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Systematic review with meta-analysis

Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis

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Abstract

The aim of using oral and sublingual immunotherapy with food allergies is to enable the safe consumption of foods containing these allergens in patients with food allergies. In the present study, a systematic review of intervention studies was undertaken; this involved the searching of eleven international databases for controlled clinical trials. We identified 1152 potentially relevant papers, from which we selected twenty-two reports of twenty-one eligible trials (i.e. eighteen randomised controlled trials and three controlled clinical trials). The meta-analysis revealed a substantially lower risk of reactions to the relevant food allergen in those receiving orally administered immunotherapy (risk ratios (RR) 0·21, 95 % CI 0·12, 0·38). The meta-analysis of immunological data demonstrated that skin prick test responses to the relevant food allergen significantly decreased with immunotherapy (mean difference −2·96 mm, 95 % CI −4·48, −1·45), while allergen-specific IgG4 levels increased by an average of 19·9 (95 % CI 17·1, 22·6) μg/ml. Sensitivity analyses excluding studies at the highest risk of bias and subgroup analyses in relation to specific food allergens and treatment approaches generated comparable summary estimates of effectiveness and immunological changes. Pooling of the safety data revealed an increased risk of local (i.e. minor oropharyngeal/gastrointestinal) adverse reactions with immunotherapy (RR 1·47, 95 % CI 1·11, 1·95); there was a non-significant increased average risk of systemic adverse reactions with immunotherapy (RR 1·08, 95 % CI 0·97, 1·19). There is strong evidence that orally administered immunotherapy can induce immunomodulatory changes and thereby promote desensitisation to a range of foods. However, given the paucity of evidence on longer-term safety, effectiveness and cost-effectiveness, orally administered immunotherapy should not be used outside experimental conditions presently.

Key words: **Food allergies: Oral immunotherapy: Sublingual immunotherapy: Systematic reviews: Meta-analyses**

Food allergies are responsible for the considerable rise in morbidity and, in some cases, mortality. There are concerns that the incidence, prevalence and severity of food allergies are increasing in many parts of the world, particularly in children[1–3]. Food allergies are associated with significant reductions in the quality of life of both the affected individuals and their family members, which lead to a combination of the restrictive lifestyle associated with living with food allergy, the often considerable difficulties in avoiding the responsible food allergens and the potential for the occurrence of sudden life-threatening anaphylactic reactions[4,5].

Until now, the cornerstones of the clinical management of food allergies have been the identification and complete avoidance of the responsible food allergen(s)[6,7] and, in those who have had severe reactions, the carriage and use of self-injectable epinephrine (adrenaline). This management strategy is challenging, requiring considerable vigilance to avoid accidental exposure[8,9]. In contrast to meticulous allergen avoidance, immunotherapy is the deliberate controlled exposure of patients with food allergy to extremely low, but progressively increasing doses of the offending allergen over a period of weeks or months[10]. The aim is to reduce immunological sensitivity to the allergen such that patients can safely consume food containing the allergen or, at the very least, not react to an accidental low-dose exposure. This approach has, for example, over the last century

Abbreviations: OIT, oral immunotherapy; RR, risk ratio; SLIT, sublingual immunotherapy.

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become an established clinical practice in relation to the treatment of severe pollen, insect venom and drug allergies. Although the first case report of successful immunotherapy to food allergies was reported over a 100 years ago[11], this treatment is yet to become established in the management of people with food allergy. The increasing numbers of people living with potentially life-threatening food allergies and the preventable loss of life from food-triggered anaphylaxis have stimulated renewed interest in the role of orally administered immunotherapy – i.e. via the oral and sublingual routes – in the management of people with food allergy. This is particularly true for patients/parents of affected children who have been heartened by the widespread media coverage of a 'cure' for food allergies, but who also often express frustration that this has not been translated into clinical practice yet. In order to inform ongoing scientific and clinical deliberations on the role of orally administered immunotherapy, in the present study, we sought to critically assess the evidence on the effectiveness, mechanisms and safety of this potentially disease-modifying treatment approach[12–20].

Methods

Literature search and study selection

We searched for randomised controlled trials, quasi-randomised controlled trials and controlled clinical trials investigating the role of oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) in children and adults with IgE-mediated (i.e. immediate hypersensitivity) food allergy. Our primary outcomes of interest were recovery rate from food allergy as assessed by the ability to consume the offending food allergen while receiving treatment (i.e. desensitisation) and, in particular, success rates for the ability to consume the food safely after completion of treatment (i.e. tolerance). Secondary outcomes of interest were immunological changes; the frequency and degree of local (i.e. minor oropharyngeal/gastrointestinal) and systematic (i.e. urticaria, angio-oedema, asthma and anaphylaxis) adverse events during treatment; quality of life; health service utilisation including emergency hospital admissions and emergency treatments; and data on costs from the perspective of health services.

For this purpose, we searched eleven international databases for published material: Cochrane Library; MEDLINE; EMBASE; LILACS; ISI Web of Science; BIOSIS; Global Health; AMED; TRIP; CAB; CINAHL (for search terms used, see Appendix 1, available online). In addition, we searched Internet-based international trial repositories such as www.clinicaltrials.gov and www.controlled-trials.com and contacted international experts in order to locate unpublished and ongoing work (see Appendix 2, available online). Our database searches covered the period from January 1990 to March 2013. The bibliographies of all eligible studies were scrutinised to identify additional possible studies. No language restrictions were imposed, and where necessary, manuscripts were translated into English.

Data abstraction

The titles and abstracts of the identified studies were checked and independently reviewed by two researchers (U. N. and G. D.). The full text of all the potentially eligible studies was assessed for eligibility against the eligibility criteria. Data were independently abstracted by two reviewers onto a customised data extraction sheet. Any disagreements were resolved through discussion, with A. S. arbitrating if an agreement could not be reached.

