**Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis**

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**Abstract**

**Background:** The European Academy of Allergy and Clinical Immunology (EAACI) is developing Guidelines for Allergen Immunotherapy (AIT) for IgE-mediated Food Allergy. To inform the development of clinical recommendations, we sought to critically assess evidence on the effectiveness, safety and cost-effectiveness of AIT in the management of food allergy.

**Methods:** We undertook a systematic review and meta-analysis that involved searching nine international electronic databases for randomized controlled trials (RCTs) and non-randomized studies (NRS). Eligible studies were independently assessed by two reviewers against pre-defined eligibility criteria. The quality of studies was assessed using the Cochrane Risk of Bias tool for RCTs and the Cochrane ACROBAT-NRS tool for quasi-RCTs. Random-effects meta-analyses were undertaken, with planned subgroup and sensitivity analyses.

**Results:** We identified 1814 potentially relevant papers from which we selected 31 eligible studies, comprising of 25 RCTs and six NRS, studying a total of 1259 patients. Twenty-five trials evaluated oral immunotherapy (OIT), five studies investigated sublingual immunotherapy (SLIT) and one study evaluated epicutaneous immunotherapy (EPIT). The majority of these studies were in children. Twenty-seven studies assessed desensitization and nine studies investigated sustained unresponsiveness post-discontinuation of AIT. Meta-analyses demonstrated a substantial benefit in terms of desensitization (risk ratio (RR)=0.16, 95%CI 0.10, 0.26) and sustained unresponsiveness (RR=0.29, 95%CI 0.08, 1.13). Only one study reported on disease-specific quality of life (QoL), which reported no comparative results between OIT and control group. Meta-analyses revealed that the risk of experiencing a systemic adverse reaction was higher in those receiving AIT, with a more marked increase in the risk of local adverse reactions. Sensitivity analysis excluding those studies judged to be at high risk of bias demonstrated the robustness of summary estimates of effectiveness and safety of AIT for food allergy. None of the studies reported data on health economic analyses.

**Conclusions:** AIT may be effective in raising the threshold of reactivity to a range of foods in children with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. It is however associated with a modest increased risk in serious systemic adverse reactions and a substantial increase in minor local adverse reactions. More data are needed in relation to adults, long term effects, the impact on QoL and the cost-effectiveness of AIT.

**Keywords:** Allergen, allergen immunotherapy, desensitization, food allergy, safety, sensitization, sustained unresponsiveness.

**BACKGROUND**

Food allergy may result in considerable morbidity and, in some cases, mortality.(1) Epidemiological studies have demonstrated that the prevalence and severity of food allergy may be increasing, particularly in children.(2-8) Food allergies can be divided into IgE-mediated acute allergic reactions manifesting as urticaria, vomiting, wheezing and anaphylaxis, and non-IgE-mediated food allergy which results from delayed, cell-mediated reactions. This systemic review is focused on IgE-mediated reactions.

Food allergies can be associated with significant reduction in disease specific quality of life (QoL) – both of individuals who suffer from food allergy and their family members.(9, 10) At present, avoidance measures are the cornerstone of management.(11) Difficulties in avoiding responsible food allergens can however result in accidental exposure and the risk of triggering potentially life-threatening anaphylaxis. Of concern is the increasing numbers of people being seen in emergency departments or who are hospitalized because of food-induced anaphylaxis.(12, 13) Individuals with food allergy therefore need to carry adrenaline (epinephrine) auto-injectors in order to self-manage anaphylaxis. This approach is however perceived as restrictive and still leaves patients at risk if accidental exposure occurs.(2, 7, 8)

Allergen immunotherapy (AIT) has been used for over a century to treat those with food allergy.(14) It involves repeated administration of gradually increasing doses of the antigens to which individuals are allergic in the hope of allowing safe exposure to the food(s) in question. Whilst AIT has become an established treatment regimen in relation to the management of, for example, pollen and insect venom allergy,(15) it has yet to become established in the routine management of food allergy.

