (2 studies)



Children (4 studies)



Adverse events by severity of allergy

The trend of increased proportion experiencing adverse reactions remained regardless of the level of severity of the allergy.

Mild/moderate (1 study)



Severe (2 studies)



Mixed (3 studies)

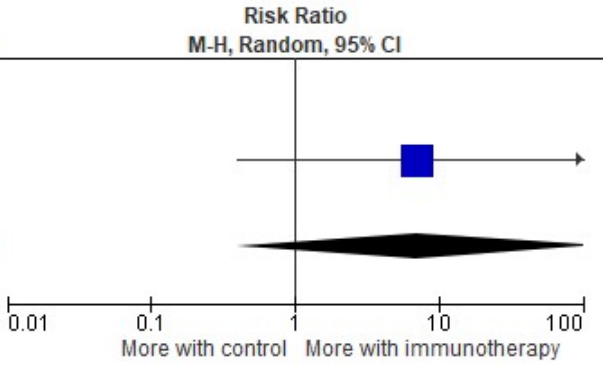


Severe reactions

Five studies measured the proportion of people with severe reactions, whether linked to therapy or not. Oral immunotherapy was not associated with an increased risk of severe reactions, whether data were pooled using a continuity correction or not.

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Lee 2013	0	14	0	12		Not estimable
Longo 2008	0	30	0	30		Not estimable
Martorell 2011	0	30	0	30		Not estimable
Pajno 2010	3	15	0	15	100.0%	7.00 [0.39, 124.83]
Salmivesi 2013	0	18	0	10		Not estimable
Total (95% CI)		**107**		**97**	**100.0%**	**7.00 [0.39, 124.83]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



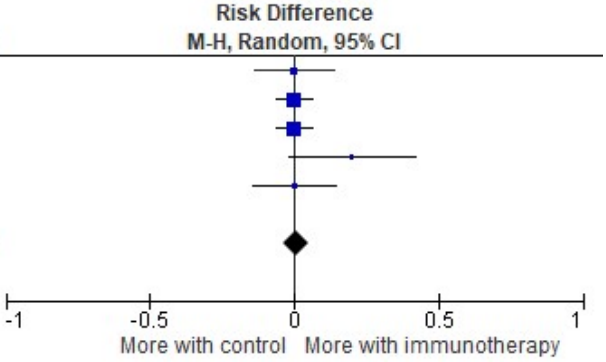
Continuity correction

Risk ratio 3.71 (0.27 to 51.84), Z 0.97, P 0.33, I^2 = 0%

Risk difference
Note that for risk differences, a pooled value of around 0 means no difference between groups.

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Lee 2013	0	14	0	12	9.4%	0.00 [-0.14, 0.14]
Longo 2008	0	30	0	30	38.9%	0.00 [-0.06, 0.06]
Martorell 2011	0	30	0	30	38.9%	0.00 [-0.06, 0.06]
Pajno 2010	3	15	0	15	3.8%	0.20 [-0.02, 0.42]
Salmivesi 2013	0	18	0	10	8.9%	0.00 [-0.14, 0.14]
Total (95% CI)		**107**		**97**	**100.0%**	**0.01 [-0.04, 0.05]**
Total events	3		0			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.38$, df = 4 (P = 0.36); $I^2 = 9\%$
Test for overall effect: Z = 0.35 (P = 0.73)



Too few events available for meaningful subgroup analysis.

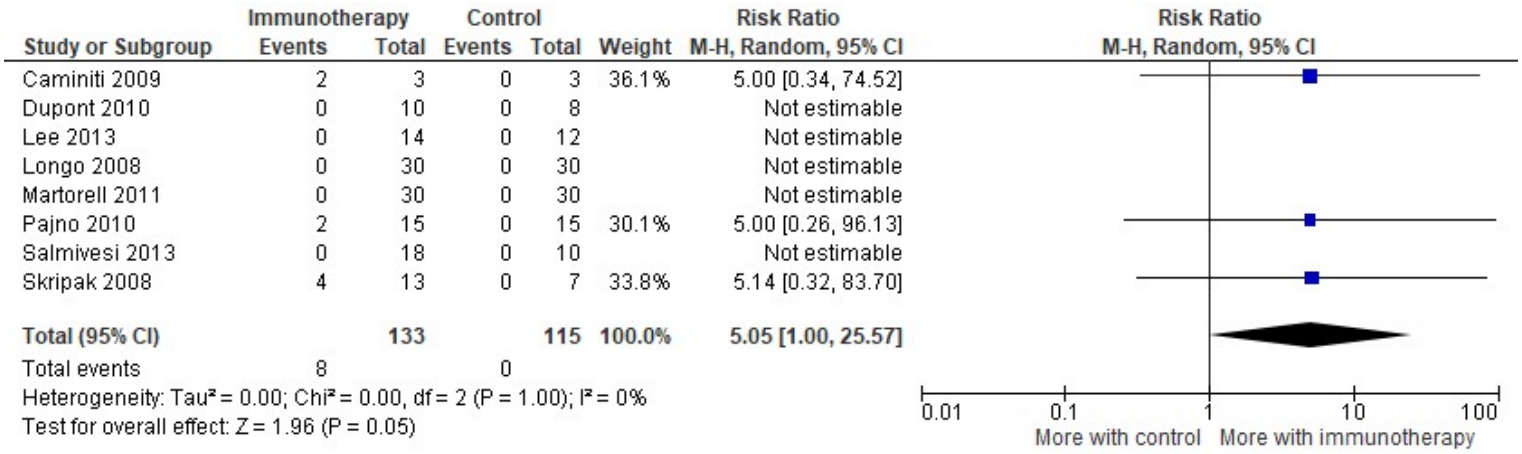
There were too few studies with data available to pool information about:

- Number of people with adverse events linked to therapy (0 studies)
- Number of people with severe adverse events related to therapy (0 studies)
- Doses associated with adverse events (2 studies)
- Doses associated with severe events (0 studies)

People given adrenaline

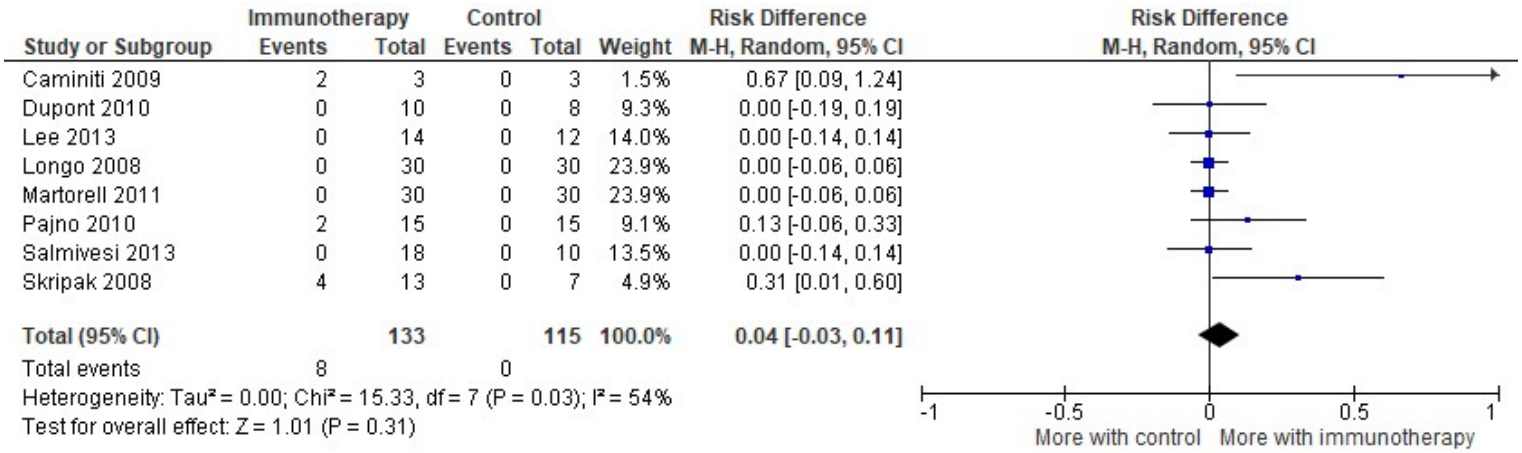
In addition to the 6 studies of oral immunotherapy, 1 study of epicutaneous immunotherapy also explored rare events such as anaphylaxis, adrenaline use and life-threatening reactions. This was a small study with 0 events in each arm so the data were pooled with oral immunotherapy. Sensitivity analysis showed that this made no difference to the trends.

In basic analysis, it appeared that immunotherapy may increase the number of people given adrenaline. However once a continuity correction was applied to account for the studies with 0 in each arm, there was no significant difference between immunotherapy and controls.



Continuity correction risk ratio 2.93 (0.6 to 14.31), Z 1.33, P 0.18, I^2 = 0%

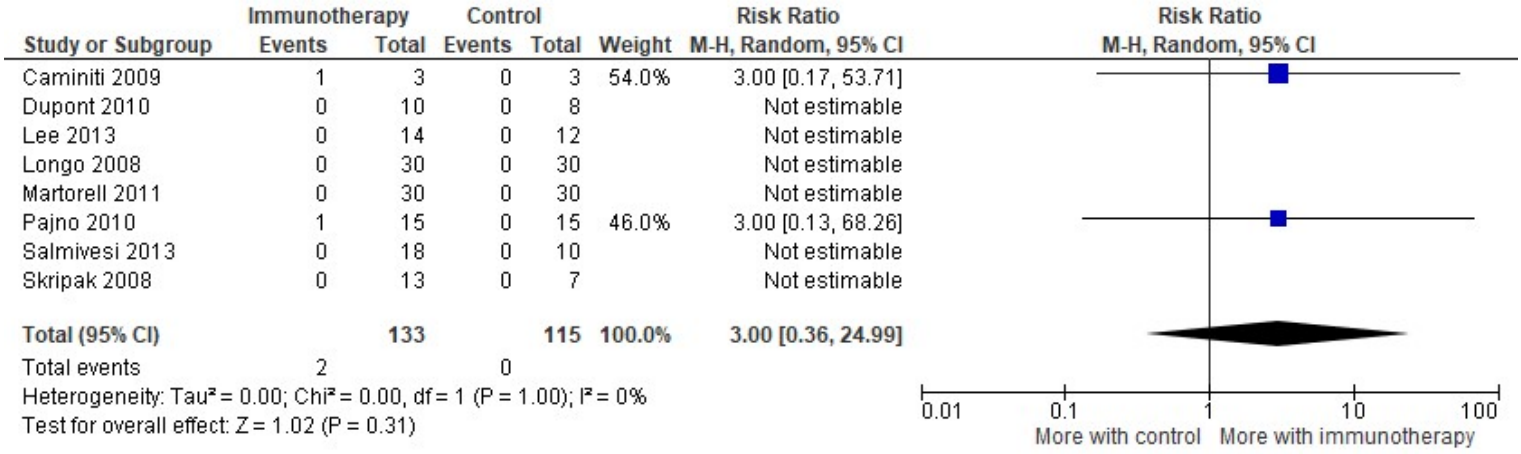
<u>Risk difference</u>
Note that for risk differences, a pooled value of around 0 means no difference between groups.



There were too few events available for meaningful subgroup analysis.

Life-threatening adverse events

There was no significant difference between groups in the proportion who experienced life-threating adverse events.



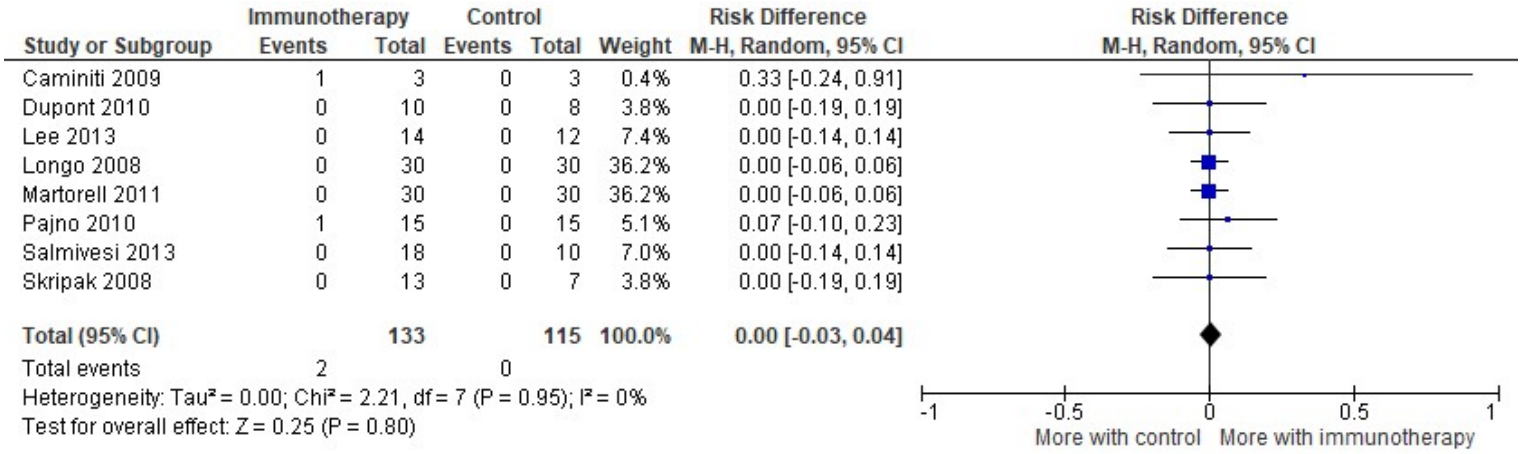
Study or Subgroup	Immunotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Caminiti 2009	1	3	0	3	54.0%	3.00 [0.17, 53.71]
Dupont 2010	0	10	0	8		Not estimable
Lee 2013	0	14	0	12		Not estimable
Longo 2008	0	30	0	30		Not estimable
Martorell 2011	0	30	0	30		Not estimable
Pajno 2010	1	15	0	15	46.0%	3.00 [0.13, 68.26]
Salmivesi 2013	0	18	0	10		Not estimable
Skripak 2008	0	13	0	7		Not estimable
Total (95% CI)		**133**		**115**	**100.0%**	**3.00 [0.36, 24.99]**
Total events	2		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)

Continuity correction risk ratio 1.59 (0.2 to 12.46), Z 0.44, P 0.66, I^2 = 0%

Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.

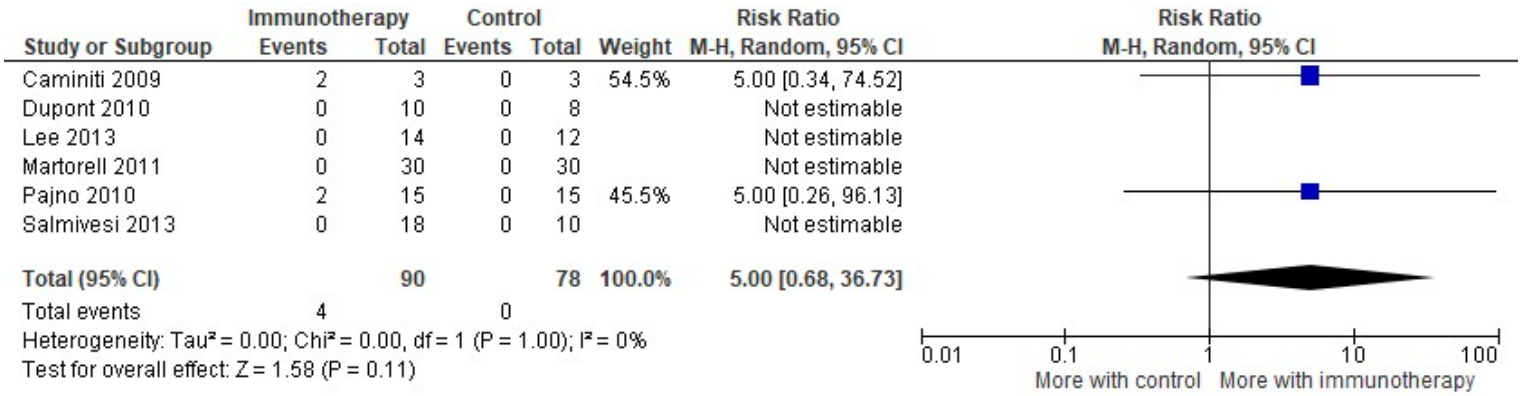


Study or Subgroup	Immunotherapy Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Caminiti 2009	1	3	0	3	0.4%	0.33 [-0.24, 0.91]
Dupont 2010	0	10	0	8	3.8%	0.00 [-0.19, 0.19]
Lee 2013	0	14	0	12	7.4%	0.00 [-0.14, 0.14]
Longo 2008	0	30	0	30	36.2%	0.00 [-0.06, 0.06]
Martorell 2011	0	30	0	30	36.2%	0.00 [-0.06, 0.06]
Pajno 2010	1	15	0	15	5.1%	0.07 [-0.10, 0.23]
Salmivesi 2013	0	18	0	10	7.0%	0.00 [-0.14, 0.14]
Skripak 2008	0	13	0	7	3.8%	0.00 [-0.19, 0.19]
Total (95% CI)		**133**		**115**	**100.0%**	**0.00 [-0.03, 0.04]**
Total events	2		0			

Heterogeneity: Tau² = 0.00; Chi² = 2.21, df = 7 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)

People with anaphylaxis

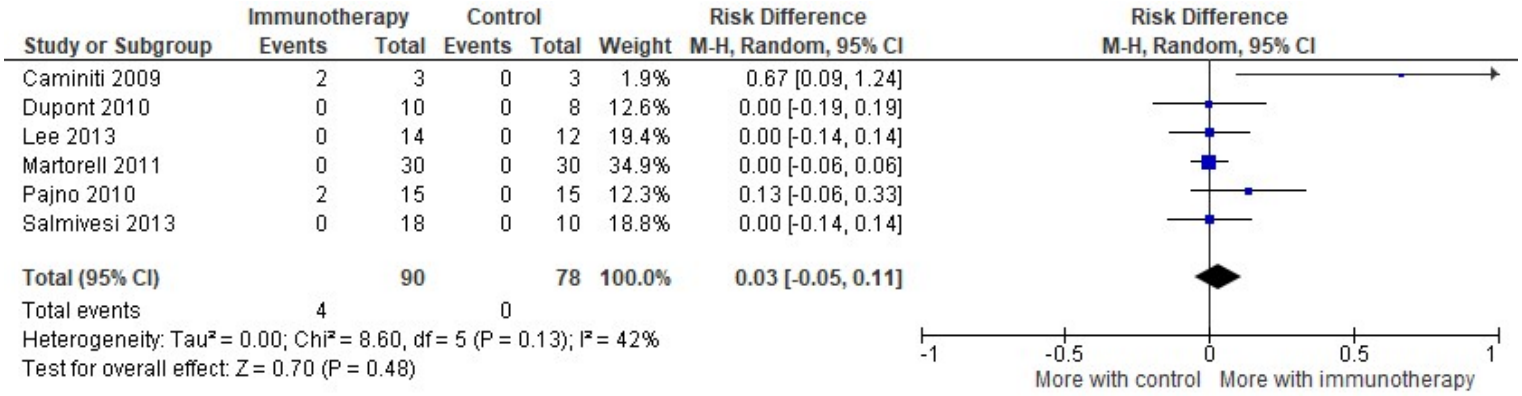
There was no significant difference between groups in the proportion with anaphylaxis.



Continuity correction risk ratio 2,76 (0.39 to 19.21), Z 1.02, P 0.31, I^2 = 0%.

Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.