Quality assessment

The methodological quality of the included randomised controlled trials and quasi-randomised controlled trials was independently assessed using the methods detailed in section eight of the *Cochrane Handbook for Systematic Reviews of Interventions*[21]. Critical appraisal of the controlled clinical trials was undertaken using the Cochrane Effective Practice and Organisation of Care (EPOC) guidelines[22]. We concentrated on using the following six parameters to assess quality: adequate sequence generation; allocation concealment; blinding/patient-related outcomes; the addressing of incomplete outcome data; the absence of selective reporting and the absence of other sources of bias. Each parameter of trial quality was graded: A – low risk of bias; B – moderate risk of bias; C – high risk of bias, and an overall assessment of quality for each trial using these three categories was carried out through consensus discussion among the reviewers.

Data synthesis

The clinical and statistical appropriateness of meta-analyses was considered for all outcomes of interest. Because of the clinical heterogeneity of the populations and interventions studied, we carried out a meta-analysis using random-effects modelling using Review Manager 5.1[21,23]. We calculated mean differences as continuous outcomes and risk ratios (RR) with 95 % CI. Because of a lack of consistency in the reporting of immunological outcomes (e.g. skin prick test, IgE and IgG4), original data were obtained from the authors of several trials. *A priori* sensitivity analyses were undertaken by study design and quality to assess the robustness of findings and explain any heterogeneity uncovered; where possible, subgroup analyses were undertaken on the basis of OIT and SLIT and the allergy being treated for. We graphically assessed for the possibility of publication bias using funnel plots.

Results

Our searches identified 1152 potentially relevant papers, from which we identified twenty-one trials (reported in twenty-two papers) that satisfied our inclusion criteria (Fig. 1). There were eighteen randomised controlled trials[14,18,24–38] and three controlled clinical trials[15,39,40] (Table 1). Of these trials, seventeen had investigated OIT[14,15,18,24,25,30–40] and four had investigated SLIT[26–29]. There was one report that included two independent randomised controlled trials on cows' milk and hens' eggs[34].

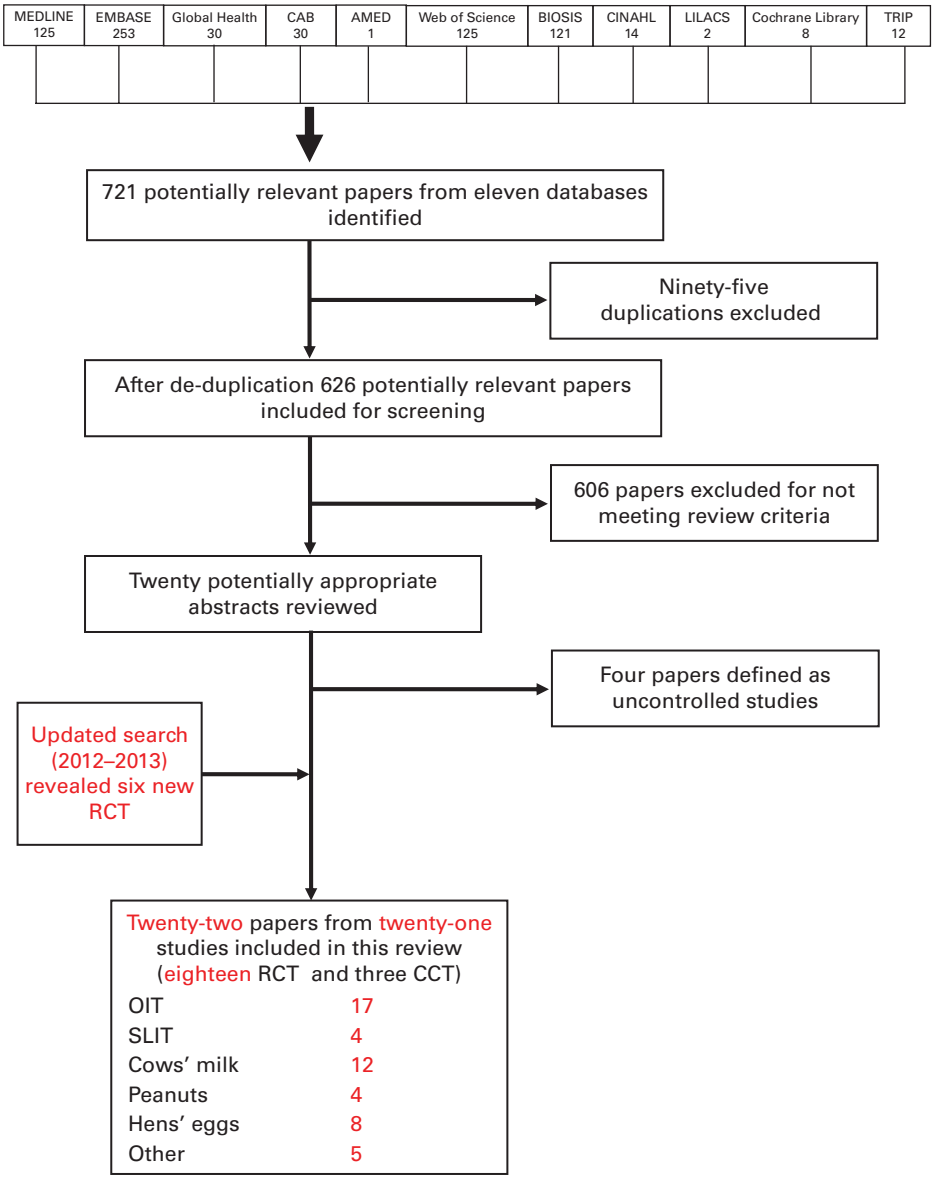

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. RCT, randomised controlled trial; CCT, controlled clinical trial; OIT, oral immunotherapy; SLIT, sublingual immunotherapy. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

Apart from these, twelve studies had focused on cows' milk[14,15,18,25,31,32,34,37,39,40], eight on hens' eggs[14,15,24,30,33,34,36,40], four on peanut[28,29,38,40] and five other studies on a variety of food allergens including hazelnut[26], peach[27], orange[40], apple[15,36,40], 'corn'[40], fish[15,36,40], bean[15,40], wheat[15] and lettuce[40] (see Appendix 3, available online). There were two follow-up studies[41,42], and these focused on SLIT for hazelnut[26] and peach allergies[27]. Translation was required for two papers[39,43]. Among the trials, sixteen had conducted studies on only children[14,15,24,25,29–39], two on only adults[26,27] and three on both children and adults[18,28,40].