The European Academy of Allergy and Clinical Immunology (EAACI) is in the process of developing the EAACI Guidelines for AIT, and this systematic review and meta-analysis is one of five inter-linked assessments of the current evidence base in relation to evaluating AIT for the treatment of food allergy, allergic rhinoconjunctivitis, venom allergy, allergic asthma and allergy prevention, which will be used to inform development of clinical recommendations. The focus of this review, which builds on our previous related reviews,(16, 17) is to assess the effectiveness, safety and cost-effectiveness of AIT in the management of IgE-mediated food allergy.

**METHODS**

Details of the methods employed in this review, including search terms and filters, databases searched, inclusion and exclusion criteria, data extraction and quality appraisal, have been previously reported.(18) We therefore confine ourselves here to a synopsis of the methods employed.

**Search strategy**

Nine international databases were searched for published material: Cochrane Library, which includes CENTRAL [Trials, Methods studies, Health Technology Assessments (HTA), Economic Evaluation database (EED)]; MEDLINE, EMBASE, ISI Web of Science, TRIP and CINAHL. The search strategy was developed on OVID MEDLINE and then adapted for the other databases (see Supporting Information - Appendix 1, search strategies 1 and 2). Our database searches covered from inception to March 31, 2016. The bibliographies of all eligible studies were scrutinized to identify additional possible studies. No language restrictions were imposed and where necessary manuscripts were translated into English.

**Inclusion criteria**

***Patient characteristics***

We focused on studies conducted on children and adults of any age with a clinician-diagnosed IgE-mediated food allergy to milk, eggs, peanuts, tree nuts and other foods with confirmation of allergic status through positive skin prick tests, specific-IgE and/or food challenge tests.

***Interventions of interest and comparators***

This review focused on AIT for different allergens, i.e. milk, eggs, tree nuts, peanuts and other foods, administered through the following routes: oral (OIT), sublingual (SLIT) and epicutaneous (EPIT). We were interested in studies comparing food allergy AIT with placebo or routine care (i.e. adrenaline auto-injector with or without antihistamines) or no treatment.

***Outcomes***

Our primary outcomes of interest were: 1) desensitization (i.e. the ability to safely consume foods containing the allergen in question while on AIT); 2) sustained unresponsiveness (i.e. the ability to safely consume foods containing the allergen in question after discontinuing AIT) at food challenge; and 3) changes in disease specific QoL using a validated instrument. Secondary outcome measures of interest were safety as assessed by local and systemic reactions in accordance with the World Allergy Organization’s (WAO) grading system of side-effects.(19, 20)

***Study designs***

We were interested in RCTs investigating the role of OIT, SLIT or EPIT in children and adults with IgE-mediated food allergy. However, given the likelihood that we would find only a limited number of RCTs, we also searched for non-randomized studies (NRS), these including non-randomized controlled clinical trials (CCTs), controlled before-and-after (CBA) studies and interrupted time series (ITS) analyses.

**Study selection**

All references were uploaded into the systematic review software DistillerSR. Titles and abstracts of identified studies were checked and independently reviewed by two researchers (UN, SD). The full text of all potentially eligible studies were assessed for eligibility against the eligibility criteria (UN, SA). Any disagreements were resolved through discussion, with SD or AS arbitrating if agreement could not be reached.

**Quality assessment strategy**

The quality of included RCTs was independently assessed by two reviewers (UN, SA) using the methods detailed in section eight of the Cochrane Handbook for Systematic Reviews of Interventions.(21) Critical appraisal of quasi-RCTs, CCTs was undertaken using the Cochrane ACROBAT tool for NRS.(22) An overall assessment of quality for each trial using these categories was arrived at through consensus discussion amongst reviewers.

**Data extraction, analysis and synthesis**

Data were independently extracted onto a customized data extraction sheet in DistillerSR by two reviewers (UN, SA) and any discrepancies were resolved by discussion or, if agreement could not be reached, by arbitration by a third reviewer (SD or AS).