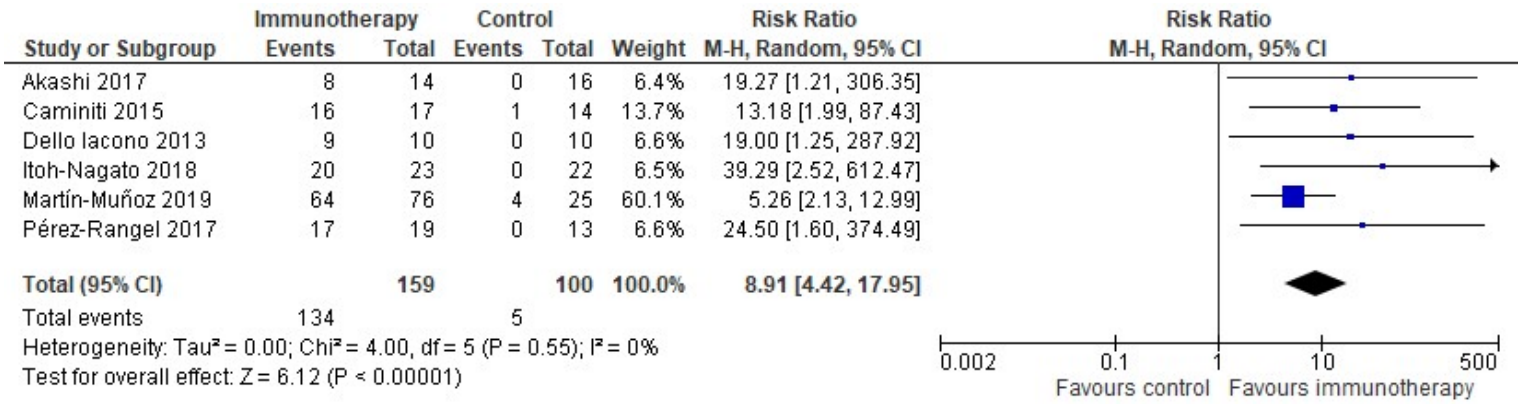


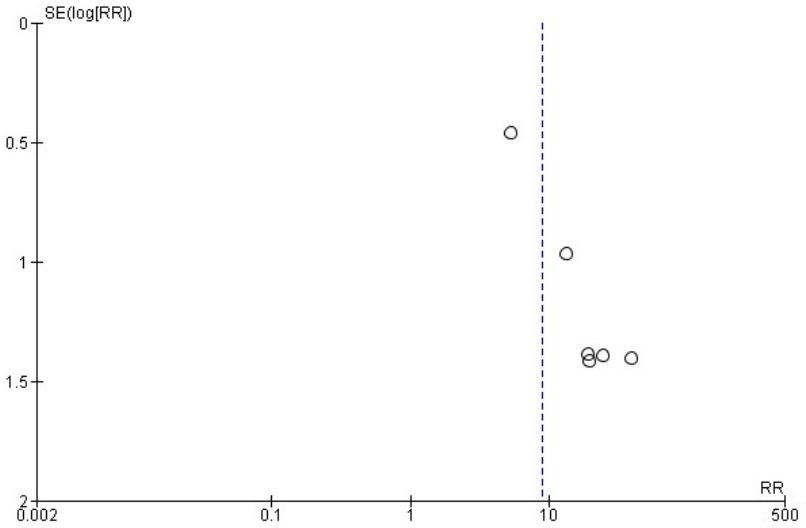
Oral immunotherapy

All included studies about hen's egg allergy investigated oral immunotherapy.

Desensitisation

Pooled data from 6 studies, all of which were in children, found increased likelihood of desensitisation compared to controls.





Risk of bias

This trend remained regardless of study risk of bias, or when studies at high risk of bias were removed. 5 studies were at low or moderate risk of bias.



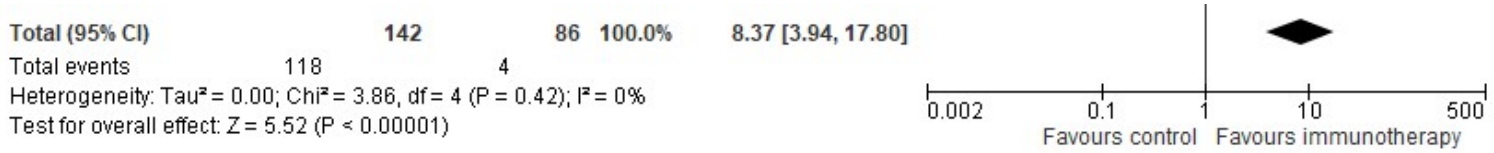
1 study was at low risk of bias.



Desensitisation by comparator

The finding of increased desensitisation held regardless of whether oral immunotherapy was compared with an elimination diet or placebo.

Elimination diet (5 studies)



Placebo (1 study)



Desensitisation by severity of allergy

The finding of increased desensitisation held regardless of the severity of hen's egg allergy.

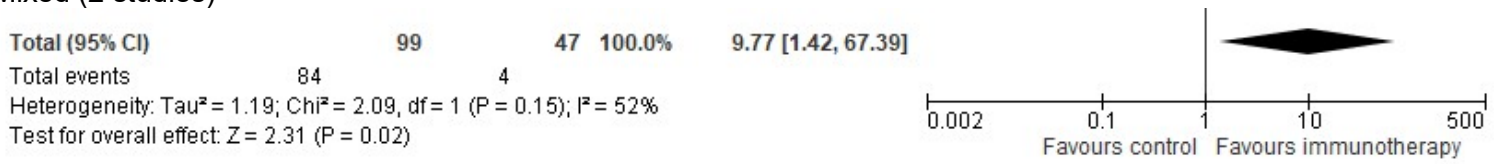
Mild/moderate (3 studies)



Severe (1 study)



Mixed (2 studies)



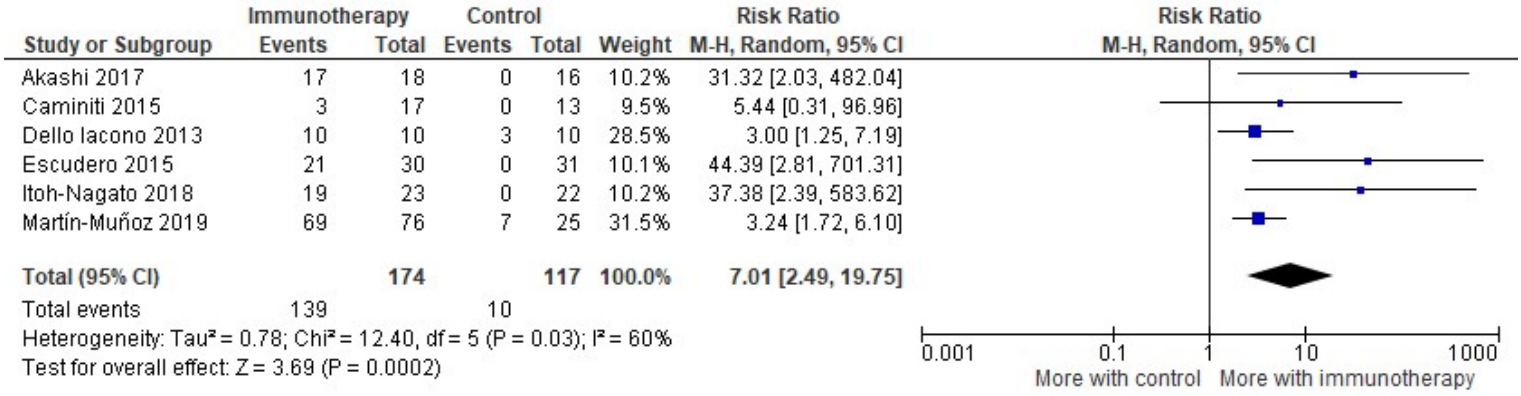
Sustained unresponsiveness

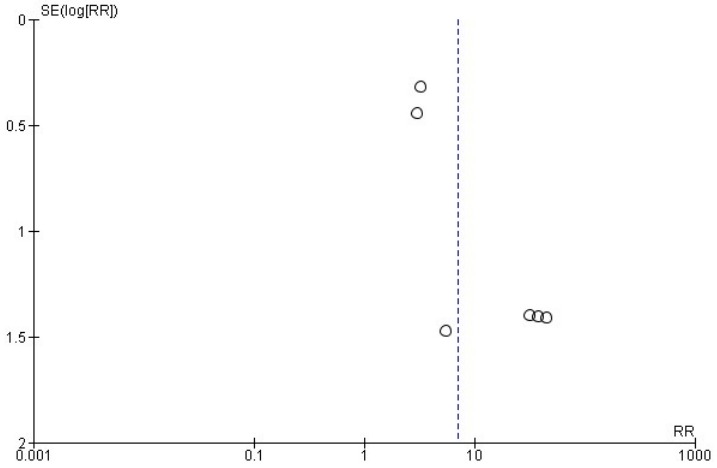
Oral immunotherapy was associated with increased proportions of sustained unresponsiveness in children (2 studies).



Adverse reactions

6 studies in children explored adverse reactions, regardless of whether linked to therapy. Oral immunotherapy was associated with increased proportion of children with adverse reactions, though the data were heterogeneous.





All 6 studies were at low or moderate risk of bias. The single study at low risk of bias did not find that oral immunotherapy significantly increased adverse reactions.



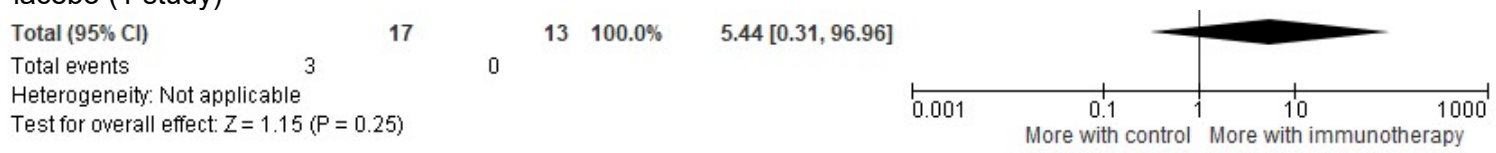
Adverse reactions by comparator

Studies which compared oral immunotherapy versus an elimination diet found that immunotherapy was associated with increased numbers of children with adverse reactions. The study that compared immunotherapy with placebo found no difference in the proportion with adverse reactions.

Elimination diet (5 studies)



Placebo (1 study)



Adverse reactions by severity of allergy

The trend towards an increased proportion experiencing adverse events held regardless of the level of severity of hen's egg allergy.

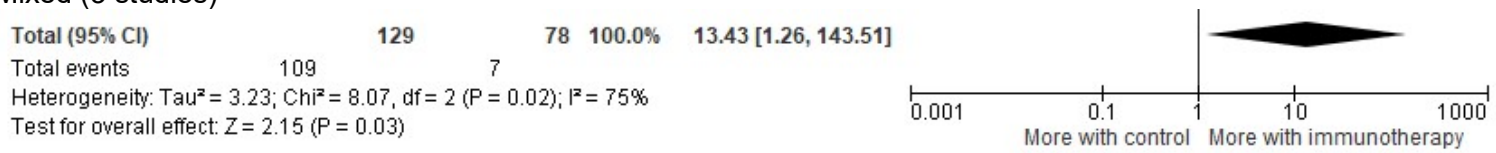
Mild/moderate (2 studies)



Severe (1 study)

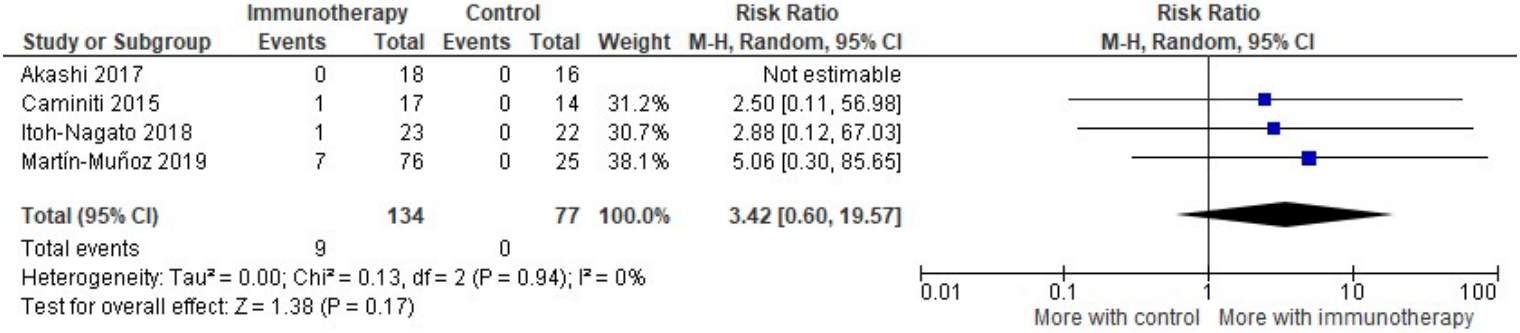


Mixed (3 studies)



Severe reactions

Four studies included data about the number of people experiencing severe reactions. These were rare. Oral immunotherapy was not associated with an increased proportion of people experiencing severe reactions.

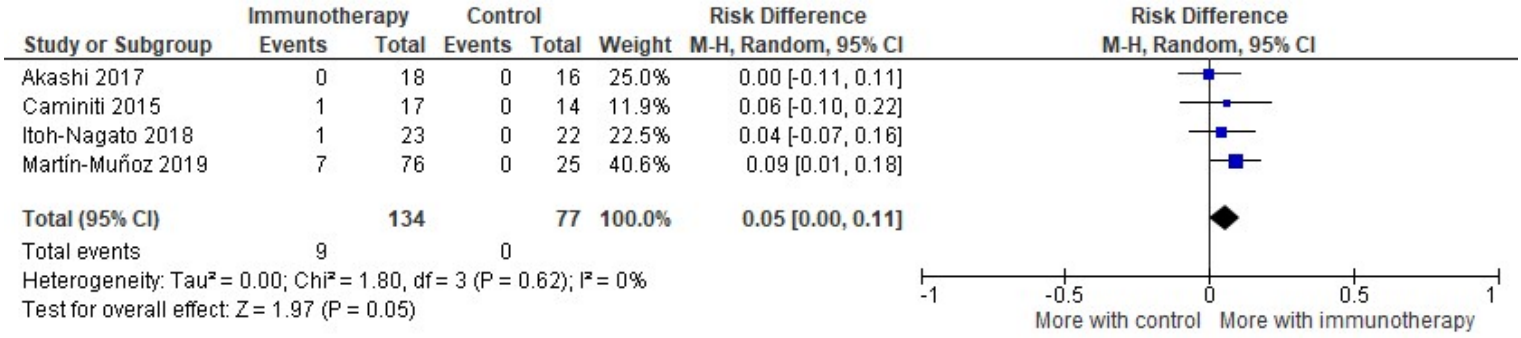


Continuity correction made minimal difference to estimates.

All 3 studies were with children. All 3 studies were at low or moderate risk of bias. The 1 study at low risk of bias also found no significant difference between groups: RR 2.50 (0.11, 56.98).

Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.



Severe reactions by comparator

The finding of no difference between groups in the proportion of people with severe reactions held regardless of whether oral immunotherapy was compared to elimination diet or placebo.

Elimination diet (2 studies)



Placebo (1 study): RR 2.50 (0.11, 56.98)

Severe reactions by severity of allergy

The finding of no difference between groups in the proportion with severe reactions held regardless of people's level of allergy severity.

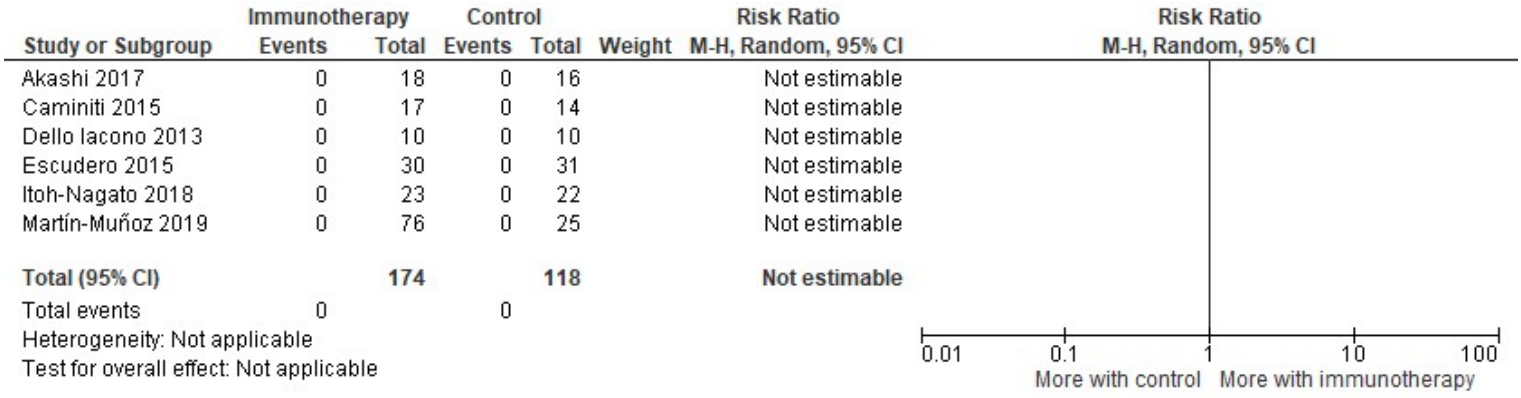
Mild/moderate (1 study): RR 2.50 (0.11, 56.98)

Mixed (2 studies)



Life threatening events

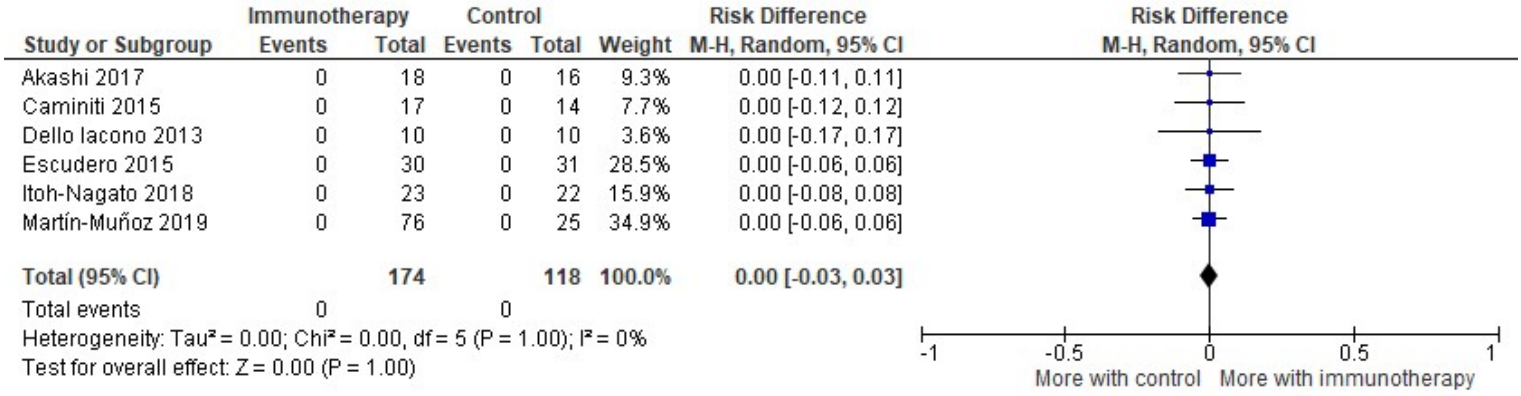
No study reported any life-threatening events.



Continuity correction risk ratio 0.79 (0.01 to 123.37), Z 0.073, P 0.92, I^2 = 0%

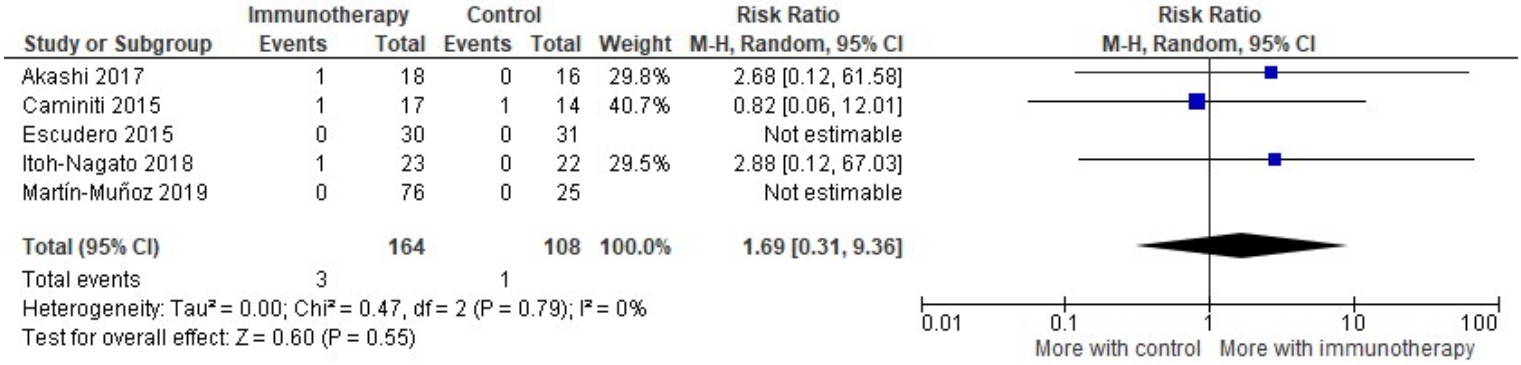
Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.