Quality assessment

Quality assessment of these studies revealed that three of the randomised controlled trials were at a low risk of bias[28,31,38], a further five randomised controlled trials[18,24,27,29,32] were judged to be at a moderate risk of bias and the remaining ten randomised controlled trials and the three controlled clinical trials[14,15,25,26,30,33–37,39,40] were all judged to be at a high risk of bias (see Appendix 4 for further details, available online).

Impact on primary outcomes

Desensitisation. The effectiveness of immunotherapy was compared with that of placebo with food avoidance/strict elimination diet[18,24–29,31,37,38] or food avoidance/strict elimination diet alone[14,15,30,32–34,36,39,40]. In two studies[35,37] that had investigated the effectiveness of OIT for cows' milk allergy, soya milk was used as the control. A meta-analysis of the risk of persisting food allergy at the completion of the intervention period as assessed by a double-blind

Table 1. Description of the included studies (*n* 21)

First author, year and country	Foods								Type of immunotherapy		Evidence of allergy			Clinical outcomes						HSU	Immunological outcomes				
	Cows' milk	Hens' eggs	Peanut	Hazelnut	Peach	Apple	Fish	Other*	OIT	SLIT	SPT	SBPCFC	DBPCFC	Desensitisation	Tolerance	QOL	LR	SR	Unscheduled visits	Cost-effectiveness	Total IgE	Sp IgE	IgG	IgG4	Other†
RCT																									
Burks (2012)[24], USA		✓							✓		✓			✓			✓					✓		✓	✓
Caminiti (2009)[25], Italy	✓								✓		✓		✓	✓			✓	✓							
Enrique (2005)[26], Spain				✓						✓	✓		✓	✓			✓	✓				✓		✓	✓
Enrique (2008)[41]‡																									
Fernandez-Rivas (2009)[27], Spain					✓					✓	✓		✓	✓			✓	✓				✓		✓	
Garcia (2010)[42]‡																									
Fleischer (2013)[28], USA			✓							✓	✓		✓	✓			✓	✓				✓		✓	✓
Kim (2011)[29], USA			✓							✓	✓		✓	✓			✓	✓				✓		✓	✓
Lacono (2013)[30], Italy		✓							✓		✓		✓	✓			✓	✓				✓			
Longo (2008)[31], Italy	✓								✓		✓		✓	✓			✓	✓	✓			✓			
Martorell (2011)[32], Spain	✓								✓		✓		✓	✓			✓	✓				✓			
Meglio (2013)[33], Italy		✓							✓		✓		✓	✓			✓	✓				✓		✓	✓
Morisset (2007)[34]§, France	✓								✓		✓	✓		✓			✓	✓				✓			
Morisset (2007)[34]‖, France		✓							✓		✓	✓		✓			✓	✓				✓			
Pajno (2010)[35], Italy	✓								✓		✓		✓	✓			✓	✓				✓		✓	
Patriarca (1998)[36], Italy	✓	✓						✓	✓		✓		✓	✓			✓	✓			✓	✓			
Salmivesi (2012)[37], Finland	✓								✓		✓		✓	✓			✓	✓							
Skripak (2008)[18], USA	✓								✓		✓		✓	✓			✓	✓			✓	✓	✓	✓	
Staden (2007)[14], Germany	✓	✓							✓				✓		✓		✓	✓			✓	✓			
Varshney (2011)[38], USA			✓						✓		✓		✓	✓			✓	✓				✓	✓	✓	✓
CCT																									
Mansouri (2007)[39], Iran	✓								✓		✓		✓	✓			✓	✓			✓	✓			
Patriarca (2003)[40], Italy	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓	✓			✓	✓				✓		✓	
Patriarca (2007)[15], Italy	✓	✓				✓	✓	✓	✓	✓	✓		✓	✓			✓	✓				✓		✓	✓

HSU, health service utilisation; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; SBPCFC, single-blind placebo-controlled food challenge; DBPCFC, double-blind placebo-controlled food challenge; QOL, quality of life; LR, local reactions; SR, systemic reactions; Sp IgE, specific IgE, RCT, randomised controlled trial; CCT, controlled clinical trial.

* Other includes orange, maize, bean and lettuce.

† Other includes IL-4, IL-5, IL-10, IL-13, tumour growth factor β, interferon-γ, basophil activation and T regulatory cells.

‡ Follow-up study.

§ Cows' milk RCT.

‖ Hens' egg RCT.