Where possible and appropriate, data were synthesized using random-effects meta-analyses following the pre-specified analysis plan. For the assessment of safety, as there were a number of studies with zero reported outcomes, in order to facilitate meta-analyses we expressed safety data as the risk of not experiencing a local or systemic reaction. All analyses were undertaken using the software Comprehensive Meta-Analysis (version 3).

**Sensitivity, subgroup analyses, and assessment for publication bias**

Sensitivity analyses were undertaken by focusing on results from double-blind RCTs. Subgroup analyses were undertaken to compare:

* Diagnosis of food allergy was confirmed by double-blind, placebo-controlled, food challenge (DBPCFC) versus without DBPCFC
* Route of administration: OIT versus SLIT versus EPIT
* Children (0-17 years) versus adults (≥18 years)
* Type of AIT protocol: conventional versus rush
* Allergens used for AIT.

Where possible, publication bias was assessed through the creation of funnel plots in Comprehensive Meta-Analysis (version 3).

**Registration and reporting of this systematic review**

This systematic review was conducted and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) with registration number: CRD42016039384.

**RESULTS**

 Our searches identified 1814 potentially relevant papers, from which we identified 31 trials that satisfied our inclusion criteria studying a total of 1259 patients (Figure 1: PRISMA flow diagram). There were 25 RCTs (23-46) and six NRS’, all of which were CCTs.(47-52) Twenty-five of these trials investigated OIT(23-27, 30, 33, 35-50, 52), one epicutaneous immunotherapy (EPIT)(28) and the remaining five investigated SLIT.(29, 31, 32, 34, 51) One report included two independent RCTs on cow’s milk (CMA) and hen’s egg (HEA).(39) Sixteen studies focused on CMA,(25, 35-37, 39-44, 47-51) 11 on HEA,(24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51) seven on peanut,(23, 32, 34, 45, 46, 50, 52) one hazelnut,(29) two peach,(31, 50) three apple,(41, 50, 51) three fish,(41, 50, 51) and two other studies focused on a variety of food allergens including orange, corn, bean, lettuce,(50) wheat and bean(51) (see Table 1 and Supporting Information: Appendix 2, Table S1). The trials were undertaken in Italy (n=9), Spain (n=7), the USA (n=6), France (n=3), Australia (n=1), Finland (n=1), Germany (n=1), Iran (n=1), Korea (n=1), and the UK (n=1).

**Quality assessment**

Quality assessment of these studies revealed that eight of the RCTs were judged to be at low risk of bias;(24, 26, 32, 34, 36, 40, 45, 46) a further five RCTs were judged as at unclear risk of bias,(28, 31, 33, 37, 43) and the remaining 12 RCTs(23, 25, 27, 29, 30, 35, 38, 39, 41, 42, 44) were judged to be at high risk of bias (see Supporting Information: Appendix 3, Table S2). The six CCTs(47-52) were all judged to be at moderate risk of bias (see Supporting Information: Appendix 4, Table S3).

**Primary outcomes**

***Desensitization***

Desensitization was assessed in 18 OIT RCTs(23-27, 33, 35-43, 45, 46) and five OIT CCTs.(47-51) There were also four SLIT RCTs(29, 31, 32, 34) and one SLIT CCT(51) that assessed desensitization. The efficacy of AIT was compared with placebo in 12 studies, eight of which used OIT(24-26, 42, 43, 45, 46) and four of SLIT;(29, 31, 32, 34) the other 17 studies, all of OIT, employed routine care (i.e. food avoidance/strict elimination diet as the comparator).(27, 30, 33, 35-39, 41, 44, 47-52)

Meta-analysis was possible with data from 27 trials investigating a total of 1218 subjects; this revealed a substantial benefit with respect to desensitization: relative risk (RR)=0.16, 95%CI 0.10, 0.26; see Figure 2(a).(23-27, 29-41, 43, 44, 46-52)