People with anaphylaxis

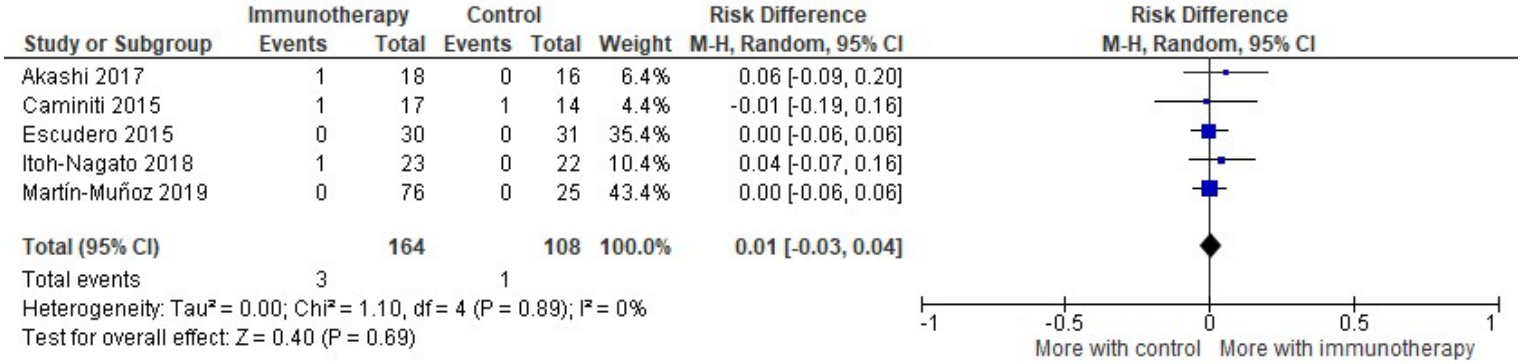
Few people experienced anaphylaxis during the studies and there was no significant difference between groups.



Continuity correction risk ratio 1.25 (0.22 to 7.1), Z 0.25, P 0.80, I^2 0.0%.

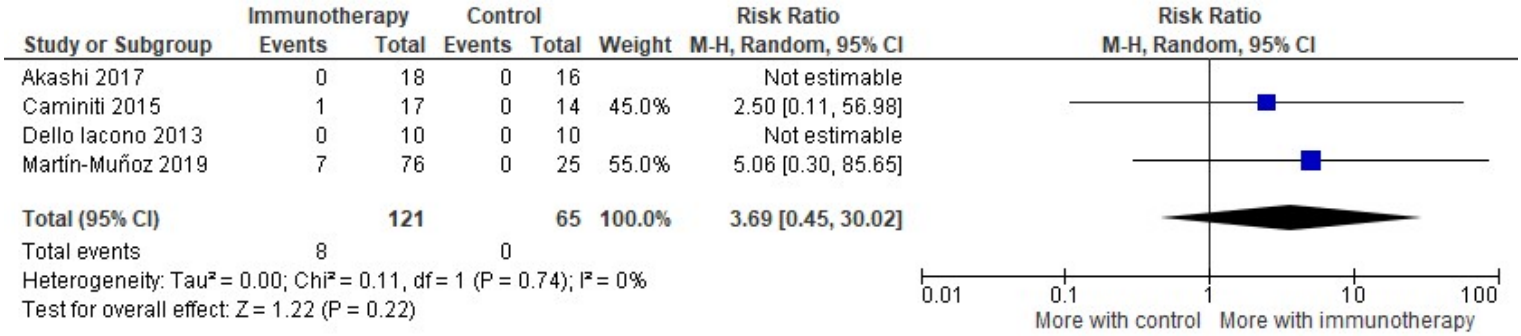
Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.



People given adrenaline

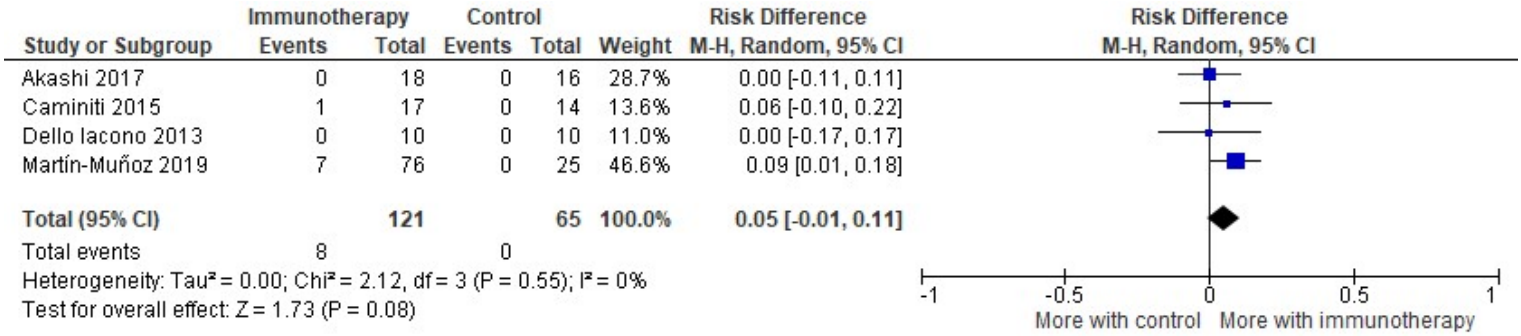
Few people were given adrenaline for adverse reactions and there was no significant difference between groups.



Continuity correction risk ratio 2.67 (0.33 to 21.58), Z 0.919, P 0.35, I^2 = 0%.

<u>Risk difference</u>

Note that for risk differences, a pooled value of around 0 means no difference between groups.



Combined data from all included allergen immunotherapy studies

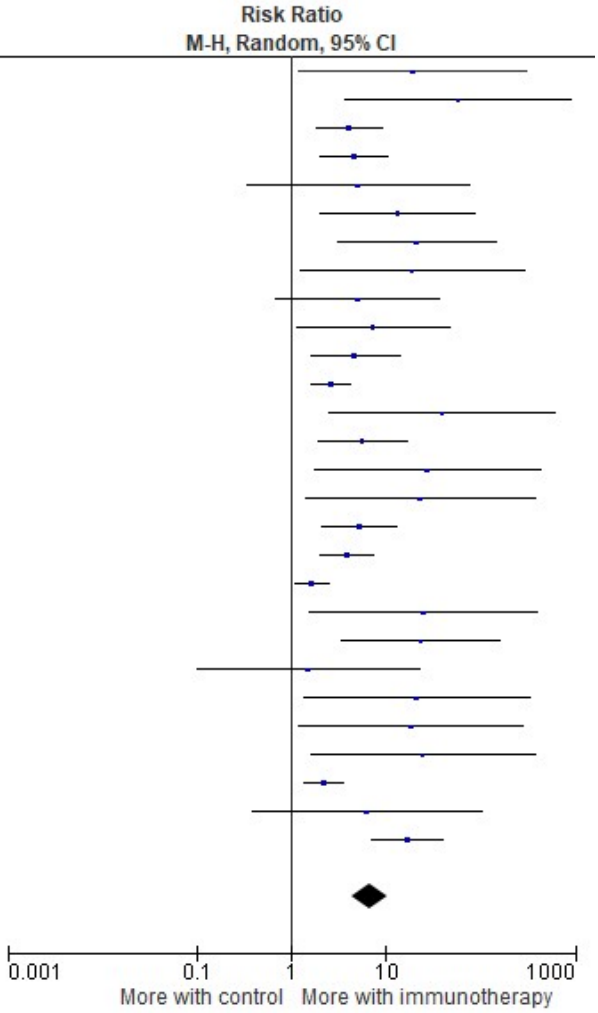
Desensitisation

28 studies included a measure of desensitisation. Measures differed across studies. There was a trend towards an increased proportion of people receiving immunotherapy achieving desensitisation compared to controls, but the studies and findings were too heterogeneous.

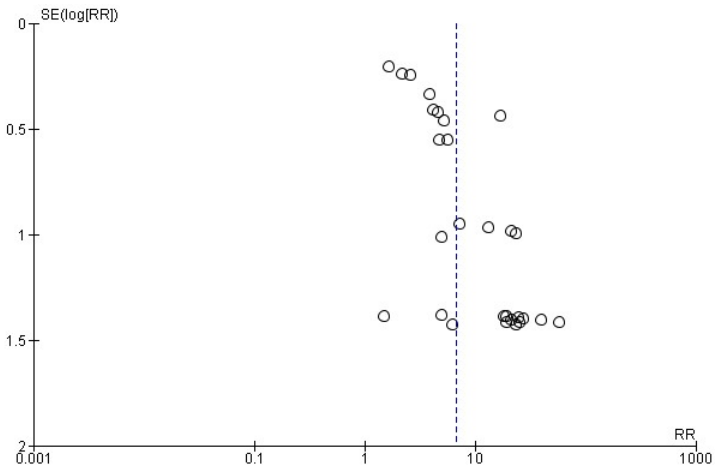
The broad trend held regardless of age group, type of food allergy, allergy severity, type of immunotherapy, study region or risk of bias.

Study or Subgroup	Immunotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Akashi 2017	8	14	0	16	1.9%	19.27 [1.21, 306.35]
Anagnostou 2014	24	39	0	46	1.9%	57.58 [3.61, 917.00]
Bird 2018	23	29	5	26	5.9%	4.12 [1.84, 9.26]
Blumchen 2019	23	31	5	31	5.8%	4.60 [2.01, 10.54]
Caminiti 2009	2	3	0	3	2.0%	5.00 [0.34, 74.52]
Caminiti 2015	16	17	1	14	3.1%	13.18 [1.99, 87.43]
Chinthrajah 2019	80	95	1	25	3.1%	21.05 [3.08, 143.94]
Dello Iacono 2013	9	10	0	10	1.9%	19.00 [1.25, 287.92]
Enrique 2005	5	11	1	11	3.0%	5.00 [0.69, 36.13]
Fauquert 2018	17	21	1	9	3.2%	7.29 [1.13, 46.78]
Fleischer 2013	14	20	3	20	5.1%	4.67 [1.58, 13.77]
Fleischer 2019	84	238	16	118	6.7%	2.60 [1.60, 4.24]
Itoh-Nagato 2018	20	23	0	22	1.9%	39.29 [2.52, 612.47]
Jones 2017	33	49	3	25	5.1%	5.61 [1.91, 16.51]
Lee 2013	14	16	0	15	1.9%	27.29 [1.77, 420.72]
Longo 2008	11	30	0	30	1.9%	23.00 [1.42, 373.46]
Martín-Muñoz 2019	64	76	4	25	5.6%	5.26 [2.13, 12.99]
Martorell 2011	27	30	7	30	6.3%	3.86 [1.99, 7.46]
Morisset 2007	18	20	12	22	6.8%	1.65 [1.10, 2.48]
Nowak-Węgrzyn 2019	12	23	0	23	1.9%	25.00 [1.57, 398.77]
Oppenheimer 1992	71	132	1	43	3.0%	23.13 [3.31, 161.51]
O'B Hourihane 2020	1	3	0	1	2.0%	1.50 [0.10, 22.62]
Pajno 2010	10	15	0	15	1.9%	21.00 [1.34, 328.86]
Patriarca 1998	12	14	0	10	2.0%	18.33 [1.21, 277.62]
Pérez-Rangel 2017	17	19	0	13	1.9%	24.50 [1.60, 374.49]
Sampson 2017	90	165	14	56	6.7%	2.18 [1.36, 3.51]
Skripak 2008	4	12	0	8	1.9%	6.23 [0.38, 101.99]
Vickery 2018	250	372	5	124	5.7%	16.67 [7.04, 39.45]
Total (95% CI)		**1527**		**791**	**100.0%**	**6.70 [4.30, 10.45]**
Total events	959		79			

Heterogeneity: Tau² = 0.70; Chi² = 92.11, df = 27 (P < 0.00001); I² = 71%
Test for overall effect: Z = 8.41 (P < 0.00001)



Funnel plot

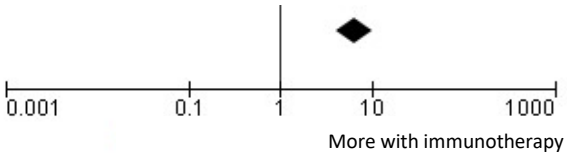


Desensitisation depending on study risk of bias

Studies at low or moderate risk of bias (21 studies)

Total (95% CI)	**1258**	**655**	**100.0%**	**6.54 [4.17, 10.27]**
Total events	769	59		

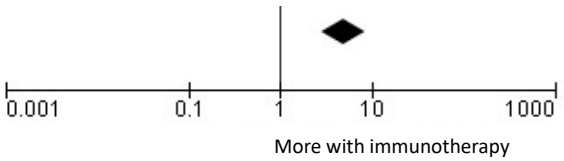
Heterogeneity: Tau² = 0.47; Chi² = 48.20, df = 20 (P = 0.0004); I² = 59%
Test for overall effect: Z = 8.17 (P < 0.00001)



Studies at low risk of bias (10 studies)

Total (95% CI)	**984**	**440**	**100.0%**	**4.93 [2.87, 8.46]**
Total events	585	53		

Heterogeneity: Tau² = 0.45; Chi² = 30.56, df = 9 (P = 0.0004); I² = 71%
Test for overall effect: Z = 5.78 (P < 0.00001)

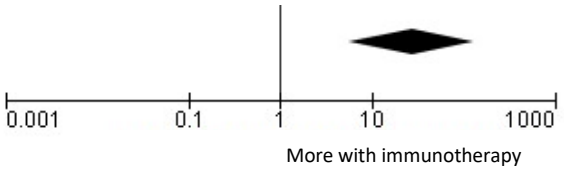


Desensitisation by study region

Asia (3 studies)

Total (95% CI)	**53**	**53**	**100.0%**	**27.49 [5.62, 134.42]**
Total events	42	0		

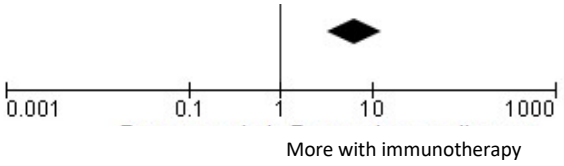
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 4.09 (P < 0.0001)



Europe (15 studies)

Total (95% CI)	**339**	**270**	**100.0%**	**6.55 [3.30, 12.99]**
Total events	256	31		

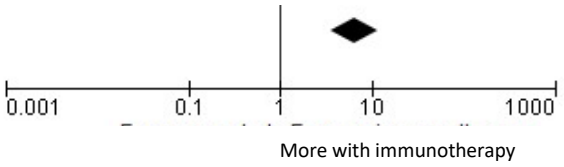
Heterogeneity: Tau² = 0.92; Chi² = 47.06, df = 14 (P < 0.0001); I² = 70%
Test for overall effect: Z = 5.38 (P < 0.00001)



North America (7 studies)

Total (95% CI)	**325**	**170**	**100.0%**	**6.60 [3.65, 11.95]**
Total events	208	13		

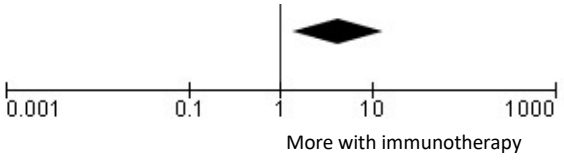
Heterogeneity: Tau² = 0.12; Chi² = 7.41, df = 6 (P = 0.28); I² = 19%
Test for overall effect: Z = 6.24 (P < 0.00001)



Mixed (3 studies)

Total (95% CI)	**775**	**298**	**100.0%**	**4.31 [1.39, 13.36]**
Total events	424	35		

Heterogeneity: Tau² = 0.90; Chi² = 22.95, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 2.53 (P = 0.01)

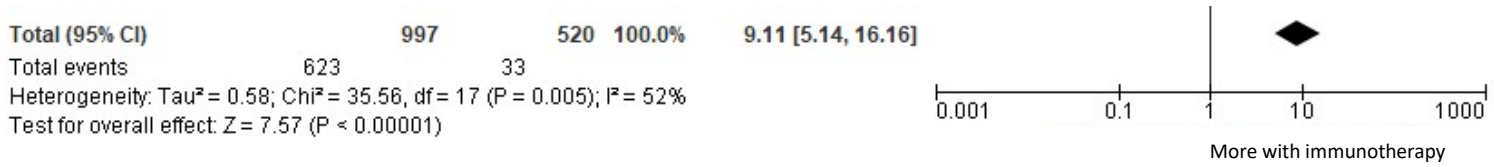


Desensitisation by age

Infants (<3 years) (2 studies)



Children (3-17 years) (18 studies)



Adults (18+ years) (2 studies)

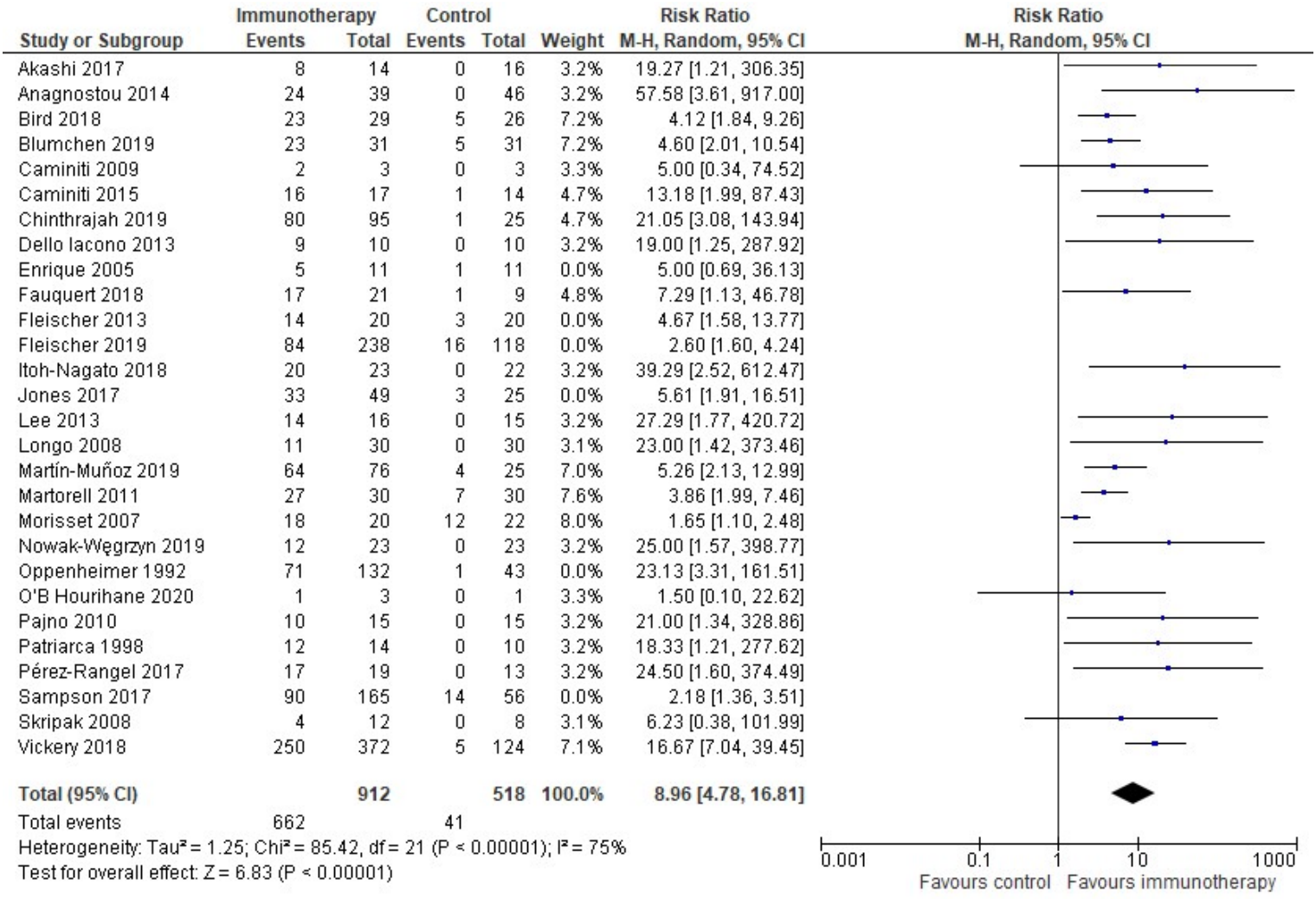


Mixed ages (6 studies)