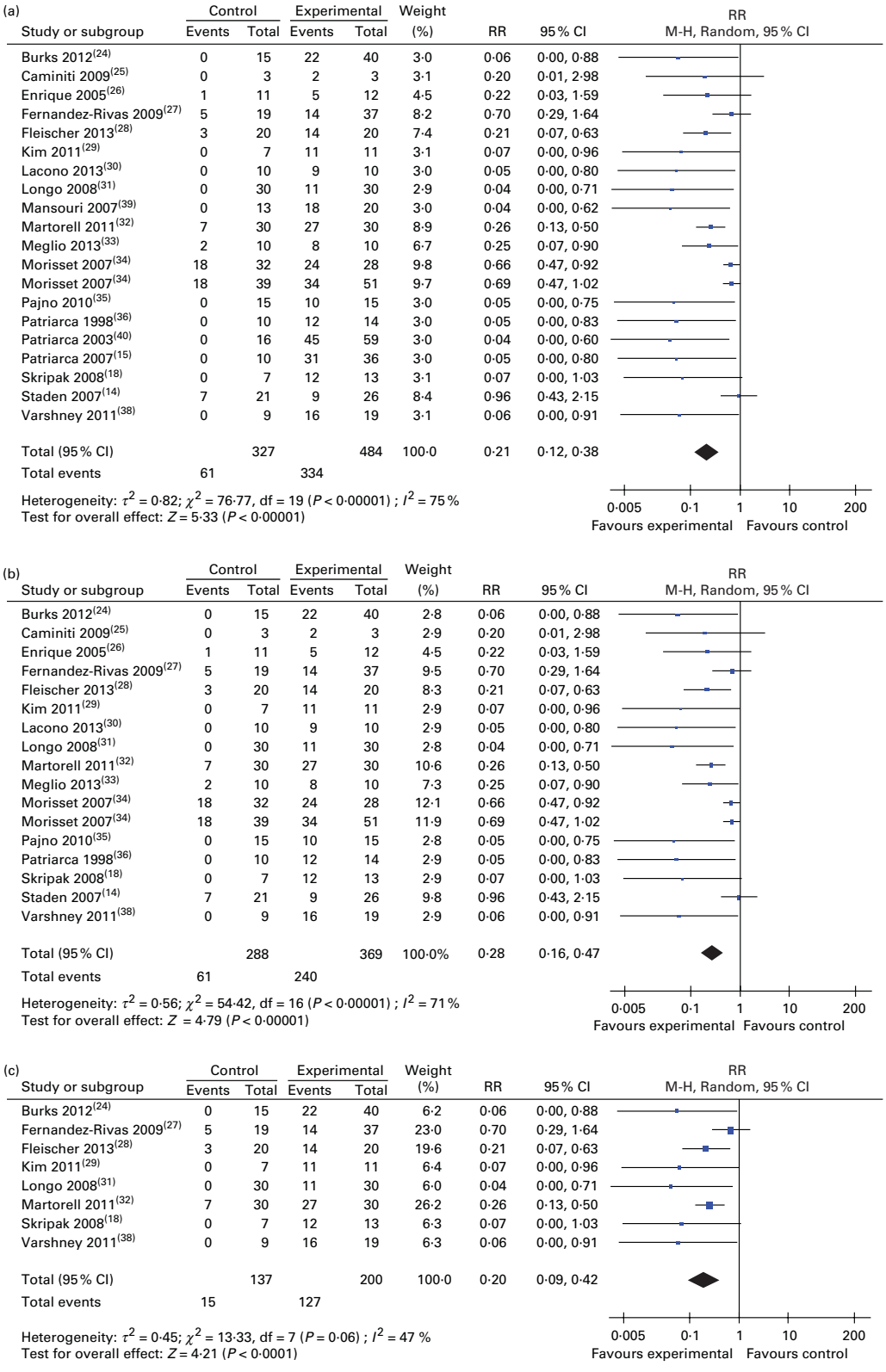

Fig. 2. (a) Risk ratios (RR) of persisting food allergy as assessed by double-blind placebo-controlled food challenge in oral immunotherapy (OIT) or sublingual immunotherapy (SLIT) *v.* controls, (b) sensitivity analysis RR of food allergy after OIT or SLIT (only randomised controlled trial) and (c) sensitivity analysis RR of food allergy after OIT or SLIT (only grade A and B studies). (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

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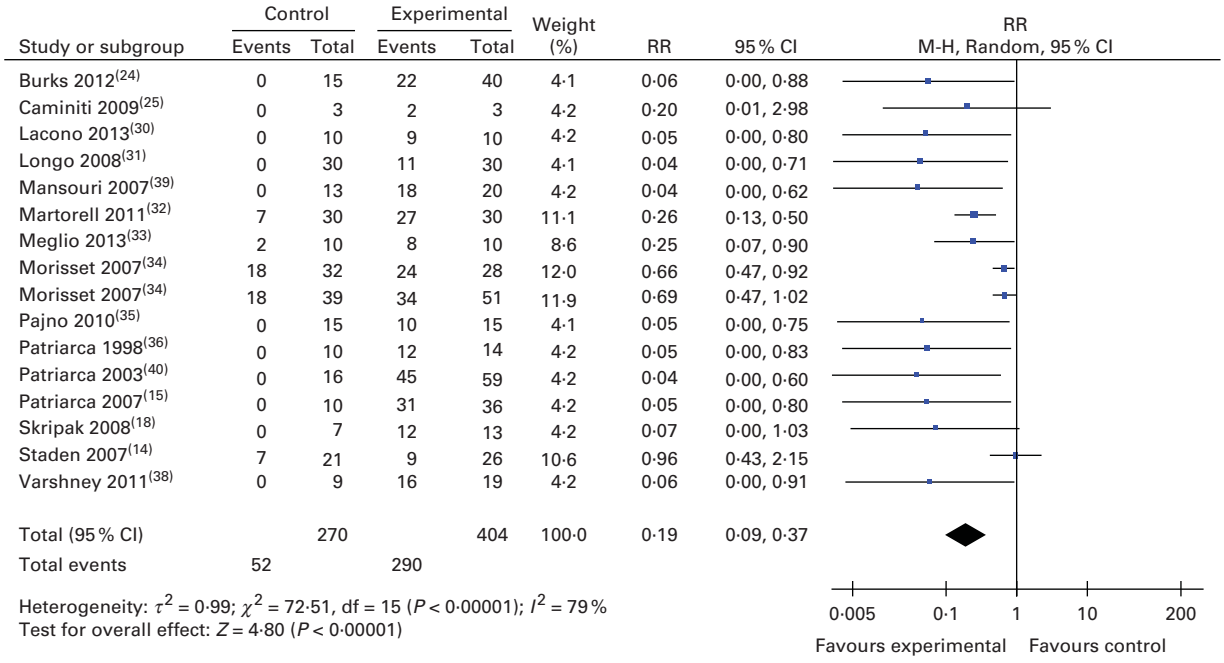