Sensitivity analyses

Sensitivity analysis of the 21 RCTs, excluding the six CCTs, also demonstrated a substantial benefit: RR=0.21, 95%CI 0.13, 0.34; see Figure 2(b).(23-27, 29-41, 43, 44, 46) A further sensitivity analysis excluding all trials judged to be at high risk of bias confirmed this substantial benefit: RR=0.15, 95%CI 0.09, 0.25; see Figure 2(c)(24, 26, 31-34, 36, 37, 40, 43, 46-52) A further sensitivity analysis excluding all trials (whether OIT or SLIT) judged to be at high risk of bias demonstrated a substantial average risk reduction (RR OIT=0.17, 95%CI 0.11, 0.26);(24, 26, 33, 36, 37, 40, 43, 46-50) (RR SLIT=0.31, 95%CI 0.10, 0.98)(31, 32, 34) (see Supplementary Materials: Appendix 5, Figures S1 and S2).

A final sensitivity analysis focusing on studies in which desensitization was confirmed by DBPCFC after OIT or SLIT also revealed substantial benefits (RR 0.15, 95%CI 0.09, 0.27; see Supplementary Materials: Appendix 5, Figure S3).(23, 25-27, 29-31, 35-41, 43, 44, 47-52)

Subgroup analyses

* Subgroup analysis based on the route of administration of AIT (OIT versus SLIT) revealed that both OIT (RR=0.14, 95%CI 0.08, 0.24; see Figure 3)(23-27, 30, 33, 35-41, 43, 44, 46-50, 52) and SLIT were effective (RR=0.26, 95%CI 0.10, 0.64; see Figure 4).(29, 31, 32, 34, 51)
* A subgroup analysis based on the age of the population studied (children aged up to 18 years old, adults ≥18 years old and mixed population that included subjects 0-55 years old) revealed a substantial average risk reduction only for children and mixed populations, but not for adults studies (RR, children’s studies=0.16, 95%CI 0.09, 0.27)(23-27, 30, 32-41, 43, 44, 46-49),

(RR, adults studies=0.56, 95%CI 0.23, 1.36)(29, 31), (RR, mixed population=0.04, 95%CI 0.01, 0.19)(50-52) (see Supplementary Materials: Appendix 5, Figures S4, S5 and S6).

* Subgroup analysis based on the type of AIT protocol (conventional versus rush) also showed a substantial average risk reduction for both methods (RR, conventional protocol=0.12, 95%CI 0.07, 0.21);(23-27, 30, 32-35, 38, 40, 43, 44, 46, 47, 49-52) (RR, rush=0.33, 95%CI 0.16, 0.65)(29, 31, 36, 37, 39, 41, 48) (see Supplementary Materials: Appendix 5, Figures S7 and S8).
* Subgroup analyses of types of allergen demonstrated that in 13 trials investigating CMA, 11 HEA and four peanut allergy OIT/SLIT substantially reduced the risk of desensitization to CMA, HEA and peanut allergy (RR CM=0.12, 95%CI 0.06, 0.25);(25, 35-37, 39-41, 43, 44, 47-51) (RR HE=0.22, 95%CI 0.11, 0.45);(24, 26, 27, 30, 33, 38, 39, 41, 44, 50, 51) (RR peanut=0.11, 95%CI 0.04, 0.31)(23, 32, 34, 46) (see Supplementary Materials: Appendix 5, Figures S9, S10 and S11. A sensitivity analysis of the 17 OIT and four SLIT RCTs found a substantial average risk reduction (RR OIT=0.18, 95%CI 0.10, 0.32);(23-27, 30, 33, 35-41, 43, 44, 46) (RR SLIT=0.31, 95%CI 0.13, 0.76)(29, 31, 32, 34) (see Supplementary Materials: Appendix 5, Figures S12 and S13).

The Funnel plot revealed evidence of potential publication bias with fewer smaller, negative studies than expected (see Figure 5).