Desensitisation by immunotherapy route

Oral (22 studies)



Epicutaneous (3 studies)



Sublingual (2 studies)



Subcutaneous (1 study)

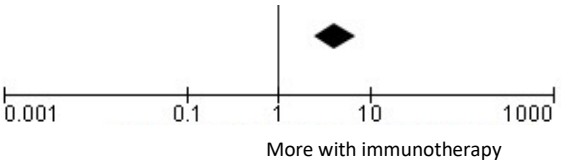
RR 23.13 (3.31 to 161.51)

Desensitisation by severity of food allergy

Mild / moderate (11 studies)

Total (95% CI)	**471**	**315**	**100.0%**	**4.19 [2.53, 6.95]**	
Total events	256	47			

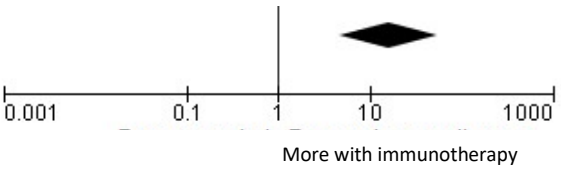
Heterogeneity: Tau² = 0.33; Chi² = 26.32, df = 10 (P = 0.003); I² = 62%
Test for overall effect: Z = 5.56 (P < 0.00001)



Severe (4 studies)

Total (95% CI)	**175**	**86**	**100.0%**	**16.20 [4.76, 55.17]**	
Total events	93	1			

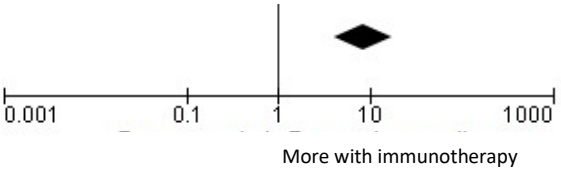
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 4.45 (P < 0.00001)



Mixed (13 studies)

Total (95% CI)	**846**	**390**	**100.0%**	**8.46 [4.08, 17.52]**	
Total events	581	31			

Heterogeneity: Tau² = 0.95; Chi² = 39.65, df = 12 (P < 0.0001); I² = 70%
Test for overall effect: Z = 5.74 (P < 0.00001)

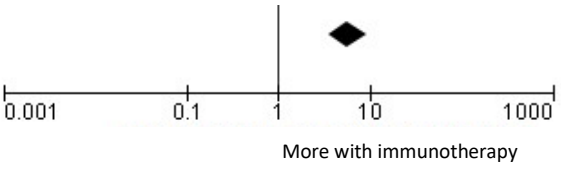


Desensitisation by comparator type

Placebo (17 studies)

Total (95% CI)	**1201**	**552**	**100.0%**	**5.78 [3.60, 9.30]**	
Total events	706	56			

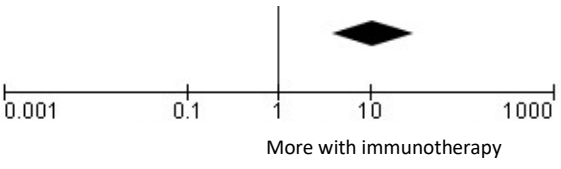
Heterogeneity: Tau² = 0.45; Chi² = 39.93, df = 16 (P = 0.0008); I² = 60%
Test for overall effect: Z = 7.25 (P < 0.00001)



Elimination diet (11 studies)

Total (95% CI)	**291**	**239**	**100.0%**	**10.85 [3.86, 30.52]**	
Total events	224	23			

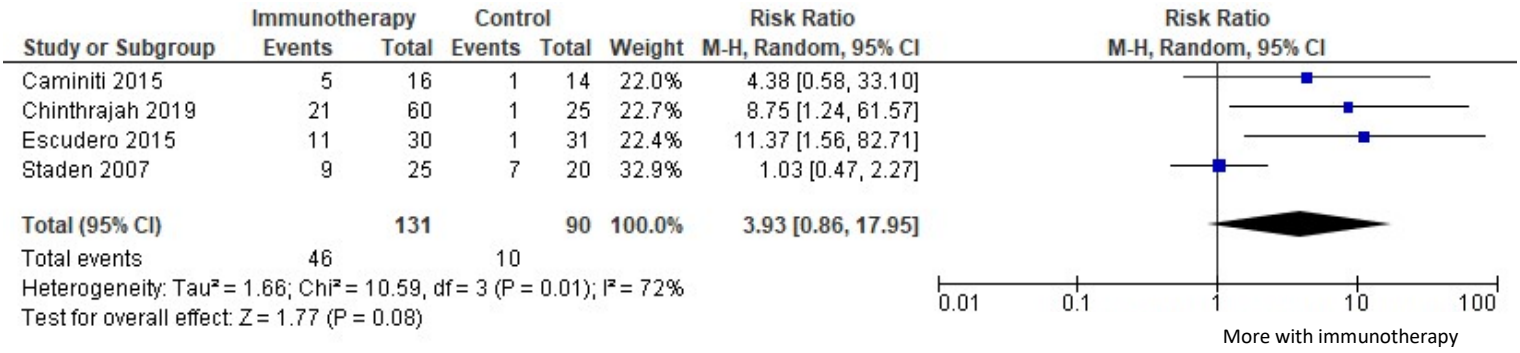
Heterogeneity: Tau² = 1.87; Chi² = 56.98, df = 10 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.52 (P < 0.00001)



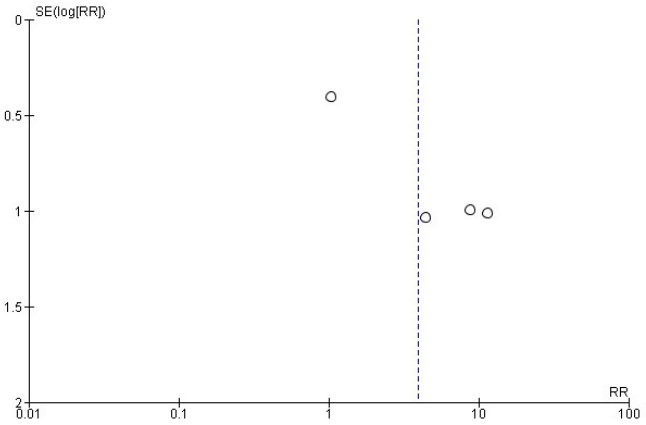
Sustained unresponsiveness

Only 4 studies included a measure of sustained unresponsiveness (ability to tolerate allergen after ceasing immunotherapy). The findings were heterogeneous and did not reach statistical significance.

All 4 studies were in children and were of oral immunotherapy. 2 studies were in hen's egg allergy, 1 in peanut and 1 in study of children with various types of allergy. 2 studies compared with placebo and 2 with elimination diet. All four studies were at low or moderate risk of bias.



Funnel plot

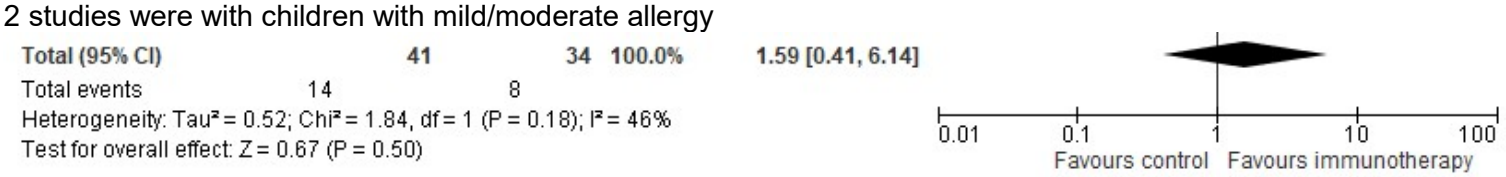


In the 2 studies at low risk of bias the trend did reach statistical significance.

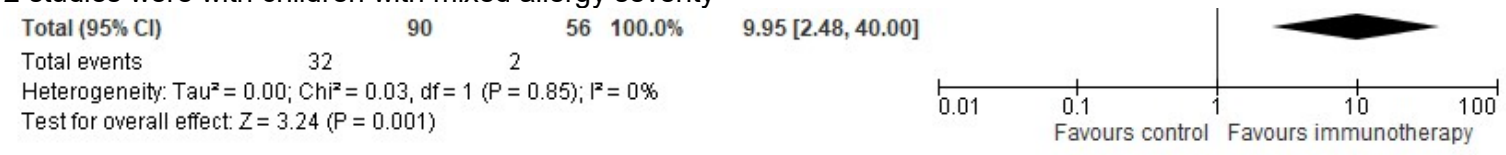


There was no difference in the trend based on the region (Europe versus North America). Studies with mixed levels of allergy severity were more likely to show a significant difference than children with mild/moderate allergy.

2 studies were with children with mild/moderate allergy



2 studies were with children with mixed allergy severity



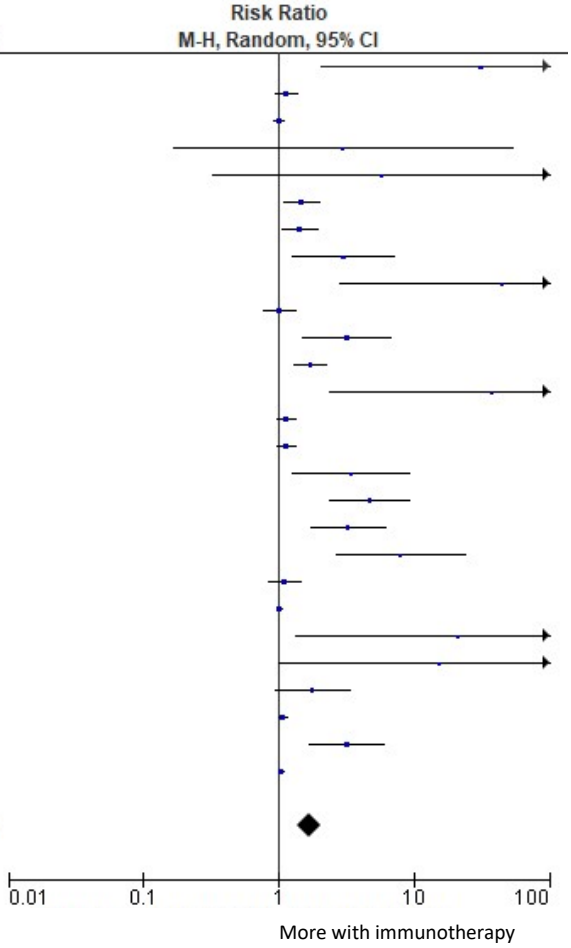
Number of people experiencing ANY adverse reaction

25 studies with 27 comparisons included a measure of adverse reactions. The definitions varied in each study (see S3). The data presented below relate to any reaction, whether linked to therapy or not. There were more adverse reactions with immunotherapy but the data were heterogeneous.

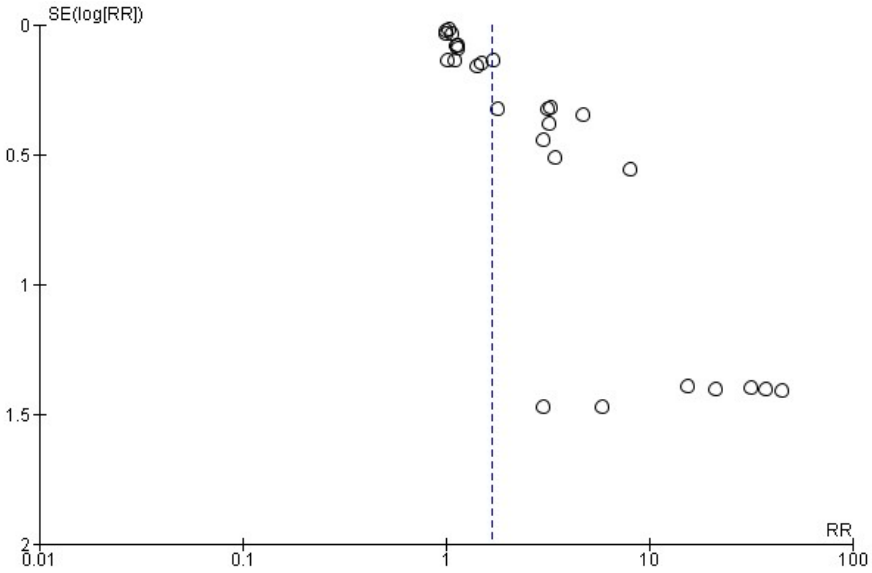
The broad trends held regardless of age group, allergy severity, type of immunotherapy, region or risk of bias

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Akashi 2017	17	18	0	16	0.5%	31.32 [2.03, 482.04]
Bird 2018	28	29	22	26	6.0%	1.14 [0.96, 1.36]
Blumchen 2019	28	28	24	24	6.2%	1.00 [0.93, 1.08]
Caminiti 2009	1	3	0	3	0.5%	3.00 [0.17, 53.71]
Caminiti 2015	3	17	0	14	0.5%	5.83 [0.33, 104.22]
Chinthrajah 2019: Peanut 0	57	60	16	25	5.5%	1.48 [1.10, 2.00]
Chinthrajah 2019 Peanut 300	32	35	16	25	5.4%	1.43 [1.05, 1.95]
Dello Iacono 2013	10	10	3	10	2.9%	3.00 [1.25, 7.19]
Escudero 2015	21	30	0	31	0.5%	44.39 [2.81, 701.31]
Fauquert 2018	19	21	8	9	5.6%	1.02 [0.78, 1.33]
Fernández-Rivas 2009	33	37	5	18	3.3%	3.21 [1.51, 6.82]
Fleischer 2019	142	238	41	118	5.6%	1.72 [1.31, 2.25]
Itoh-Nagato 2018	19	23	0	22	0.5%	37.38 [2.39, 583.62]
Jones 2017: V-100	24	24	22	25	6.0%	1.13 [0.96, 1.33]
Jones 2017: V-250	25	25	22	25	6.0%	1.13 [0.96, 1.33]
Lee 2013	12	14	3	12	2.5%	3.43 [1.26, 9.35]
Longo 2008	30	30	6	30	3.6%	4.69 [2.37, 9.31]
Martín-Muñoz 2019	69	76	7	25	3.9%	3.24 [1.72, 6.10]
Martorell 2011	24	30	3	30	2.2%	8.00 [2.69, 23.75]
Nowak-Węgrzyn 2019	20	23	18	23	5.6%	1.11 [0.85, 1.45]
O'B Hourihane 2020	130	132	42	43	6.2%	1.01 [0.96, 1.06]
Pajno 2010	10	15	0	15	0.5%	21.00 [1.34, 328.86]
Patriarca 1998	10	14	0	10	0.5%	15.40 [1.01, 235.72]
Salmivesi 2013	16	18	5	10	3.8%	1.78 [0.94, 3.37]
Sampson 2017	164	165	52	56	6.2%	1.07 [0.99, 1.15]
Staden 2007	25	25	6	20	3.8%	3.17 [1.67, 6.02]
Vickery 2018	367	372	118	124	6.2%	1.04 [0.99, 1.08]
Total (95% CI)		**1512**		**789**	**100.0%**	**1.68 [1.37, 2.05]**
Total events	1336		439			

Heterogeneity: Tau² = 0.17; Chi² = 777.81, df = 26 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.04 (P < 0.00001)

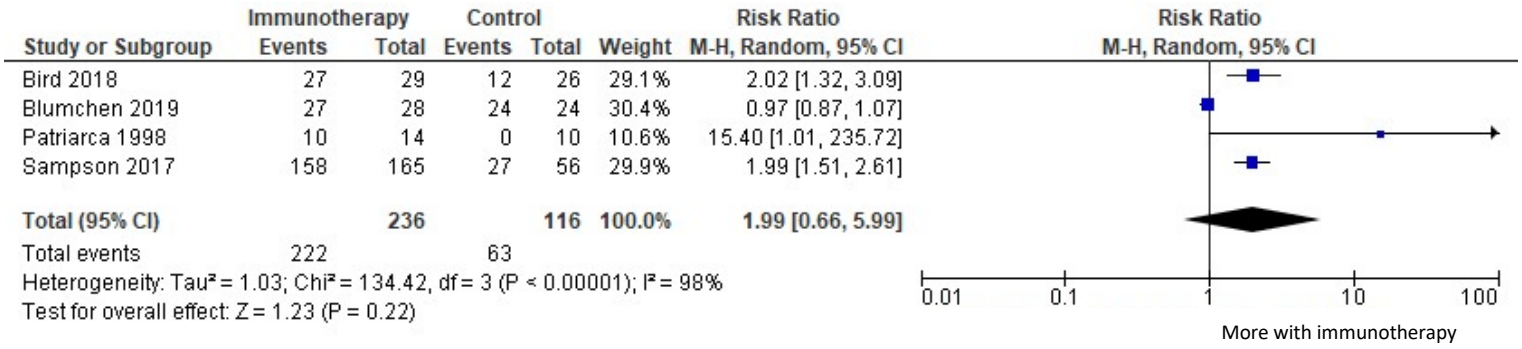


Funnel plot

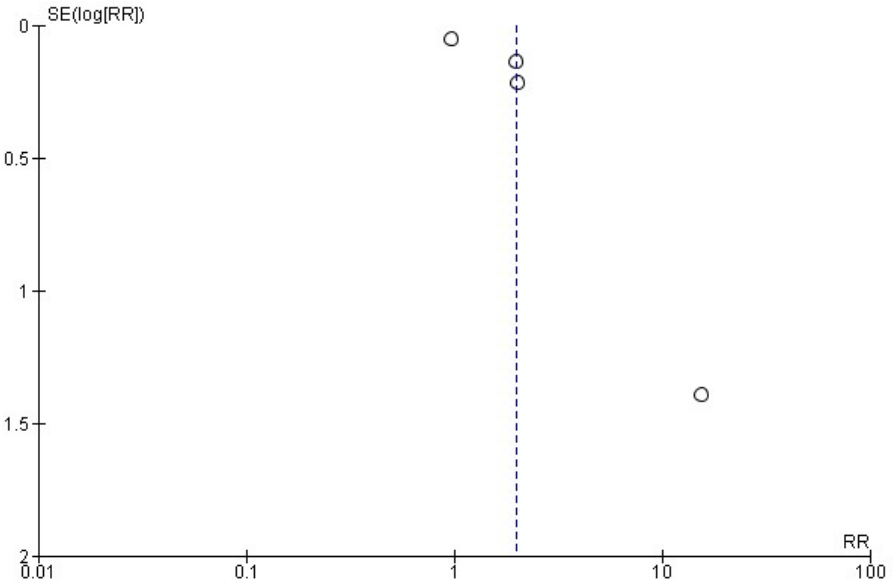


Number of people experiencing adverse reactions related to therapy

Only 4 studies contained data about adverse reactions explicitly linked to active or control therapy. Immunotherapy was not more likely to increase adverse reactions, but the data were too heterogeneous.



Funnel plot



3 of the studies focused on peanut, one on multiple allergens.