Fig. 3. Risk ratios (RR) of persisting food allergy as assessed by double-blind placebo-controlled food challenge in oral immunotherapy *v.* controls. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

placebo-controlled food challenge was possible based on data obtained from all the twenty trials, which revealed a substantially reduced average risk of persisting food allergy in treated patients (RR 0·21, 95% CI 0·12, 0·38; Fig. 2(a)) [14,15,18,24–36,38–40]. A sensitivity analysis omitting the studies that had utilised a clinical diagnosis of food allergy (well-documented reaction within 60 min of consuming food and elevated specific IgE levels and/or a positive skin prick test) as an inclusion criterion instead of a confirmatory double-blind placebo-controlled food challenge made little difference to the summary estimates (RR 0·26, 95% CI 0·15, 0·45) (see Appendix 5, Supplementary Fig. S1, available online)

Sensitivity analysis of the seventeen randomised controlled trials found a comparable average risk reduction (RR 0·28, 95% CI 0·16, 0·47; Fig. 2(b)). Further sensitivity analysis excluding all the trials judged to be at a high risk of bias also demonstrated a substantial average risk reduction (RR 0·20, 95% CI 0·09, 0·42)[18,24,27–29,31,32,38] (Fig. 2(c)).

Subgroup analyses revealed that both oral (RR 0·19, 95% CI 0·09, 0·37) and sublingual approaches had comparable effectiveness (RR 0·30, 95% CI 0·12, 0·78) (Figs. 3 and 4, respectively).

Furthermore, we were able to carry out subgroup analyses for eight trials that had investigated immunotherapy for cows' milk allergy, four trials on hens' egg allergy and three trials on peanut allergy. These analyses demonstrated that OIT approaches substantially reduced the risk of cows' milk (RR 0·14, 95% CI 0·04, 0·44)[18,25,31,32,34–36,39], hens' egg (RR 0·19, 95% CI 0·04, 0·99)[24,30,33,34] and peanut (RR 0·16, 95% CI 0·06, 0·41)[28,29,38] allergies (see Appendix 5, Supplementary Figs. S2, S3 and S4, available online).

There was no clear evidence of publication bias (Fig. 5).

Tolerance. Long-term tolerance was investigated by two studies, with it being studied after OIT in children with allergy to cows' milk and hens' eggs[14,24]. After completion of the desensitisation and maintenance phases, the subjects were subjected to a 1- to 2-month strict elimination (washout)

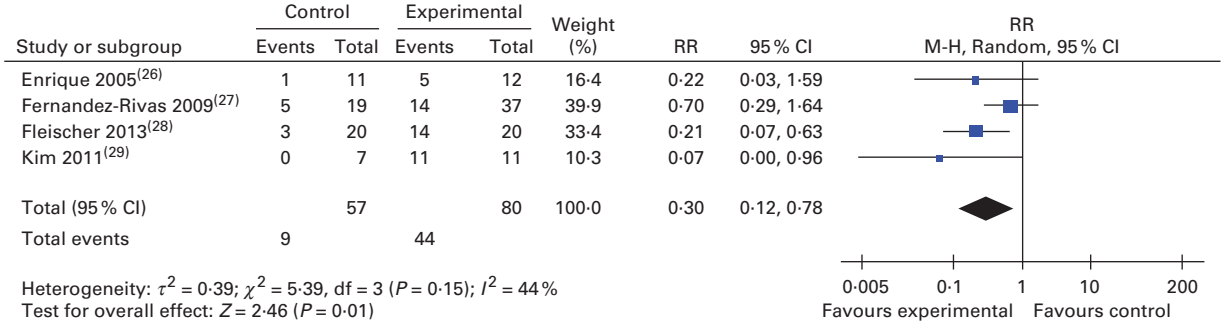

Fig. 4. Risk ratios (RR) of persisting food allergy as assessed by double-blind placebo-controlled food challenge in sublingual immunotherapy *v.* controls. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

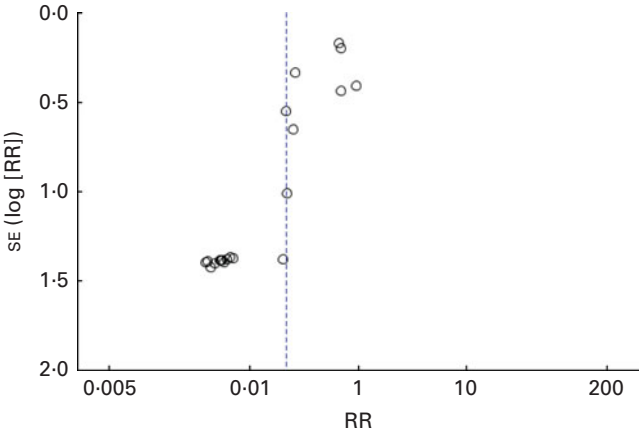

Fig. 5. Funnel plot showing: risk ratios (RR) of persistent food allergy after oral or sublingual immunotherapy. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

period before the follow-up double-blind placebo-controlled food challenge. Burks *et al.*[24] reported that of the forty children undergoing hens' egg OIT, eleven (28 %) were considered to have sustained unresponsiveness after cessation of OIT (i.e. tolerance). Staden *et al.*[14] reported that there was no difference in the development of long-term tolerance between OIT and control subjects (35 *v.* 36 %), suggesting that regular allergen exposure was required to maintain the state of desensitisation.

Impact on secondary outcomes

Immunological outcomes. Many of the trials included data on the effects of OIT or SLIT on immunological outcomes (Appendices 6 and 7, available online). Skin prick test responses to the responsible food allergen before and after immunotherapy were measured by fifteen studies[14,15,18,24,27–30,32–34,38–40], food allergen-specific IgE levels by eighteen studies [14,15,18,24,26–32,34–36,38–40] and food allergen-specific IgG4 levels by eleven studies[15,18,24,26–29,33,35,38,40].