***Sustained unresponsiveness post-discontinuation of AIT***

There were seven OIT RCTs,(24, 26, 30, 33, 42, 44, 45) and two OIT CCTs(48, 52) that investigated the longer-term effects of AIT between two weeks and 36 months after discontinuation of AIT (see Table 1 and Appendix 2: Table S1). Meta-analysis revealed the benefits of OIT (RR=0.29, 95%CI 0.08, 1.13)(24, 26, 30, 33, 44, 48) (see Figure 6).

The Funnel plot also revealed evidence of potential publication bias with fewer smaller, negative studies than expected (see Figure 7).

***Disease specific quality of life***

Only one OIT RCT reported disease-specific QoL of patients and their families.(23) This study used a validated questionnaire for parents, the Food Allergy Quality of Life Questionnaire Parent Form (FAQLQ-PF) however no comparative results between OIT and the control group were reported at the end of the first phase of the study. Results are reported for the end of the second phase of the study at which time the control group had also received OIT.

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**Secondary Outcomes**

***Safety***

Systemic reactions

Data on the occurrence of systemic adverse reactions during AIT were available from 25 trials.(23-27, 29-31, 33, 35, 36, 39, 40, 42-51) (Table 1). However, there were different formats of reporting systemic reactions between trials, and we were therefore only able to pool data from seven studies.(26, 29, 31, 35, 40, 46, 49) Meta-analyses of *not* experiencing a systemic reactions was higher in those receiving control: RR=1.09, 95%CI 1.00, 1.19) (see Figure 8).(26, 29, 31, 35, 40, 46, 49).

Subgroup analysis demonstrated that the risk of experiencing a systemic reactions was higher in those receiving AIT (RR of *not* experiencing a reaction in controls=1.16, 95%CI 1.03, 1.30).(26, 35, 40, 46, 49) In contrast, data from two SLIT studies showed no difference between arms (RR of *not* experiencing a reaction in controls=0.98, 95%CI 0.85, 1.14)(29, 31) (see Supplementary Materials: Appendix 5, Figures S14 and S15 ).

Sensitivity analysis excluding all trials judged to be at high risk of bias after OIT or SLIT demonstrated either a borderline difference (RR of *not* experiencing a reaction in controls=1.10, 95%CI 0.99, 1.23)(26, 31, 40, 46, 49) or a significant difference in the rate of systemic reactions between the two arms after OIT (RR of *not* experiencing a reaction in controls=1.17, 95%CI 1.03, 1.33)(26, 40, 46, 49) (see Supplementary Materials -Appendix 5, Figures S16 and S17).

A subgroup analysis of CMA trials found that the risk of experiencing a systemic reactions was higher in the AIT arm (RR of *not* experiencing a reaction in controls=1.19, 95%CI 1.03, 1.37)(35, 40, 49) (see Supplementary Materials: Appendix 5, Figure S18). Subgroup analysis of systemic reactions during OIT from five children’s studies to cow’s milk, egg or peanut showed a significant difference between the two arms, however the pooled data from the two studies with adult populations using SLIT for peach or hazelnut allergy found no clear evidence of a difference in systemic reactions between the treatment arms and the control arms (RR of *not* experiencing a reaction in controls, children=1.16, 95%CI 1.03, 1.30);(26, 35, 40, 46, 49) (RR of *not* experiencing a reaction in controls, adult=0.98, 95% CI 0.85, 1.14)(29, 31) The lack of a significant effect in adults may reflect a lack of precision (as the point estimate suggests benefit), which in turn is a function of the paucity of large trials in adult populations.

 (see Supplementary Materials: Appendix 5, Figures S19 and S20).

Local reactions

Data on occurrenceof local adverse reactions during AIT (minor oropharyngeal/gastrointestinal/ perioral rash) were available from 28 trials.(23-31, 33, 35-51) (see Table 1). However, there were different formats of reporting reactions between trials, and we were therefore only able to pool data from nine studies. Meta-analyses of local reactions obtained from these nine trials demonstrated that AIT was associated with an increased risk of local reactions (RR of *not* experiencing a reaction in controls 2.12, 95%CI 1.50, 3.00)(24, 26, 35, 37-40, 49) (see Figure 9).