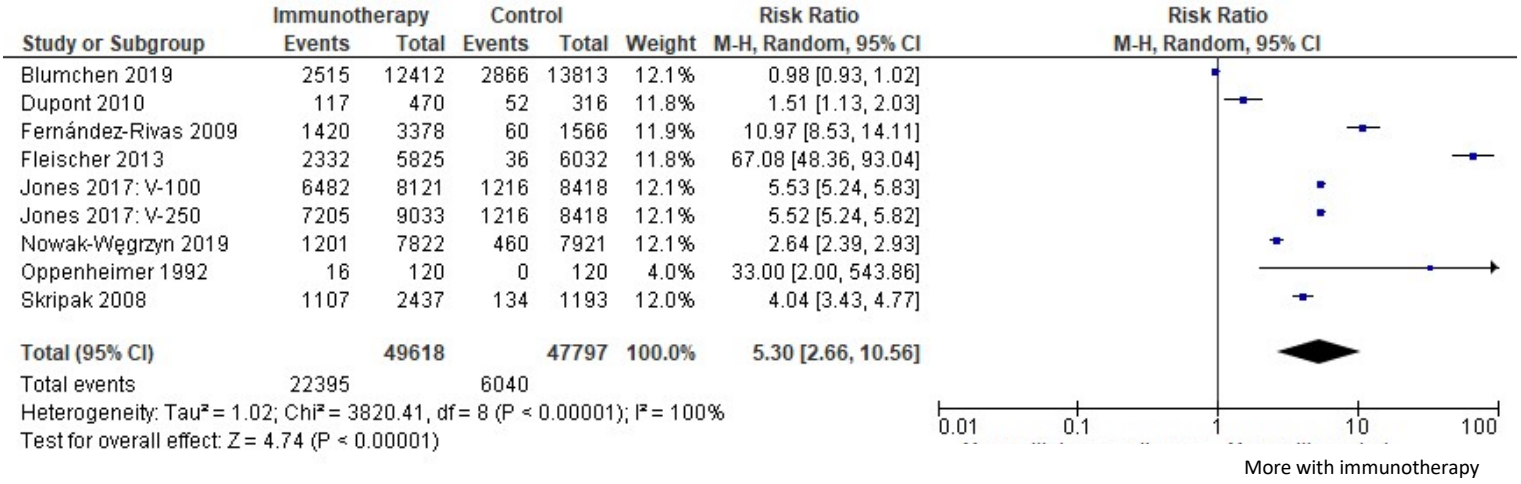
For peanut all three studies were at low risk of bias. Immunotherapy did not increase adverse reactions linked to therapy, but the data were heterogeneous.



The study exploring multiple food allergies was at high risk of bias: RR 15.4 (1.01 to 235.72)

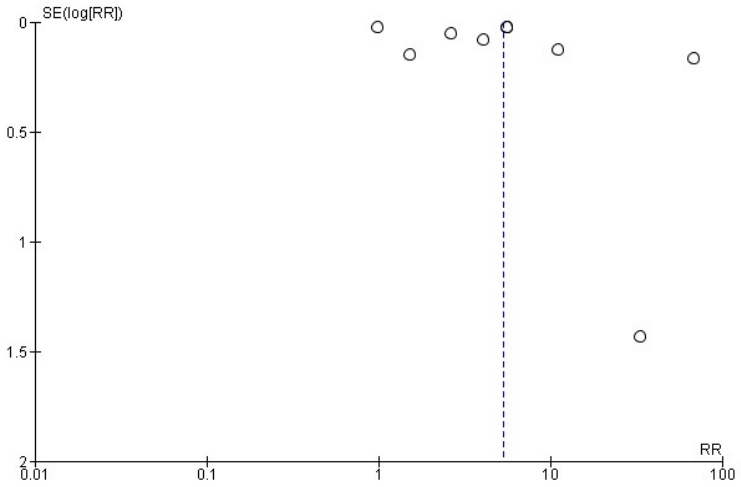
Number of doses associated with ANY adverse reaction

In 9 comparisons, there was a trend towards doses of active immunotherapy increasing the likelihood of any adverse reaction (not necessarily linked to therapy), but the data were heterogeneous. The trend held regardless of study risk of bias. Studies in adults and North America were more likely to show a negative impact.



All studies used placebo, not elimination diet

Funnel plot



Doses with adverse events by study risk of bias

Low or moderate risk of bias (8 comparisons)



Low risk of bias (4 comparisons)

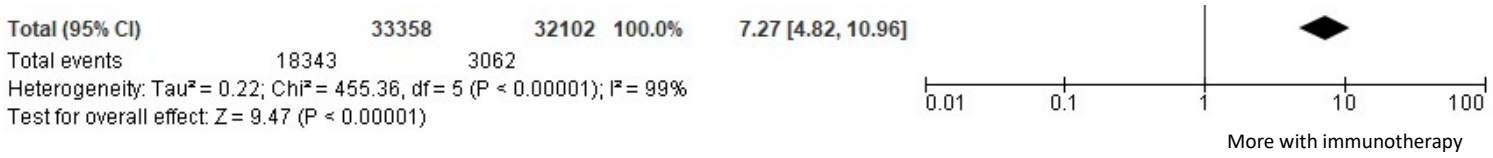


Doses with adverse events by study region

Europe (3 studies)



North America (6 comparisons)



Doses with adverse events by age

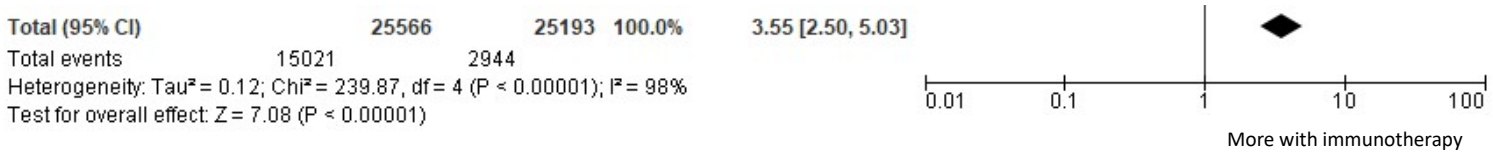
Children (2 studies)



Adults (2 studies)

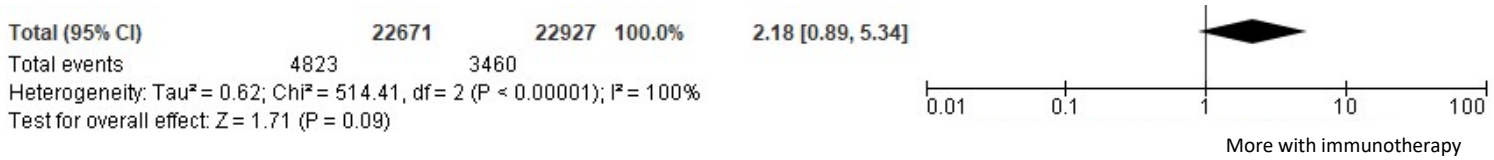


Mixed (5 comparisons)



Doses with adverse events by administration route

Oral (3 studies)



Epicutaenous (3 comparisons)



Subcutaneous (1 study)

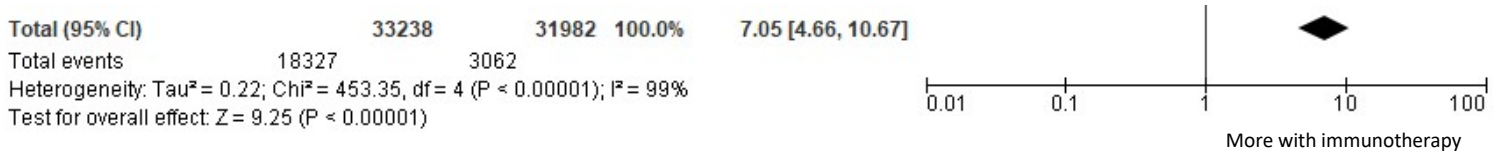


Sublingual (2 studies)



Doses with adverse events by severity of food allergy

Mild/moderate (5 comparisons)



Severe (1 study)

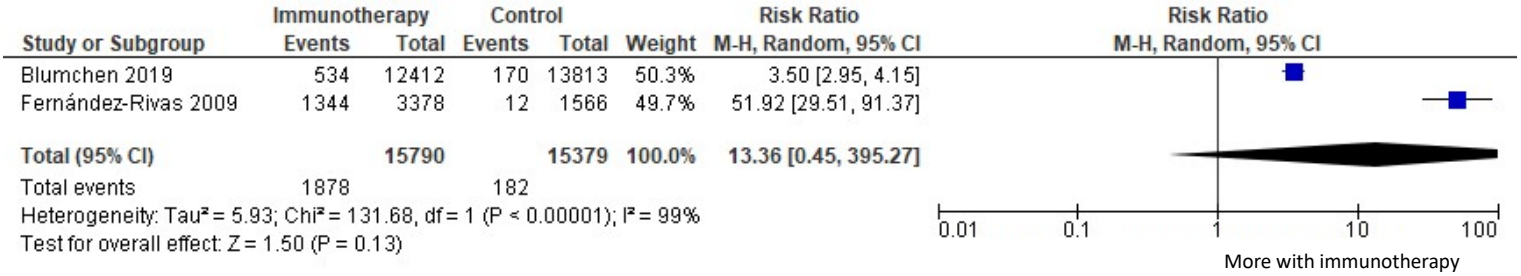


Mixed (3 studies)

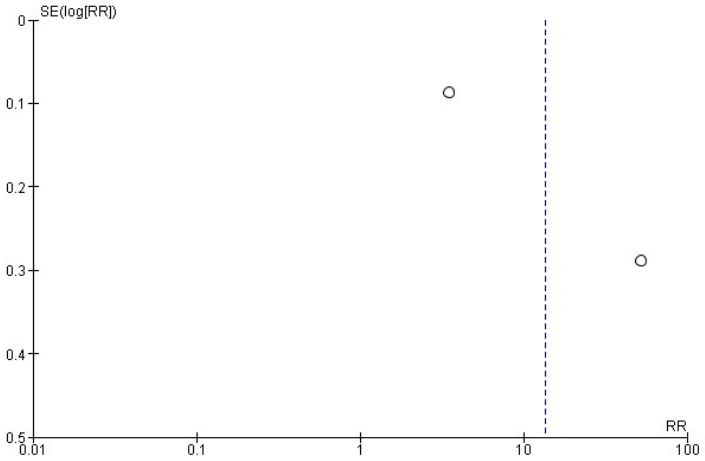


Number of doses experiencing adverse reactions related to therapy

Only 2 studies explored doses with adverse reactions explicitly linked to therapy. The pooled data suggested that immunotherapy did not increase the risk but this conclusion cannot be relied on. The data were heterogeneous and both of the studies independently suggested increased numbers of immunotherapy doses had adverse events compared with control doses.



Funnel plot

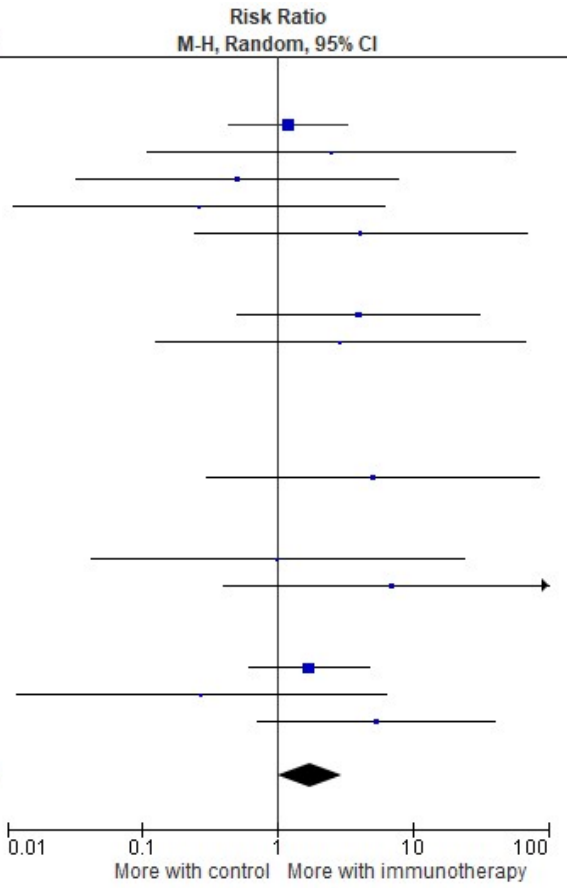


Number of people experiencing severe adverse reactions

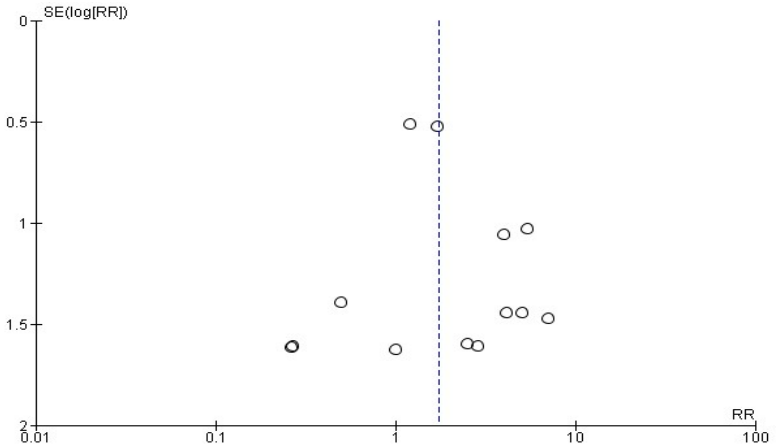
There were 13 calculable comparisons about severe adverse reactions. All calculable studies were at low or moderate risk of bias. This analysis suggested a small increase in the risk of severe adverse reactions with immunotherapy, however once studies with 0 events in all arms were taken into account there was no significant difference in severe reactions with immunotherapy compared to placebo.

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Akashi 2017	0	18	0	16		Not estimable
Bird 2018	0	29	0	26		Not estimable
Blumchen 2019	7	28	5	24	28.7%	1.20 [0.44, 3.29]
Caminiti 2015	1	17	0	14	3.0%	2.50 [0.11, 56.98]
Chinthrajah 2019: Peanut 0	1	50	1	25	3.9%	0.50 [0.03, 7.67]
Chinthrajah 2019 Peanut 300	0	32	1	25	2.9%	0.26 [0.01, 6.18]
Fauquert 2018	4	21	0	9	3.7%	4.09 [0.24, 68.94]
Fernández-Rivas 2009	0	37	0	18		Not estimable
Fleischer 2013	0	20	0	20		Not estimable
Fleischer 2019	8	238	1	118	6.9%	3.97 [0.50, 31.34]
Itoh-Nagato 2018	1	23	0	22	3.0%	2.88 [0.12, 67.03]
Jones 2017: V-100	0	24	0	25		Not estimable
Jones 2017: V-250	0	25	0	25		Not estimable
Lee 2013	0	14	0	12		Not estimable
Longo 2008	0	30	0	30		Not estimable
Martín-Muñoz 2019	7	76	0	25	3.7%	5.06 [0.30, 85.65]
Martorell 2011	0	30	0	30		Not estimable
Nowak-Węgrzyn 2019	0	21	0	23		Not estimable
O'B Hourihane 2020	1	132	0	43	2.9%	0.99 [0.04, 23.92]
Pajno 2010	3	15	0	15	3.5%	7.00 [0.39, 124.83]
Patriarca 1998	0	14	0	10		Not estimable
Salmivesi 2013	0	18	0	10		Not estimable
Sampson 2017	20	165	4	56	27.6%	1.70 [0.61, 4.75]
Staden 2007	0	25	1	20	3.0%	0.27 [0.01, 6.27]
Vickery 2018	16	372	1	124	7.3%	5.33 [0.71, 39.81]
Total (95% CI)		**1474**		**765**	**100.0%**	**1.73 [1.01, 2.97]**
Total events	69		14			

Heterogeneity: Tau² = 0.00; Chi² = 8.19, df = 12 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.98 (P = 0.05)



Funnel plot



We used Revman 5.4 (Cochrane) to undertake meta-analysis. The Cochrane manual notes that Revman does not include studies where all arms have zero events when calculating risk ratios: “The standard practice in meta-analysis of odds ratios and risk ratios is to exclude studies from the meta-analysis where there are no events in both arms. This is because such studies do not provide any indication of either the direction or magnitude of the relative treatment effect. Whilst it may be clear that events are very rare on both the experimental intervention and the comparator intervention, no information is provided as to which group is likely to have the higher risk, or on whether the risks are of the same or different orders of magnitude.”

We reported using this convention in the text of the systematic review, but also took steps to check that the trends were not different when 0 events in each arm were accounted for. We did this by looking at the risk difference and also by undertaking a continuity correction (adding 0.05 to the numerators and denominators where all study arms had 0 events).

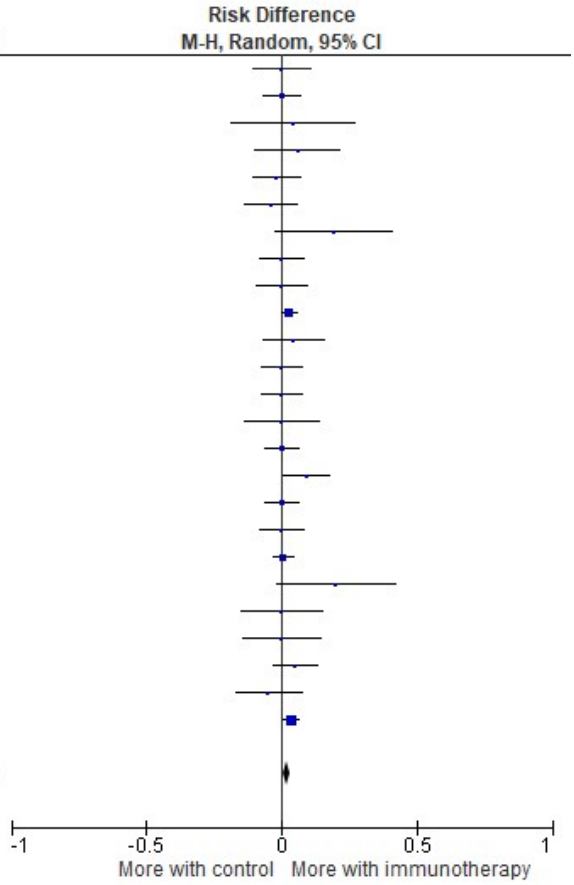
Risk difference using data from ALL studies, including 0 events

Note that for risk differences, a pooled value of around 0 means no difference between groups.