Allergen skin prick tests. The results of allergen skin prick tests were expressed in differing formats. However, we were able to conduct a meta-analysis of skin prick test data obtained from five studies using a combination of published data and original data supplied by the investigators. OIT/SLIT reduced the magnitude of the mean wheal diameter response to the responsible food allergen by −2·96 (95 % CI −4·48, −1·45) mm (Fig. 6), and of the ten studies that had failed to provide us with original data[14,15,31,34,36], eight[14,15,24,26,30–32,35] reported that OIT/SLIT reduced skin prick test reactivity, with three studies reporting no change[28,33,35]. Subgroup analysis of data showed that OIT for cows' milk allergy also reduced the magnitude of the mean wheal diameter response to cows' milk by −3·42 (95 % CI −6·18, −0·66) mm (see Appendix 5, Supplementary Fig. S5, available online).

Food allergen-specific IgE tests. The results of food allergen-specific IgE tests were expressed in differing formats, but we were able to conduct a meta-analysis of food allergen-specific IgE data obtained from six studies using published data and original data supplied by the investigators. Completion of OIT/SLIT did not significantly reduce the allergen-specific IgE levels (−5·2 (95 % CI −12·3, 1·99) kU/l; Fig. 7). Of the studies that had failed to provide us with original data and not included in the meta-analysis, four[24,27,28,35] reported that orally administered immunotherapy did not change the allergen-specific IgE levels and seven[14,15,29,30,32,33,40] reported that OIT/SLIT reduced their levels. Subgroup analysis of data showed that OIT also did not significantly reduce these levels (−8·96 for cows' milk allergy, 95 % CI −28·64, 10·73; see Appendix 5, Supplementary Fig. S6, available online).

Food allergen-specific IgG4 tests. The results of food allergen-specific IgG4 tests were expressed in differing formats, but we were able to conduct a meta-analysis of allergen-specific IgG4 data obtained from three studies using published data and original data supplied by the investigators. OIT/SLIT increased the allergen-specific IgG4 levels by 19·9 (95 % CI 17·1, 22·6) μg/ml (Fig. 8), and five of the seven studies that had failed to provide us with original data and not included in the meta-analysis also reported increases in their levels[15,24,27,29,40] and two studies[28,33] reported no changes. Subgroup analysis of food allergen-specific IgG4 levels during OIT for cows' milk allergy also showed an increase in their levels (19·8 (95 % CI 14·32, 25·34) μg/ml; see Appendix 5, Supplementary Fig. S7, available online).

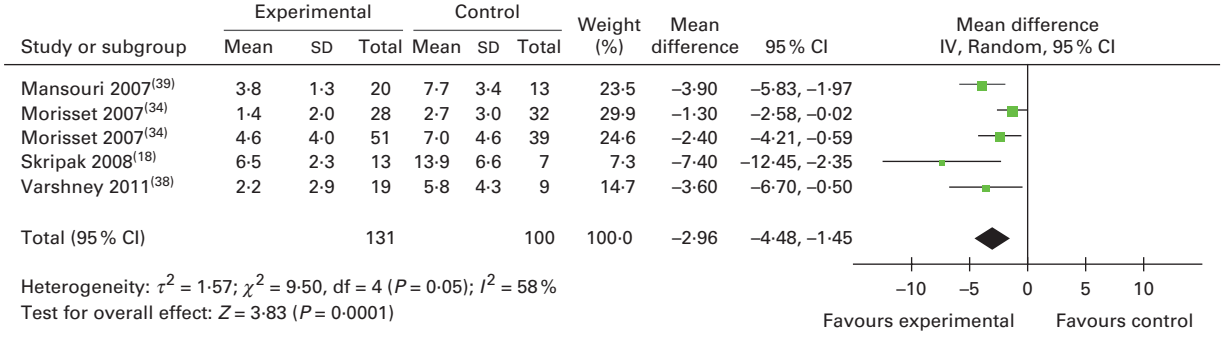

Fig. 6. Skin prick test (wheal in mm) following oral immunotherapy for food allergy. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

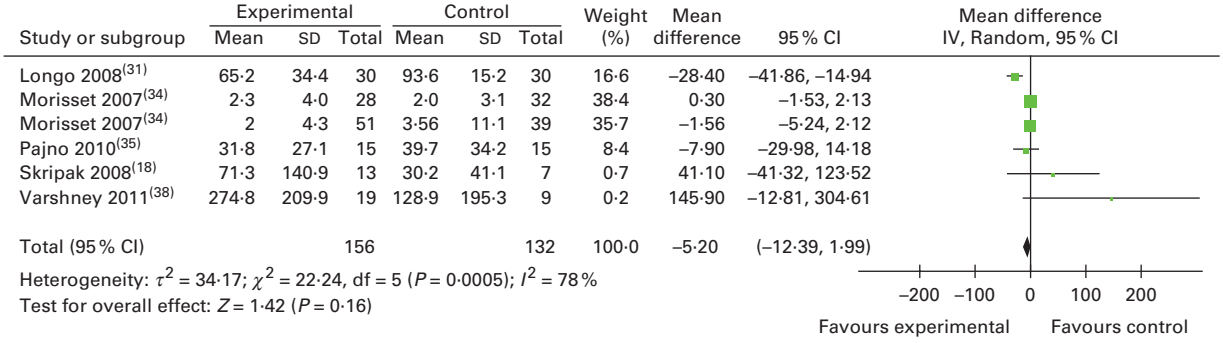

Fig. 7. Specific IgE levels (kU/l) following oral immunotherapy for food allergy. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

Safety

Systemic reactions. Data on the occurrence of systemic (i.e. urticaria, asthma and anaphylaxis) adverse reactions were available from five trials. Meta-analysis of safety data obtained from these trials indicated a modest increased risk of systemic adverse reactions associated with treatment, but this was imprecisely estimated (RR 1·08, 95% CI 0·97, 1·19)[26,27,35,36,38,39] (Fig. 9). Some studies reported no 'severe' side effects[24,30,32,33]. Focusing on only higher-quality studies (i.e. grade A and B studies) in a sensitivity analysis produced comparable summary estimates of the risk of adverse events (RR 1·02, 95% CI 0·89, 1·17) (see Appendix 5, Supplementary Fig. S8, available online)[27,38]. However, subgroup analysis of safety data obtained from OIT studies[35,36,39] for cows' milk allergy more clearly demonstrated these increased risks (RR 1·23, 95% CI 1·03, 1·48; see Appendix 5, Supplementary Fig. S9, available online).