Subgroup analysis of local adverse events demonstrated higher risk of reactions in those receiving OIT (RR of *not* experiencing a reaction in controls=2.14, 95%CI 1.47, 3.12)(24, 26, 37-40, 49) (see Supplementary Materials: Appendix 5, Figure S21). A further sensitivity analysis excluding all trials judged to be at high risk of bias also showed an increased risk of local reactions in the treatment arms compared with the control arms (RR of *not* experiencing a reaction in controls=2.58, 95%CI 1.37, 4.89)(24, 26, 37, 40, 49) (see Supplementary Materials: Appendix 5, Figure S22). Local reactions during OIT from only RCTs subgroup analysis demonstrated higher risk of local reactions in the AIT group (RR of *not* experiencing a reaction in controls=2.08, 95%CI 1.43, 3.02)(24, 26, 35, 37-40) (see Supplementary Materials- Appendix 5, Figure S23). Another subgroup analysis of local reactions during OIT for CMA from either RCTs and CCTs or only RCTs also demonstrated increased risk of having local reactions in the AIT group (from RCTs and CCTs, RR of *not* experiencing a reaction in controls=3.48, 95%CI 1.89, 6.43);(35, 37, 39, 40, 49) (from RCTs, RR of *not* experiencing a reaction in controls=3.29, 95%CI 1.50, 7.23)(35, 37, 39, 40) (see Supplementary Materials: Appendix 5, Figures S24 and S25). Local reactions during OIT for HEA also found an increased risk of local reactions in the AIT arm (RR of *not* experiencing a reaction in controls=1.55, 95%CI 1.09, 2.22)(24, 26, 38, 39) (see Supplementary Materials: Appendix 5, Figure S26).

The effect of the AIT protocol (conventional versus rush) on the occurrence of local reactions during the treatment was available only from OIT trials. Both, conventional and rush AIT protocols demonstrated an increased risk of local reactions in the treatment arm compared with the controls (RR of *not* experiencing a reaction in controls, conventional=2.58, 95% CI 1.46, 4.55)(24, 26, 35, 38, 40, 49) (RR of *not* experiencing a reaction in controls, rush=2.23, 95% CI 0.57, 8.80)(37, 39)(see Supplementary Materials: Appendix 5, Figures S27 and S28).

***Health economic analysis***

None of the studies reported data on cost-effectiveness.

**DISCUSSION**

**Summary of main findings**

This systematic review and meta-analysis has found evidence that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT. This evidence comes mainly from studies in children and it is therefore still unclear if AIT is effective for adults. Pooling of the safety data demonstrated an increased risk of local and systemic reactions with AIT. No fatalities were reported during AIT. Only one study assessed QoL,(23) which reported no comparative results between OIT and the control group. We found no data investigating the cost-effectiveness of AIT in patients with food allergy.

**Strengths and limitations of this work**

We believe that this systematic review is the most robust investigation undertaken to date to support the use of AIT in children and adults with food allergy.(53-60) A key strength of our systematic review was the comprehensiveness of the searches. We carefully identified and scrutinized the characteristics of all possible terms, including MeSH, EMTREE and free keywords for different types of food allergy and AIT. In addition, we encompassed all available bodies of evidence from all randomized and NRS, with a range of planned subgroup and sensitivity analyses.

The main limitations of this systematic review stem from the heterogeneity of included populations, interventions, outcomes, diversity of AIT protocols and treatment modalities, and definition of outcomes (e.g. adverse reactions). Due to the heterogeneity of studies, the meta-analyses need to be interpreted with caution. In an attempt to account for this heterogeneity, we undertook random-effects meta-analyses which produce more conservative assessments of benefits than would have been obtained using fixed-effects meta-analyses. That said, this is an area that will warrant further exploration of the possible sources of heterogeneity in follow-on work. We were also limited by the lack of data on long-term adverse outcomes (e.g. eosinophilic eesophagitis) and lack of data on cost-effectiveness. Studies which were published after our cut-off date 31st March 2016 are not included in this review which may have provided additional evidence to support the effectiveness and safety of OIT.(61)

**Conclusions**

We found that AIT may be effective in raising the threshold of reactivity to a range of foods in patients with IgE-mediated food allergy whilst receiving (i.e. desensitization) and post-discontinuation of AIT, but was associated with an increased risk of local and systemic adverse events. Future trials need in particular to investigate the effectiveness of AIT in adults, long term effects,understand the impact of AIT on disease-specific QoL of patients and family members, and establish the cost-effectiveness of AIT for food allergy.