Study or Subgroup	Immunotherapy Events	Total	Control Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Akashi 2017	0	18	0	16	1.4%	0.00 [-0.11, 0.11]
Bird 2018	0	29	0	26	3.6%	0.00 [-0.07, 0.07]
Blumchen 2019	7	28	5	24	0.3%	0.04 [-0.19, 0.27]
Caminiti 2015	1	17	0	14	0.7%	0.06 [-0.10, 0.22]
Chinthrajah 2019: Peanut 0	1	50	1	25	2.3%	-0.02 [-0.11, 0.07]
Chinthrajah 2019 Peanut 300	0	32	1	25	1.7%	-0.04 [-0.14, 0.06]
Fauquert 2018	4	21	0	9	0.4%	0.19 [-0.03, 0.41]
Fernández-Rivas 2009	0	37	0	18	2.6%	0.00 [-0.08, 0.08]
Fleischer 2013	0	20	0	20	2.0%	0.00 [-0.09, 0.09]
Fleischer 2019	8	238	1	118	20.9%	0.03 [-0.00, 0.05]
Itoh-Nagato 2018	1	23	0	22	1.3%	0.04 [-0.07, 0.16]
Jones 2017: V-100	0	24	0	25	2.9%	0.00 [-0.08, 0.08]
Jones 2017: V-250	0	25	0	25	3.0%	0.00 [-0.07, 0.07]
Lee 2013	0	14	0	12	0.9%	0.00 [-0.14, 0.14]
Longo 2008	0	30	0	30	4.2%	0.00 [-0.06, 0.06]
Martín-Muñoz 2019	7	76	0	25	2.3%	0.09 [0.01, 0.18]
Martorell 2011	0	30	0	30	4.2%	0.00 [-0.06, 0.06]
Nowak-Węgrzyn 2019	0	21	0	23	2.3%	0.00 [-0.08, 0.08]
O'B Hourihane 2020	1	132	0	43	12.8%	0.01 [-0.03, 0.04]
Pajno 2010	3	15	0	15	0.3%	0.20 [-0.02, 0.42]
Patriarca 1998	0	14	0	10	0.7%	0.00 [-0.15, 0.15]
Salmivesi 2013	0	18	0	10	0.8%	0.00 [-0.14, 0.14]
Sampson 2017	20	165	4	56	2.4%	0.05 [-0.03, 0.13]
Staden 2007	0	25	1	20	1.1%	-0.05 [-0.17, 0.07]
Vickery 2018	16	372	1	124	24.8%	0.03 [0.01, 0.06]
Total (95% CI)		**1474**		**765**	**100.0%**	**0.02 [0.01, 0.03]**
Total events	69		14			

Heterogeneity: Tau² = 0.00; Chi² = 17.47, df = 24 (P = 0.83); I² = 0%

Test for overall effect: Z = 2.88 (P = 0.004)

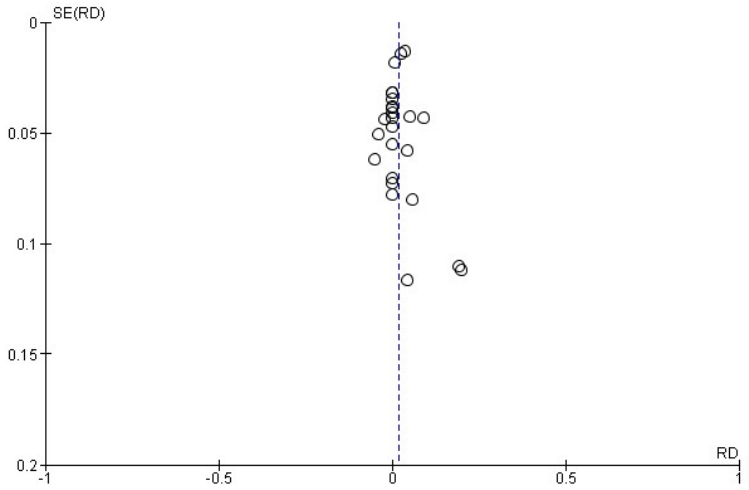


Continuity correction

There were 25 comparisons when including data with a continuity correction. Adding 0.05 to studies where all arms have 0 events suggested no significant difference in severe reactions with immunotherapy compared to placebo.

RR = 1.6 (0.93 to 2.76), Z score 1.7, p value 0.088, I^2 = 0.0%, Tau^2 = 0.0

<u>Funnel plot</u>

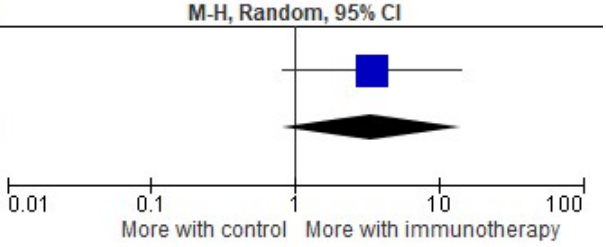


Number of people experiencing severe reactions related to therapy

Only two studies included data about severe reactions explicitly linked to therapy. There was no statistically significant increase in risk with immunotherapy, but the data were sparse and there was a wide potential range.

	Immunotherapy		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Patriarca 1998	0	14	0	10		Not estimable
Sampson 2017	20	165	2	56	100.0%	3.39 [0.82, 14.06]
Total (95% CI)		**179**		**66**	**100.0%**	**3.39 [0.82, 14.06]**
Total events	20		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)

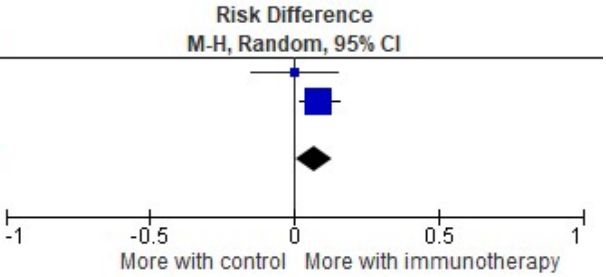


Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.

	Immunotherapy		Control			Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Patriarca 1998	0	14	0	10	17.5%	0.00 [-0.15, 0.15]
Sampson 2017	20	165	2	56	82.5%	0.09 [0.02, 0.16]
Total (95% CI)		**179**		**66**	**100.0%**	**0.07 [0.01, 0.13]**
Total events	20		2			

Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 1 (P = 0.31); I² = 1%
Test for overall effect: Z = 2.15 (P = 0.03)

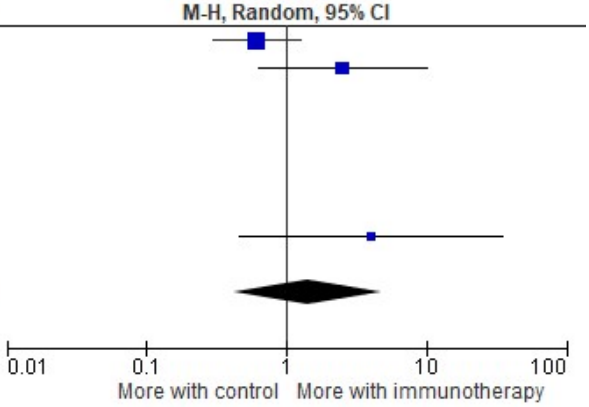


Number of doses with severe reactions

There was no significant difference between immunotherapy and controls in the number of doses with severe reactions, regardless of the cause. However the data were heterogeneous.

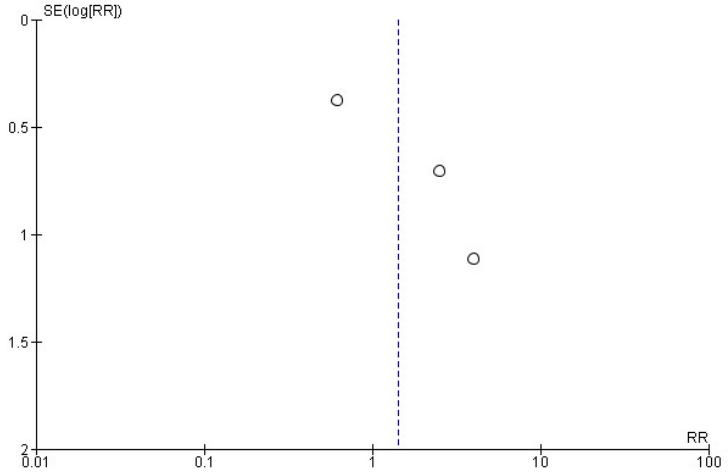
Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blumchen 2019	11	12412	20	13813	47.2%	0.61 [0.29, 1.28]
Dello Iacono 2013	5	10	2	10	32.7%	2.50 [0.63, 10.00]
Fernández-Rivas 2009	0	3378	0	1566		Not estimable
Fleischer 2013	0	5825	0	6029		Not estimable
Jones 2017: V-100	0	8121	0	8418		Not estimable
Jones 2017: V-250	0	9033	0	8418		Not estimable
Nowak-Węgrzyn 2019	0	7822	0	7921		Not estimable
Oppenheimer 1992	4	120	1	120	20.1%	4.00 [0.45, 35.27]
Total (95% CI)		**46721**		**46295**	**100.0%**	**1.41 [0.42, 4.76]**
Total events	20		23			

Heterogeneity: Tau² = 0.67; Chi² = 4.92, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.56 (P = 0.58)



All calculable comparisons were with placebo.

Funnel plot



Continuity correction

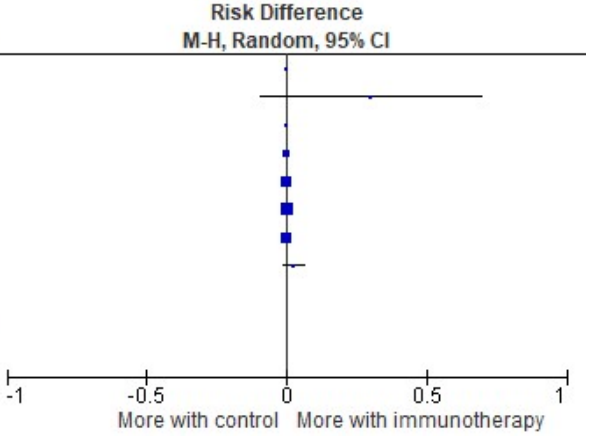
Adding 0.05 to zero events: risk ratio 0.89 (0.48 to 1.66), Z 0.363, p 0.717, I^2 = 0.0%

Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Blumchen 2019	11	12412	20	13813	2.3%	-0.00 [-0.00, 0.00]
Dello Iacono 2013	5	10	2	10	0.0%	0.30 [-0.10, 0.70]
Fernández-Rivas 2009	0	3378	0	1566	1.6%	0.00 [-0.00, 0.00]
Fleischer 2013	0	5825	0	6029	14.0%	0.00 [-0.00, 0.00]
Jones 2017: V-100	0	8121	0	8418	27.2%	0.00 [-0.00, 0.00]
Jones 2017: V-250	0	9033	0	8418	30.2%	0.00 [-0.00, 0.00]
Nowak-Węgrzyn 2019	0	7822	0	7921	24.7%	0.00 [-0.00, 0.00]
Oppenheimer 1992	4	120	1	120	0.0%	0.03 [-0.01, 0.06]
Total (95% CI)		**46721**		**46295**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	20		23			

Heterogeneity: Tau² = 0.00; Chi² = 5.87, df = 7 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)

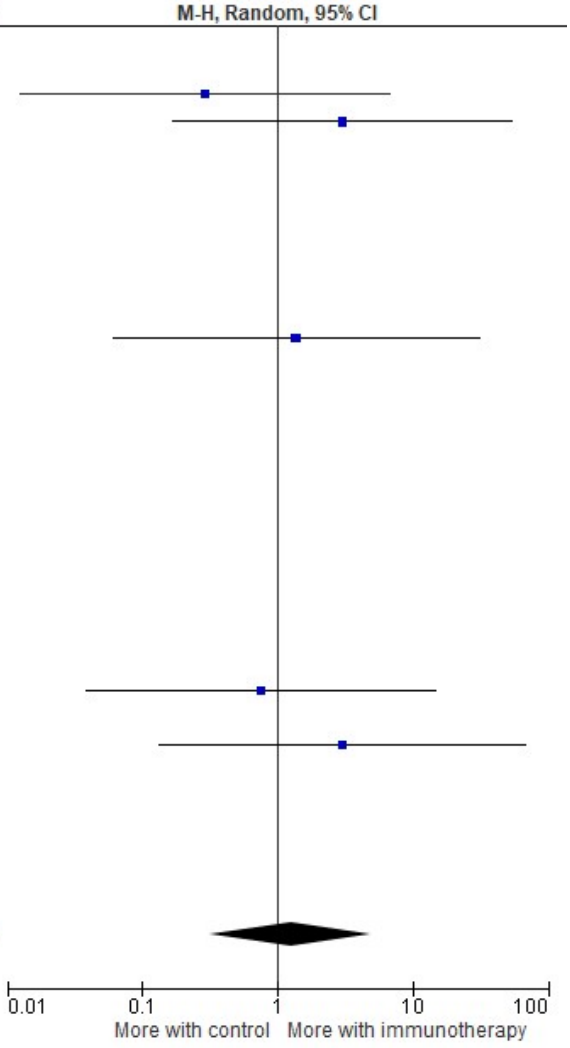


Number of people experiencing life-threatening adverse reactions

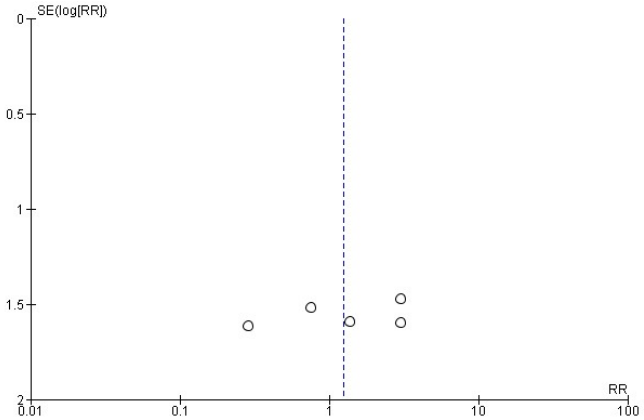
5 studies had calculable data. All calculable comparisons were with placebo, not elimination diet. Both this and analyses which corrected for the rarity of events found no significant difference in the proportion of people with immunotherapy or placebo having life-threatening reactions.

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Akashi 2017	0	18	0	16		Not estimable
Bird 2018	0	29	0	26		Not estimable
Blumchen 2019	0	28	1	24	18.6%	0.29 [0.01, 6.74]
Caminiti 2009	1	3	0	3	22.3%	3.00 [0.17, 53.71]
Caminiti 2015	0	17	0	13		Not estimable
Chinthrajah 2019: Peanut 0	0	60	0	25		Not estimable
Chinthrajah 2019 Peanut 300	0	35	0	25		Not estimable
Dello Iacono 2013	0	10	0	10		Not estimable
Dupont 2010	0	10	0	8		Not estimable
Enrique 2005	0	12	0	11		Not estimable
Escudero 2015	0	30	0	31		Not estimable
Fauquert 2018	1	21	0	9	19.2%	1.36 [0.06, 30.64]
Fernández-Rivas 2009	0	37	0	18		Not estimable
Fleischer 2013	0	20	0	20		Not estimable
Fleischer 2019	0	238	0	118		Not estimable
Itoh-Nagato 2018	0	23	0	22		Not estimable
Jones 2017: V-100	0	24	0	25		Not estimable
Jones 2017: V-250	0	25	0	25		Not estimable
Keet 2012	0	20	0	10		Not estimable
Lee 2013	0	14	0	12		Not estimable
Longo 2008	0	30	0	30		Not estimable
Martín-Muñoz 2019	0	76	0	25		Not estimable
Martorell 2011	0	30	0	30		Not estimable
Nowak-Węgrzyn 2019	0	21	0	23		Not estimable
Oppenheimer 1992	0	3	1	8	20.9%	0.75 [0.04, 14.71]
O'B Hourihane 2020	0	132	0	43		Not estimable
Pajno 2010	1	15	0	15	19.0%	3.00 [0.13, 68.26]
Patriarca 1998	0	14	0	10		Not estimable
Salmivesi 2013	0	18	0	10		Not estimable
Skripak 2008	0	13	0	7		Not estimable
Staden 2007	0	25	0	20		Not estimable
Vickery 2018	0	372	0	124		Not estimable
Total (95% CI)		**1423**		**796**	**100.0%**	**1.25 [0.32, 4.87]**
Total events	3		2			

Heterogeneity: Tau² = 0.00; Chi² = 1.61, df = 4 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)



Funnel plot

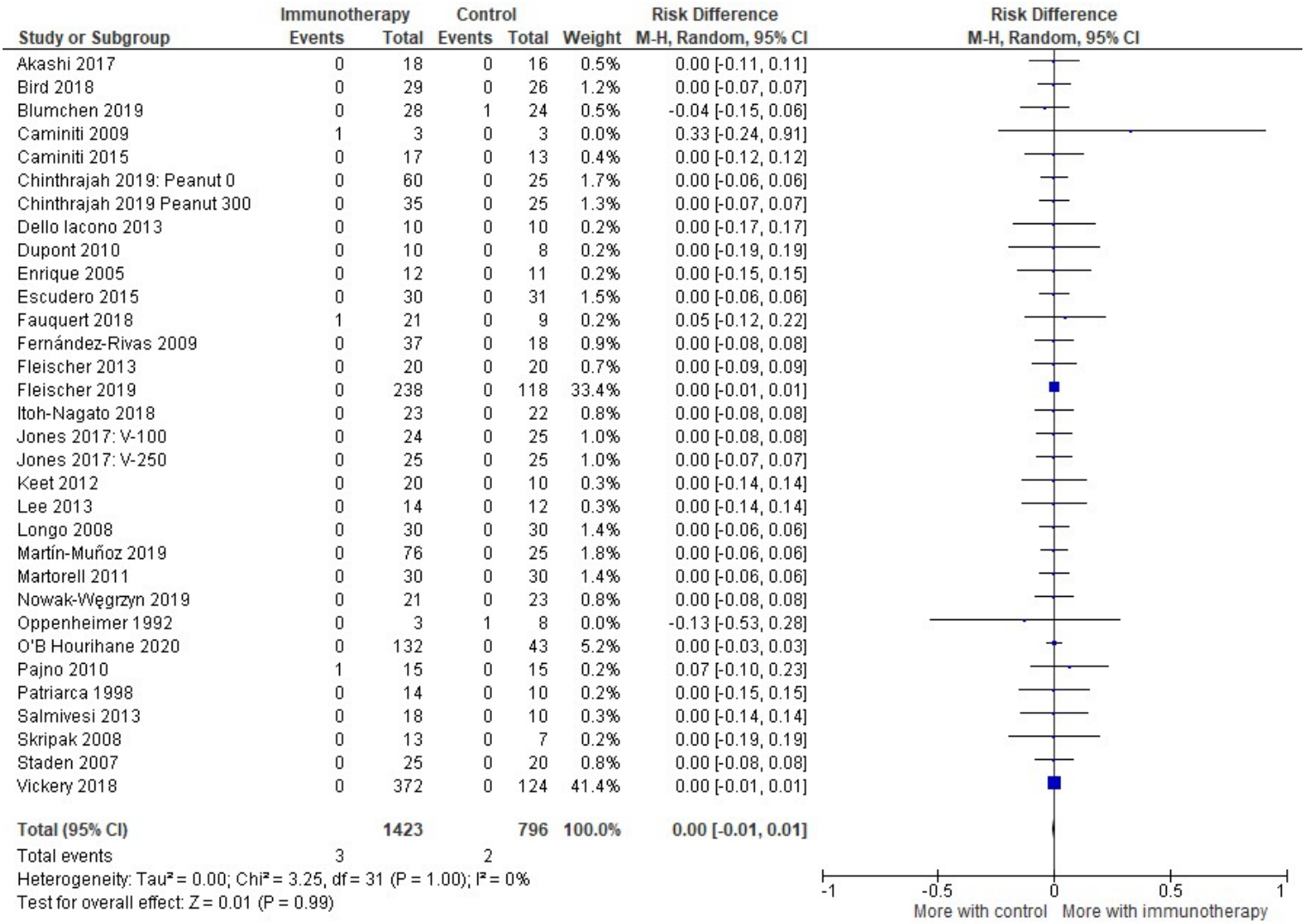


Continuity correction

Risk ratio 0.96 (0.25 to 3.66), Z 0.057, p 0.95, I^2 = 0.0%

Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.