Local reactions. Data on the occurrence of local (minor oropharyngeal/gastrointestinal) adverse reactions were available from nine studies; these revealed an increased risk associated with OIT/SLIT (RR 1·47, 95% CI 1·11, 1·95) (Fig. 10). Studies not included in the meta-analysis reported the incidence of local reactions in relation to doses administered, indicating that OIT was associated with an increase in local reactions[24,28,30]. Including only grade A and B studies in a sensitivity analysis demonstrated a small non-significant increased risk of local reactions associated with immunotherapy (RR 2·08, 95% CI 0·87, 4·99; see Appendix 5, Supplementary Fig. S10, available online)[24,27,32,38]. Subgroup analysis of data obtained from trials on OIT for cows' milk allergy suggested an increased risk in the treatment arm, but this was imprecisely estimated (RR 2·03, 95% CI 0·87, 4·73; see Appendix 5, Supplementary Fig. S11, available online).

Other outcomes. None of the studies had reported on the other outcomes of interest, namely quality of life of patients and their families; use of health services including emergency hospital admissions and emergency treatments; and data on cost-effectiveness considerations.

Details of unpublished and ongoing studies are summarised in Appendix 8 (available online).

Discussion

Statement of principal findings

The present systematic review and meta-analysis has found that orally administered immunotherapy is likely to be effective in substantially reducing the risk of persisting food allergy in children and adults with IgE-mediated food allergy to a range of foods while receiving treatment (i.e. desensitisation was successfully achieved). The increases in allergen exposure that people are able to tolerate while on treatment are clinically relevant and are likely to prevent many of the reactions associated with accidental exposure. It remains unclear as to whether orally administered immunotherapy induces clinical tolerance (i.e. long-term cure). For example, Burks *et al.*[24] reported that OIT induced tolerance in 28% of those treated, whereas Staden *et al.*[14] found no increase in tolerance over and above that observed in the control subjects. The lack of consensus on clinical tolerance is important because of the need for regular exposure to allergenic foods to maintain a state of desensitisation. These treated patients, therefore, at

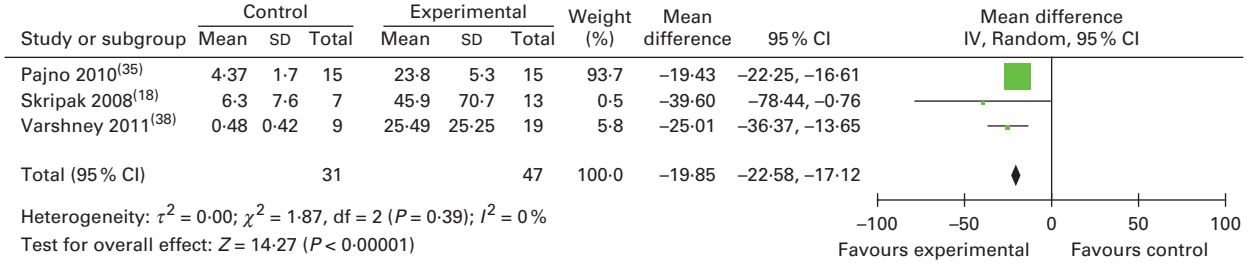

Fig. 8. IgG4 levels (μg/ml) following oral immunotherapy for food allergy. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

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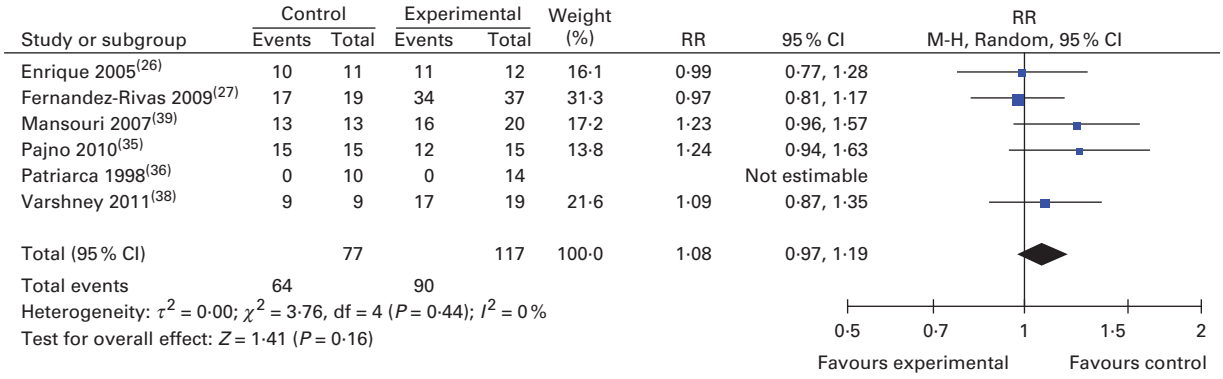

Fig. 9. Safety data – absence of systemic reactions during oral immunotherapy or sublingual immunotherapy for food allergy. RR, risk ratio. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

present need to move from a situation in which they are meticulously avoiding the food in question to a state in which regular consumption of the food is necessary in order to maintain a desensitised state. Such a state of desensitisation may be associated with improved quality of life; however, the psychological consequences (if any) of such a radical change in management strategy may in some individuals adversely affect the quality of life. These issues need to be addressed by appropriate trials. Immunotherapy is associated with an increased risk of local side effects and, more importantly, may also be associated with a modest increased risk of systemic side effects, necessitating very careful intensive monitoring of patients and high-level clinical support (i.e. access to specialist advice 24 h a day, 7 d a week). The cost implications for health services of treating immunotherapy-associated adverse events, the supervision of immunotherapy dose increases in clinical areas and the provision of high-level clinical support have not been addressed by any of the studies identified and also clearly need further investigation.