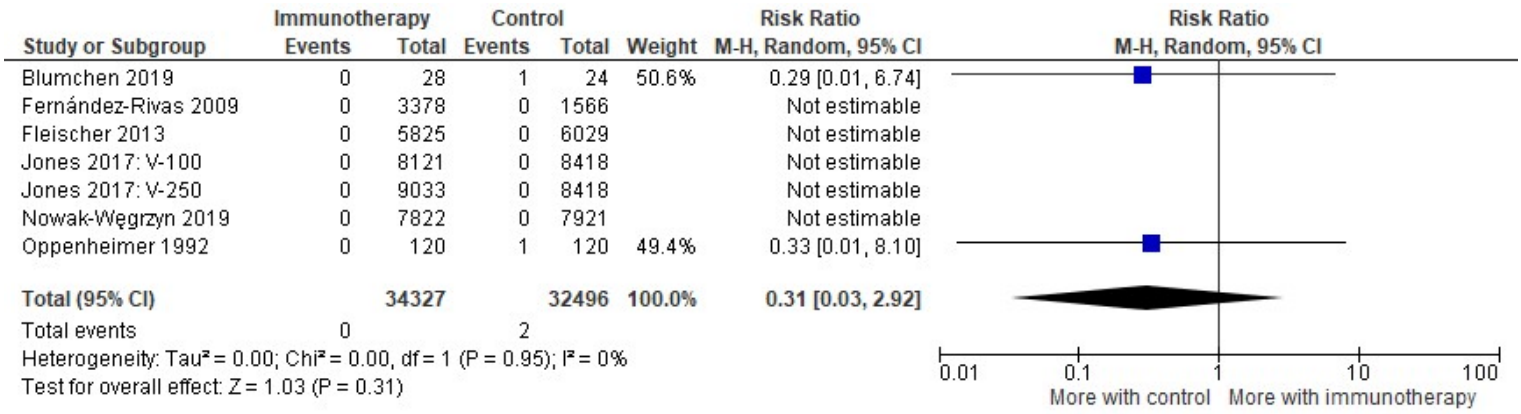
Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Akashi 2017	0	18	0	16	0.5%	0.00 [-0.11, 0.11]
Bird 2018	0	29	0	26	1.2%	0.00 [-0.07, 0.07]
Blumchen 2019	0	28	1	24	0.5%	-0.04 [-0.15, 0.06]
Caminiti 2009	1	3	0	3	0.0%	0.33 [-0.24, 0.91]
Caminiti 2015	0	17	0	13	0.4%	0.00 [-0.12, 0.12]
Chinthrajah 2019: Peanut 0	0	60	0	25	1.7%	0.00 [-0.06, 0.06]
Chinthrajah 2019 Peanut 300	0	35	0	25	1.3%	0.00 [-0.07, 0.07]
Dello Iacono 2013	0	10	0	10	0.2%	0.00 [-0.17, 0.17]
Dupont 2010	0	10	0	8	0.2%	0.00 [-0.19, 0.19]
Enrique 2005	0	12	0	11	0.2%	0.00 [-0.15, 0.15]
Escudero 2015	0	30	0	31	1.5%	0.00 [-0.06, 0.06]
Fauquert 2018	1	21	0	9	0.2%	0.05 [-0.12, 0.22]
Fernández-Rivas 2009	0	37	0	18	0.9%	0.00 [-0.08, 0.08]
Fleischer 2013	0	20	0	20	0.7%	0.00 [-0.09, 0.09]
Fleischer 2019	0	238	0	118	33.4%	0.00 [-0.01, 0.01]
Itoh-Nagato 2018	0	23	0	22	0.8%	0.00 [-0.08, 0.08]
Jones 2017: V-100	0	24	0	25	1.0%	0.00 [-0.08, 0.08]
Jones 2017: V-250	0	25	0	25	1.0%	0.00 [-0.07, 0.07]
Keet 2012	0	20	0	10	0.3%	0.00 [-0.14, 0.14]
Lee 2013	0	14	0	12	0.3%	0.00 [-0.14, 0.14]
Longo 2008	0	30	0	30	1.4%	0.00 [-0.06, 0.06]
Martín-Muñoz 2019	0	76	0	25	1.8%	0.00 [-0.06, 0.06]
Martorell 2011	0	30	0	30	1.4%	0.00 [-0.06, 0.06]
Nowak-Węgrzyn 2019	0	21	0	23	0.8%	0.00 [-0.08, 0.08]
Oppenheimer 1992	0	3	1	8	0.0%	-0.13 [-0.53, 0.28]
O'B Hourihane 2020	0	132	0	43	5.2%	0.00 [-0.03, 0.03]
Pajno 2010	1	15	0	15	0.2%	0.07 [-0.10, 0.23]
Patriarca 1998	0	14	0	10	0.2%	0.00 [-0.15, 0.15]
Salmivesi 2013	0	18	0	10	0.3%	0.00 [-0.14, 0.14]
Skripak 2008	0	13	0	7	0.2%	0.00 [-0.19, 0.19]
Staden 2007	0	25	0	20	0.8%	0.00 [-0.08, 0.08]
Vickery 2018	0	372	0	124	41.4%	0.00 [-0.01, 0.01]
Total (95% CI)		**1423**		**796**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	3		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.25$, $df = 31$ ($P = 1.00$); $I^2 = 0\%$

Test for overall effect: $Z = 0.01$ ($P = 0.99$)

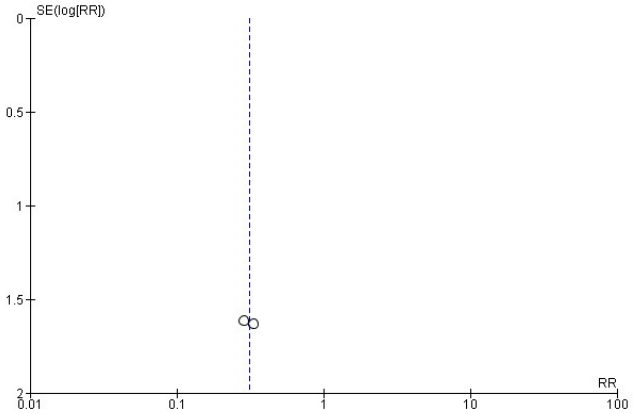
Number of doses associated with life-threatening adverse reactions

There was no difference in the risk of life-threatening adverse reactions based on doses of immunotherapy or placebo.



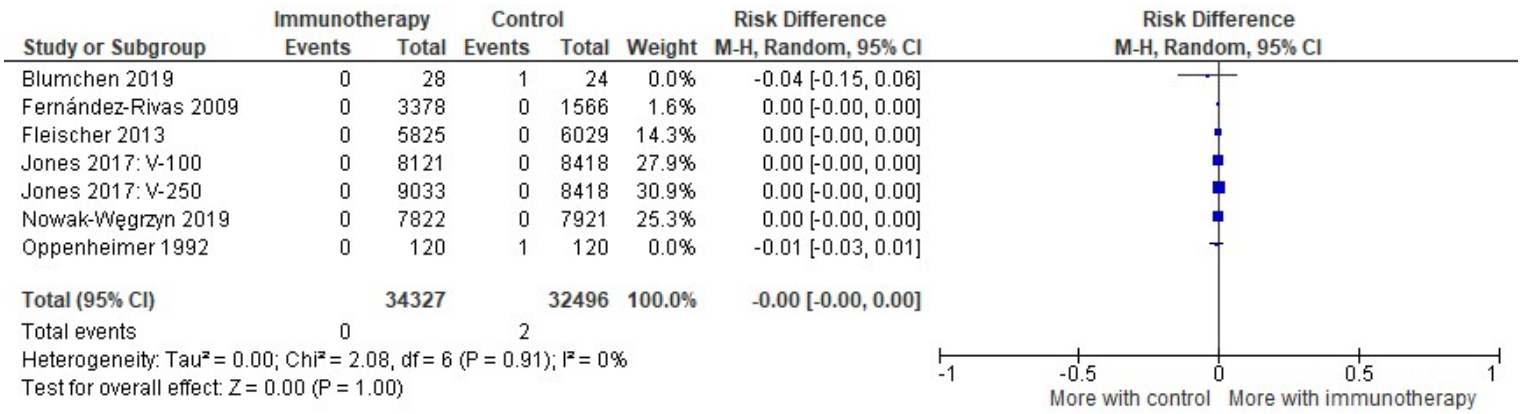
Continuity correction

Risk ratio 0.52 (0.06 to 4.6), Z 0.594, p 0.55, I^2 = 0.0%



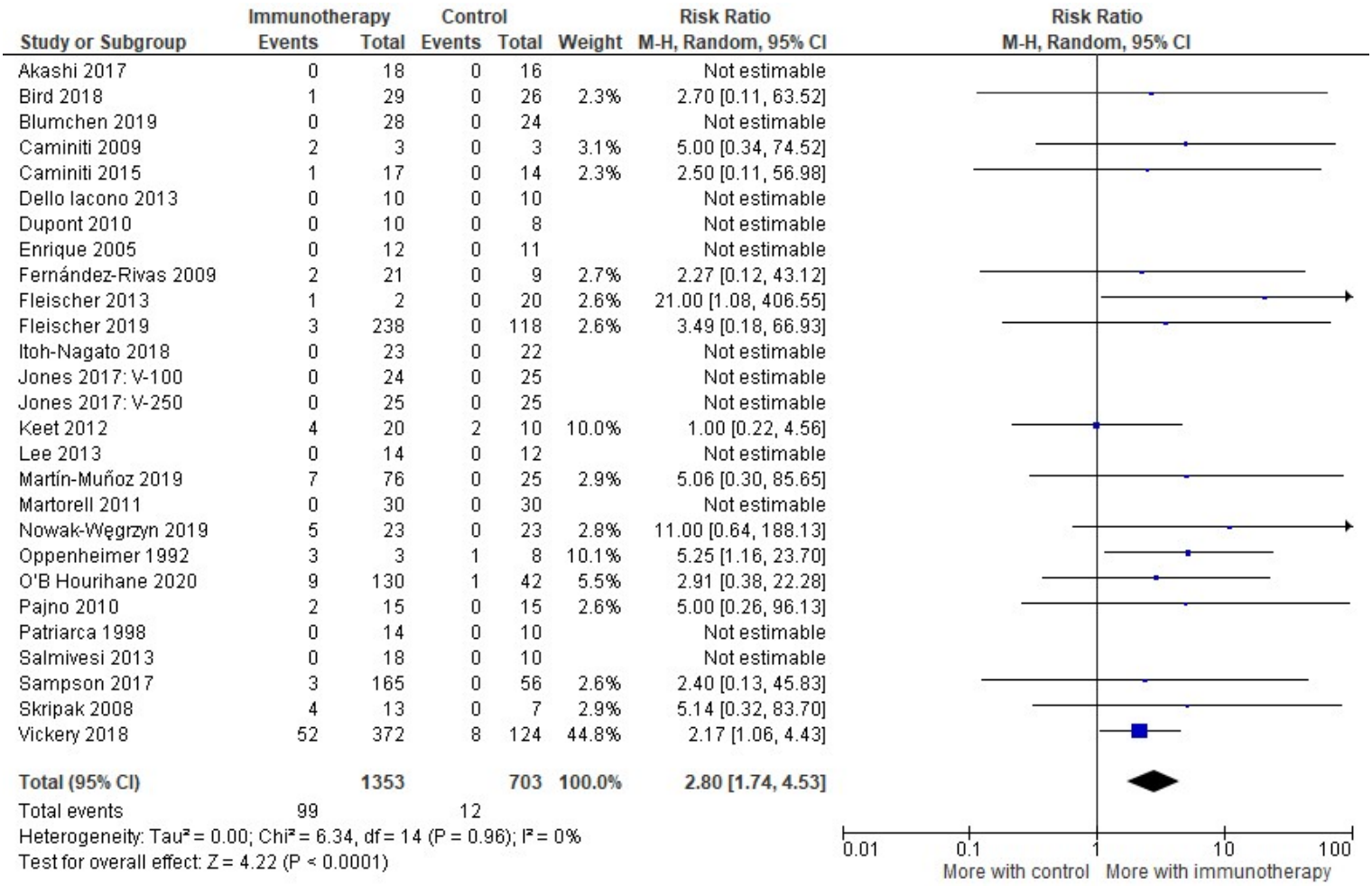
Risk difference

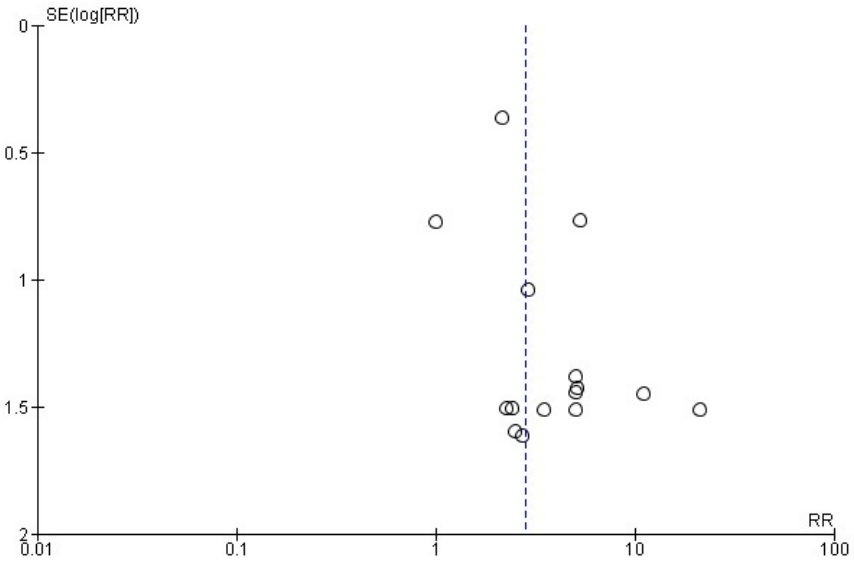
Note that for risk differences, a pooled value of around 0 means no difference between groups.



Number of people who received adrenaline

People receiving immunotherapy were more likely than controls to have received adrenaline for an adverse reaction during the study.



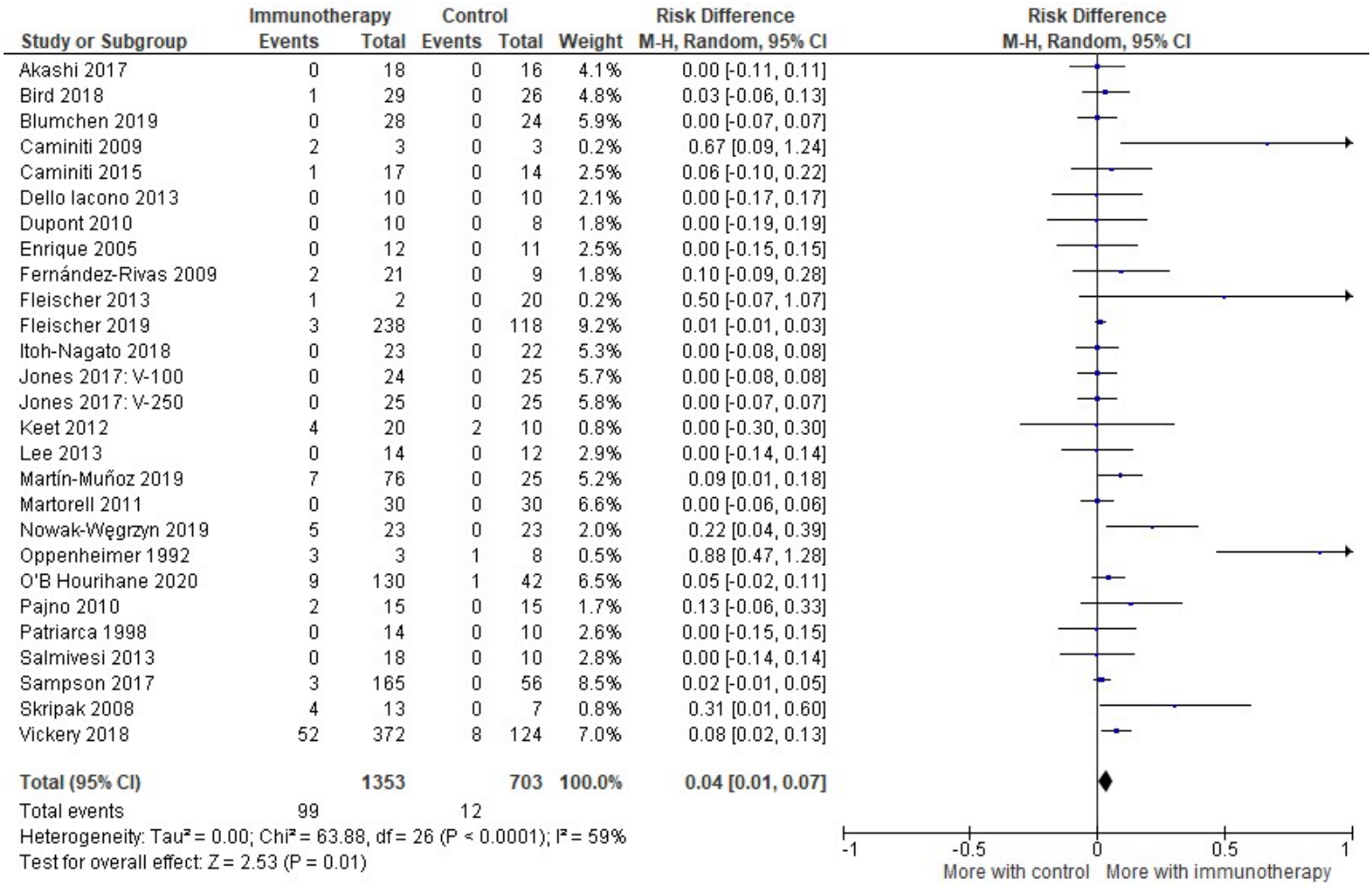


Continuity correction

Risk ratio 2.3 (1.41 to 3.76), Z 3.33, p 0.0008, I^2 0.0%

Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.



Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Akashi 2017	0	18	0	16	4.1%	0.00 [-0.11, 0.11]
Bird 2018	1	29	0	26	4.8%	0.03 [-0.06, 0.13]
Blumchen 2019	0	28	0	24	5.9%	0.00 [-0.07, 0.07]
Caminiti 2009	2	3	0	3	0.2%	0.67 [0.09, 1.24]
Caminiti 2015	1	17	0	14	2.5%	0.06 [-0.10, 0.22]
Dello Iacono 2013	0	10	0	10	2.1%	0.00 [-0.17, 0.17]
Dupont 2010	0	10	0	8	1.8%	0.00 [-0.19, 0.19]
Enrique 2005	0	12	0	11	2.5%	0.00 [-0.15, 0.15]
Fernández-Rivas 2009	2	21	0	9	1.8%	0.10 [-0.09, 0.28]
Fleischer 2013	1	2	0	20	0.2%	0.50 [-0.07, 1.07]
Fleischer 2019	3	238	0	118	9.2%	0.01 [-0.01, 0.03]
Itoh-Nagato 2018	0	23	0	22	5.3%	0.00 [-0.08, 0.08]
Jones 2017: V-100	0	24	0	25	5.7%	0.00 [-0.08, 0.08]
Jones 2017: V-250	0	25	0	25	5.8%	0.00 [-0.07, 0.07]
Keet 2012	4	20	2	10	0.8%	0.00 [-0.30, 0.30]
Lee 2013	0	14	0	12	2.9%	0.00 [-0.14, 0.14]
Martín-Muñoz 2019	7	76	0	25	5.2%	0.09 [0.01, 0.18]
Martorell 2011	0	30	0	30	6.6%	0.00 [-0.06, 0.06]
Nowak-Węgrzyn 2019	5	23	0	23	2.0%	0.22 [0.04, 0.39]
Oppenheimer 1992	3	3	1	8	0.5%	0.88 [0.47, 1.28]
O'B Hourihane 2020	9	130	1	42	6.5%	0.05 [-0.02, 0.11]
Pajno 2010	2	15	0	15	1.7%	0.13 [-0.06, 0.33]
Patriarca 1998	0	14	0	10	2.6%	0.00 [-0.15, 0.15]
Salmivesi 2013	0	18	0	10	2.8%	0.00 [-0.14, 0.14]
Sampson 2017	3	165	0	56	8.5%	0.02 [-0.01, 0.05]
Skripak 2008	4	13	0	7	0.8%	0.31 [0.01, 0.60]
Vickery 2018	52	372	8	124	7.0%	0.08 [0.02, 0.13]
Total (95% CI)		**1353**		**703**	**100.0%**	**0.04 [0.01, 0.07]**
Total events	99		12			

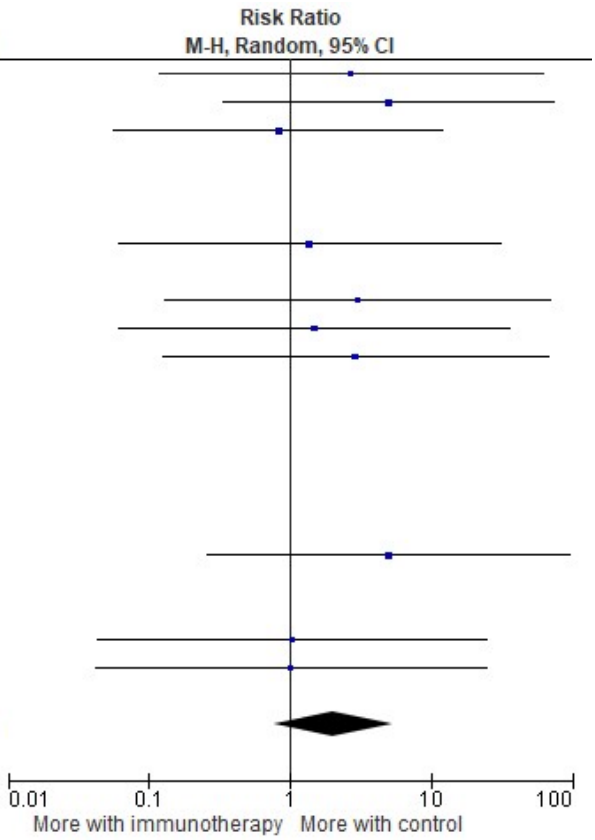
Heterogeneity: Tau² = 0.00; Chi² = 63.88, df = 26 (P < 0.0001); I² = 59%