Insights into the mechanisms of action

In contrast to previous reviews on this subject[20,43–49], we also studied and synthesised data on immunological outcomes. Overall, the immunological data suggest that orally administered immunotherapy induces changes in skin prick tests (reduced response) and antigen-specific IgG4 levels (increased) similar to those reported with conventional allergen immunotherapy and during the natural early-life development of tolerance to food allergens[50]. The majority of the studies reported that orally administered immunotherapy did not reduce allergen-specific IgE levels, and this was confirmed by the meta-analysis. The disparity in the ability of orally administered immunotherapy to reduce skin prick test reactivity to the responsible allergens while failing to reduce serum allergen-specific IgE levels may be a consequence of increased levels of allergen-specific IgG4 inhibiting IgE cross-linking by competing with IgE for the binding of allergens[51]. It is also possible that reduced skin prick test reactivity may be a consequence of the effects of orally administered immunotherapy on non-IgE components of the skin prick test, e.g. mast cells, or possibly the generation of IgE with a reduced binding affinity for the allergens.

Strengths and weaknesses of this work

We believe that this is the most comprehensive and detailed systematic review and meta-analysis on this subject ever

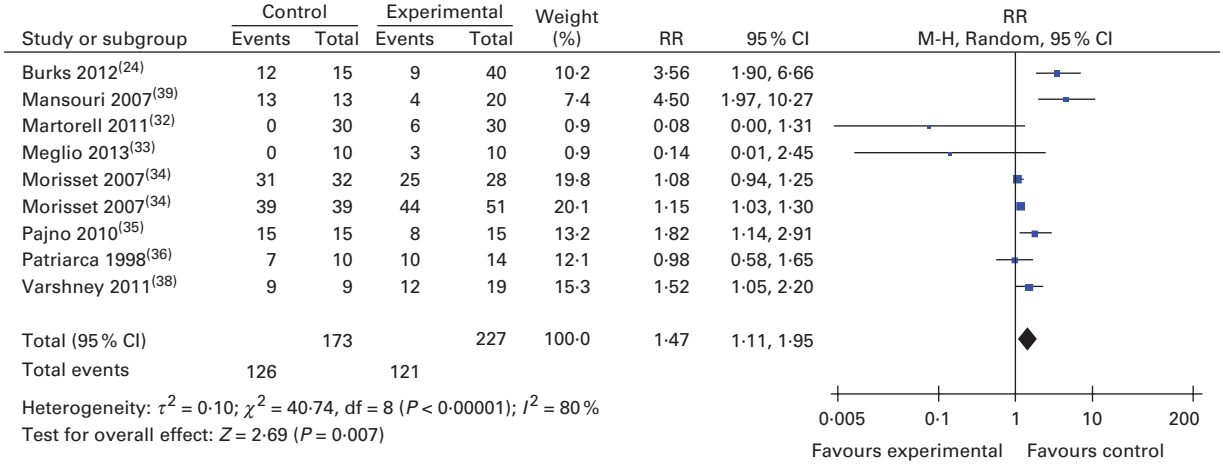

Fig. 10. Safety data – absence of local reactions during oral immunotherapy or sublingual immunotherapy for food allergy. RR, risk ratio. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn)

undertaken. This work has been conducted to international standards and, furthermore, has both drawn on a substantially greater evidence base and has considerable methodological strengths over previous reviews on this subject[20,43–49]. It provides a state-of-the-art overview of the experimental evidence on this clinically important subject together with detailed subgroup/sensitivity analyses based on allergy to specific foods, mode of immunotherapy and study design. The quality assessment acknowledged the inherent weakness of uncontrolled trials in young children with food allergy, whereby food allergies in early life naturally resolve as tolerance develops, e.g. cows' milk allergy.

The main potential limitations of this work stem from the heterogeneity of the populations, interventions and outcomes studied/reported on; it is, therefore, important that, in keeping with the random-effects meta-analyses employed, care be taken in interpreting the findings as average effects across studies. That said, our various subgroup and sensitivity analyses, with accompanying reductions in heterogeneity in some cases (see Fig. 2(b) and (c), Appendix 5, Figs. S1 and S4, available online), generated broadly comparable findings, which suggests that the overall conclusions are very likely to be robust. Although we found that orally administered immunotherapy is associated with an increased likelihood of relatively mild local side effects, because of inconsistencies in the definition and reporting, our meta-analyses of side effects were limited to a minority of studies and to a handful of studies at a low risk of bias. Clearly, further trials using standardised reporting of side effects are required to fully assess the risks associated with orally administered immunotherapy. A further limitation is the failure of some investigators to provide us with original data; however, the reported effects of immunotherapy in these studies are consistent with the results of our meta-analyses. Future studies also need to determine longer-term outcomes, as most studies to date have been short-term ones with less than 2 years of follow-up. Finally, we have uncovered data on ongoing studies, the findings of which will, once incorporated into our planned updates of this systematic review and meta-analysis, offer greater precision around the summary estimates.

Implications for clinical care and further research

In summary, orally administered immunotherapy for IgE-mediated food allergy is a promising re-emerging treatment approach, which has the potential to play an important disease-modifying role in people with a range of food allergies. Current treatment regimens are, however, associated with an increased risk of local reactions and possibly also more serious systemic reactions; therefore, orally administered immunotherapy is not suitable for use in routine clinical care and should not under any circumstances be considered as a self-administered treatment approach. There is a pressing need to develop safer treatment protocols and establish the longer-term effectiveness, safety and cost-effectiveness of this potentially curative treatment approach.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114513002353

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