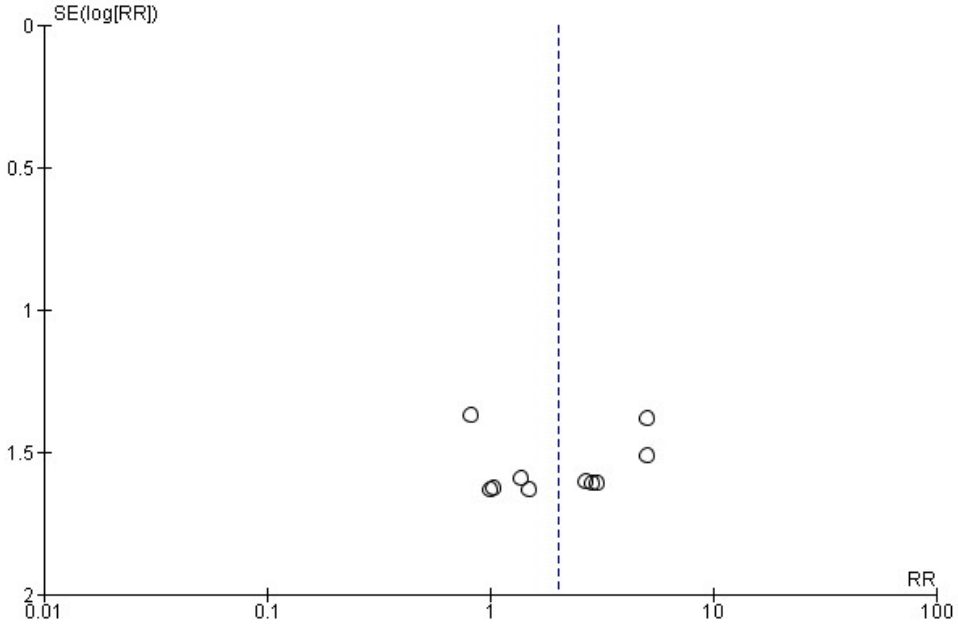
Test for overall effect: Z = 2.53 (P = 0.01)

Number of people experiencing anaphylaxis

Study or Subgroup	Immunotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Akashi 2017	1	18	0	16	9.3%	2.68 [0.12, 61.58]
Caminiti 2009	2	3	0	3	12.5%	5.00 [0.34, 74.52]
Caminiti 2015	1	17	1	14	12.7%	0.82 [0.06, 12.01]
Dupont 2010	0	10	0	8		Not estimable
Enrique 2005	0	12	0	11		Not estimable
Escudero 2015	0	30	0	31		Not estimable
Fauquert 2018	1	21	0	9	9.5%	1.36 [0.06, 30.64]
Fernández-Rivas 2009	0	37	0	18		Not estimable
Fleischer 2013	1	20	0	20	9.3%	3.00 [0.13, 69.52]
Fleischer 2019	1	238	0	118	9.0%	1.49 [0.06, 36.39]
Itoh-Nagato 2018	1	23	0	22	9.2%	2.88 [0.12, 67.03]
Jones 2017: V-100	0	24	0	25		Not estimable
Jones 2017: V-250	0	25	0	25		Not estimable
Lee 2013	0	14	0	12		Not estimable
Martín-Muñoz 2019	0	76	0	25		Not estimable
Martorell 2011	0	30	0	30		Not estimable
O'B Hourihane 2020	0	132	0	43		Not estimable
Pajno 2010	2	15	0	15	10.5%	5.00 [0.26, 96.13]
Patriarca 1998	0	14	0	10		Not estimable
Salmivesi 2013	0	18	0	10		Not estimable
Sampson 2017	1	165	0	56	9.0%	1.03 [0.04, 24.93]
Vickery 2018	1	372	0	124	9.0%	1.01 [0.04, 24.52]
Total (95% CI)		**1314**		**645**	**100.0%**	**2.02 [0.78, 5.27]**
Total events	12		1			

Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 9 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)





Continuity correction

Risk ratio 0.49 (0.51 to 3.48), Z 0.575, p 0.565, I^2 = 0,0%

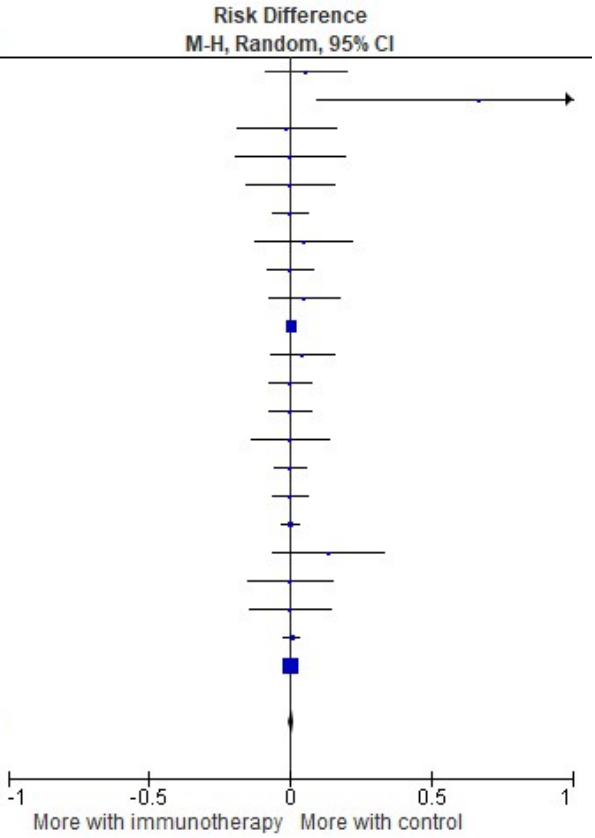
Risk difference

Note that for risk differences, a pooled value of around 0 means no difference between groups.

Study or Subgroup	Immunotherapy Events	Immunotherapy Total	Control Events	Control Total	Weight	Risk Difference M-H, Random, 95% CI
Akashi 2017	1	18	0	16	0.3%	0.06 [-0.09, 0.20]
Caminiti 2009	2	3	0	3	0.0%	0.67 [0.09, 1.24]
Caminiti 2015	1	17	1	14	0.2%	-0.01 [-0.19, 0.16]
Dupont 2010	0	10	0	8	0.2%	0.00 [-0.19, 0.19]
Enrique 2005	0	12	0	11	0.3%	0.00 [-0.15, 0.15]
Escudero 2015	0	30	0	31	1.8%	0.00 [-0.06, 0.06]
Fauquert 2018	1	21	0	9	0.2%	0.05 [-0.12, 0.22]
Fernández-Rivas 2009	0	37	0	18	1.1%	0.00 [-0.08, 0.08]
Fleischer 2013	1	20	0	20	0.4%	0.05 [-0.08, 0.18]
Fleischer 2019	1	238	0	118	29.6%	0.00 [-0.01, 0.02]
Itoh-Nagato 2018	1	23	0	22	0.5%	0.04 [-0.07, 0.16]
Jones 2017: V-100	0	24	0	25	1.2%	0.00 [-0.08, 0.08]
Jones 2017: V-250	0	25	0	25	1.2%	0.00 [-0.07, 0.07]
Lee 2013	0	14	0	12	0.4%	0.00 [-0.14, 0.14]
Martín-Muñoz 2019	0	76	0	25	2.2%	0.00 [-0.06, 0.06]
Martorell 2011	0	30	0	30	1.8%	0.00 [-0.06, 0.06]
O'B Hourihane 2020	0	132	0	43	6.4%	0.00 [-0.03, 0.03]
Pajno 2010	2	15	0	15	0.2%	0.13 [-0.06, 0.33]
Patriarca 1998	0	14	0	10	0.3%	0.00 [-0.15, 0.15]
Salmivesi 2013	0	18	0	10	0.3%	0.00 [-0.14, 0.14]
Sampson 2017	1	165	0	56	8.8%	0.01 [-0.02, 0.03]
Vickery 2018	1	372	0	124	42.5%	0.00 [-0.01, 0.02]
Total (95% CI)		**1314**		**645**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	12		1			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.30$, $df = 21$ ($P = 0.96$); $I^2 = 0\%$

Test for overall effect: $Z = 0.94$ ($P = 0.35$)

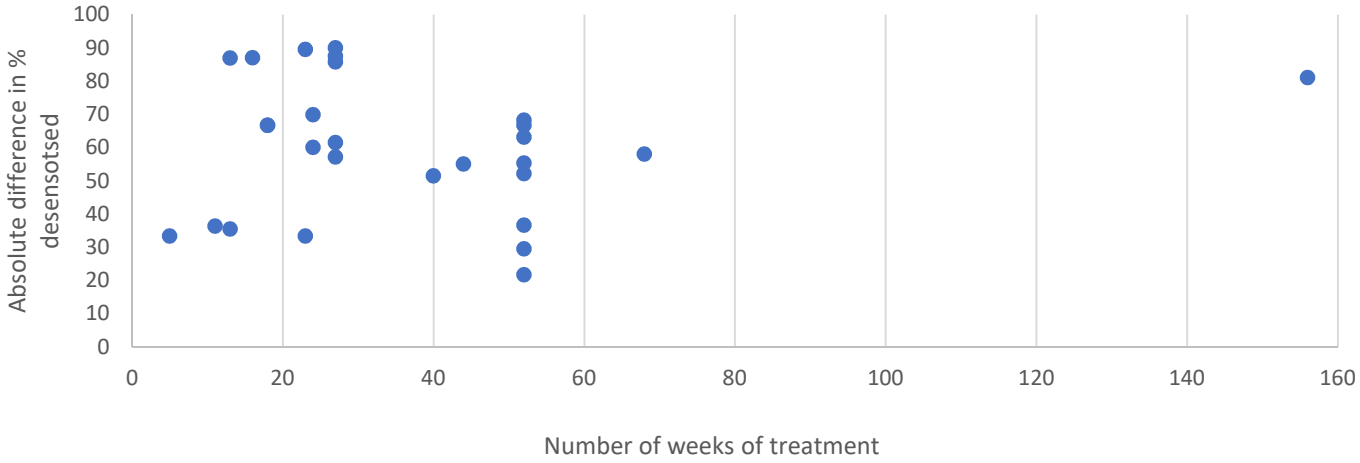


Relationship between weeks of therapy and outcomes

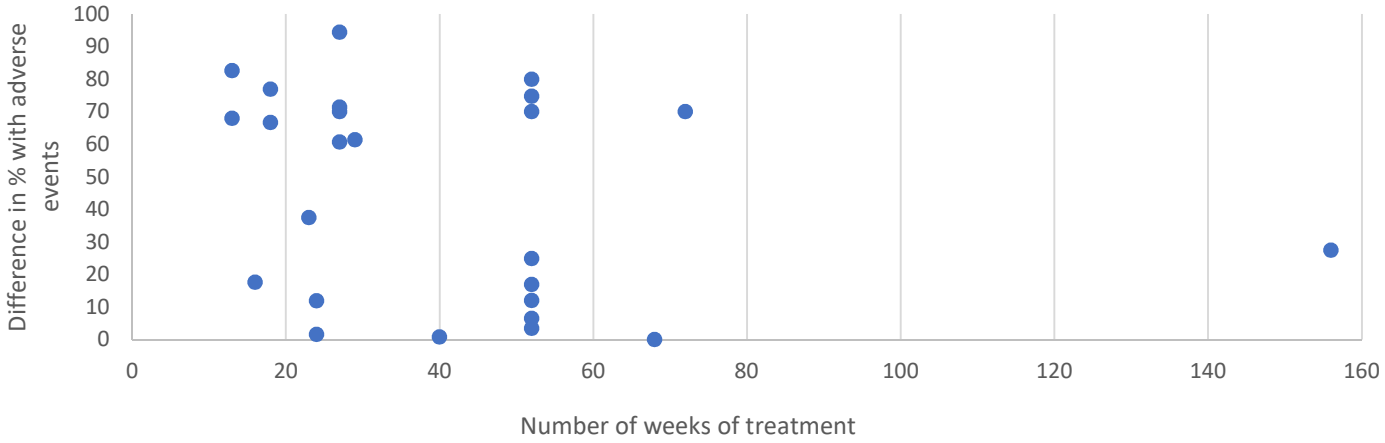
We found no clear impact of the duration of treatment on outcomes.

Data for all food allergies

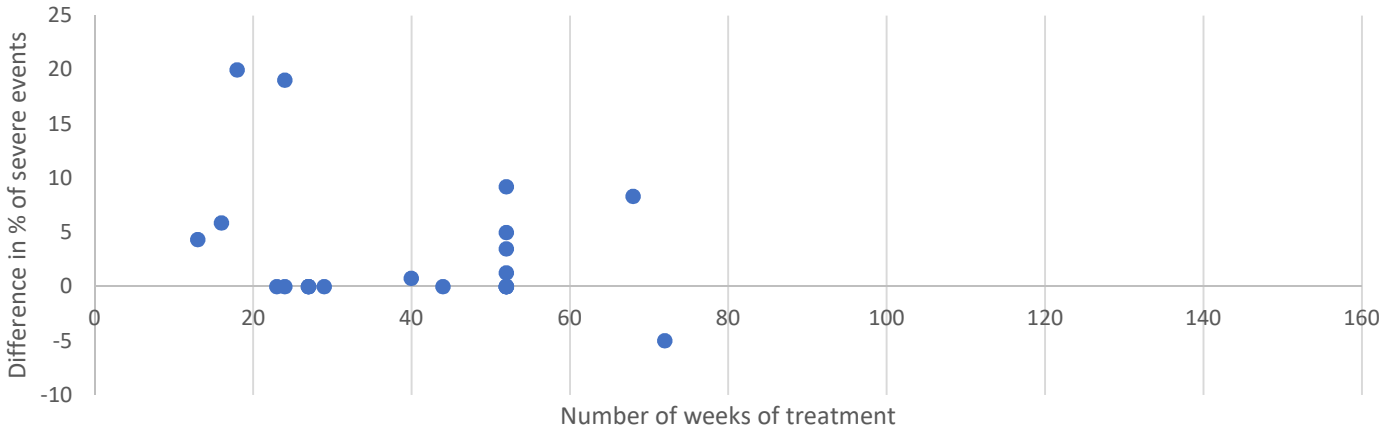
Total number of weeks therapy vs absolute difference in % **desensitised** (intervention minus placebo)



Total number of weeks therapy vs absolute difference in % with **adverse events** (intervention - placebo)



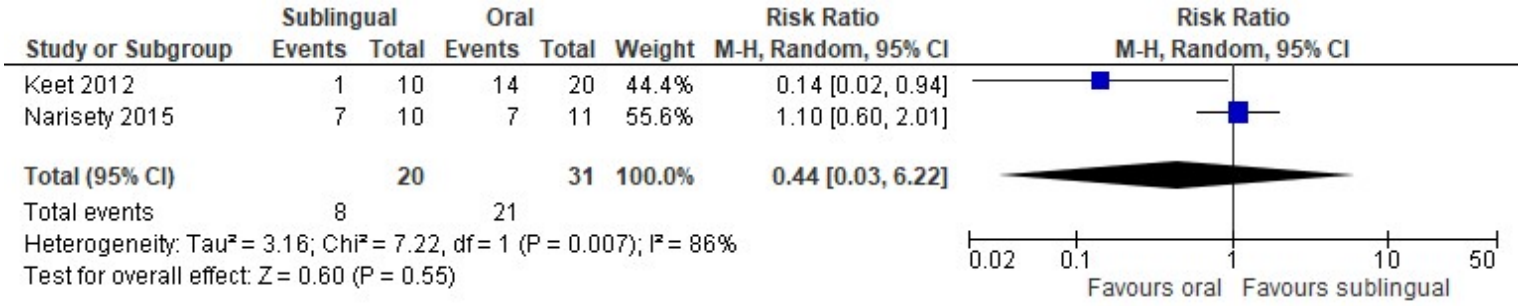
Total number of weeks therapy vs absolute difference in % with **severe adverse events** (intervention - placebo)



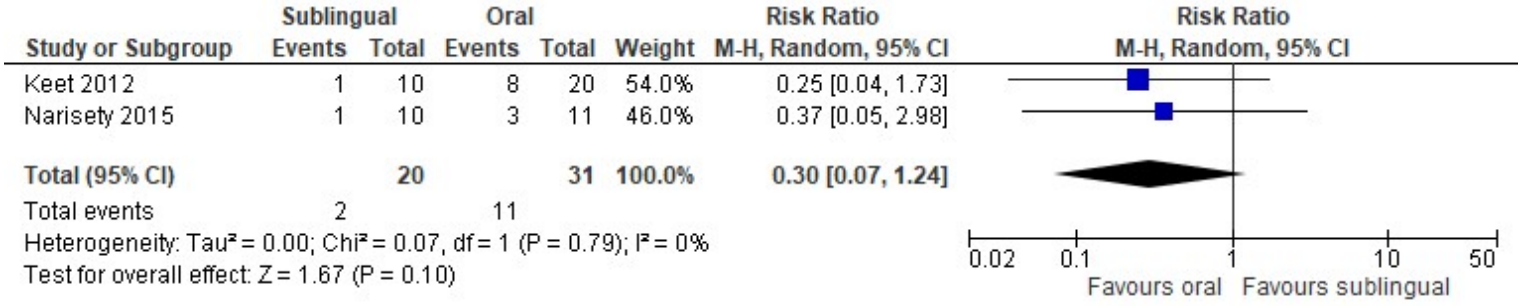
Direct comparison of oral versus sublingual immunotherapy

There were only two studies directly comparing oral versus sublingual immunotherapy. These focused on different populations, with different regimes and measurement approaches. It is therefore not appropriate to combine and generalise the findings. Based on the limited information available, there was no significant difference between oral and sublingual immunotherapy in desensitisation, sustained unresponsiveness or adverse reactions. There was a trend towards greater efficacy and increased adverse reactions with oral immunotherapy, but this did not reach statistical significance and the data were heterogeneous.

Desensitisation



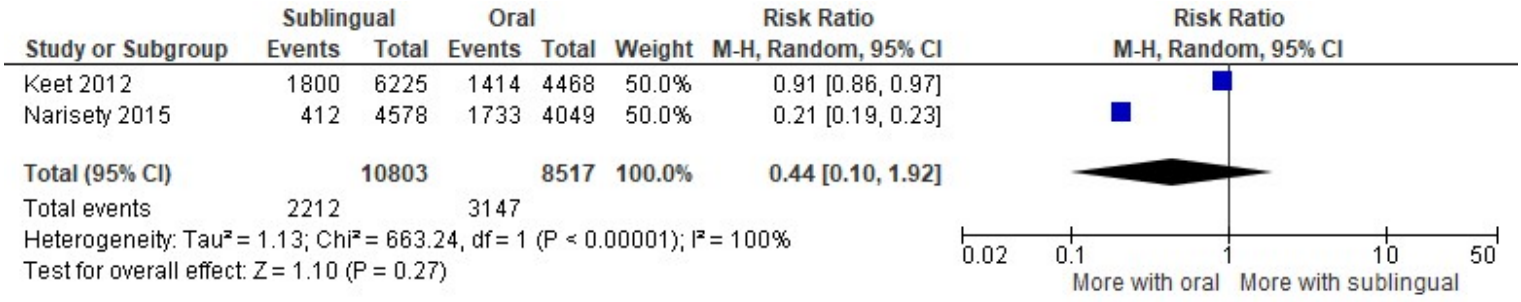
Sustained unresponsiveness



Adverse events

Measured in different ways in the two studies (people versus doses) so cannot combine apart from:

Doses with adverse events (2 studies)



There was no comparable data to combine for severe adverse events.