**Conflicts of interest:** U Nurmatov, no conflicts of interest; Sangeeta Dhami reports grants from EAACI to carry out the review; S Arasi reports other from Evidence-Based Health Care Ltd during the conduct of the study; G Pajno reports grants from Stallergenes during the conduct of the study; M Fernandez Rivas reports grants from European Union, grants from Instituto de Salud Carlos Ill, Ministerio de Ciencia, Espaha, grants from Ministerio de Economia, Espaha, personal fees from DBV, personal fees from Aimmune, Reacta Biotech, personal fees from ALK Abello, Merck, GSK, non-financial support from EAACI, personal fees and non-financial support from Fundaci6n SEAIC, other from Hospital Clinico San Carlos and Universidad Complutense de Madrid, outside the submitted work; In addition, Fernandez Rivas has a patent PT0042/2013 issued; A Muraro reports personal fees from Novartis , personal fees from Meda Mylan, outside the submitted work; G Roberts has a patent use of sublingual immunotherapy to prevent the development of allergy in at risk infants. issued and his University has received payments for activities he has undertaken giving expert advice to ALK, presenting at company symposia for ALK, Allergen Therapeutics and Meda plus as a member of an Independent Data Monitoring Committee for Merck; 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**Table 1. Description of the included studies (n=31)**

| **Study** **(First author, year, country)** | **Food allergen (s)** | **Route AIT** | **Comparator** | **Evidence of allergy (mandatory inclusion criteria)** | **Clinical outcomes** |
| --- | --- | --- | --- | --- | --- |
| **Cow's milk** | **Hen's egg** | **Peanut** | **Hazelnut** | **Peach**  | **Apple** | **Fish**  | **Other(s)** | **OIT** | **SLIT** | **EPIT** | **Placebo**  | **Routine care** **(food avoidance)** | **Desensitization** | **Sustained unresponsiveness** | **DR-QoL** | **Occurred AEs / medication use** |
| **Clinical history** |  **SPT &/ or sIgE** | **OFC** | **SBPCFC** | **DBPCFC** | **SRs** | **LRs** |
| **RCT (n=25)** |
| Anagnostou, 2014, UK |   |   | X |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X | X |   | X | X | X |
| Burks, 2012, USA |   | X |   |   |   |   |   |   | X |   |  | X |   | X | X |   |   |   | X | X |   | X | X |
| Caminiti, 2009, Italy | X |   |   |   |   |   |   |   | X |   |  | X  |   | X | X |   |   | X | X |   |   | X | X |
| Caminiti, 2015; Italy  |   | X |   |   |   |   |   |   | X |   |  | X |   | X | X |   |   | X | X | X |   | X | X |
| Dello Iacono, 2013, Italy |   | X |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X | X |   |   | X | X |
| Dupont, 2010, France | X |  |  |  |  |  |  |  |  |  | X | X |  | X | X | X |   |  | X |  |  | X | X |
| Enrique, 2005, Spain |   |   |   | X |   |   |   |   |   | Xⱡ |  | X |   | X | X |   |   | X | X |   |   | X | X |
| Escudero, 2015, Spain |   | X |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X |   | X |   | X | X |
| Fernandez-Rivas, 2009, Spain |   |   |   |   | X |   |   |   |   | X\* |  | X |   | X | X |   |   | X | X |   |   | X | X |
| Fleischer, 2012, USA |   |   | X |   |   |   |   |   |   | X |  | X |   |   |   |   |   |   | X |   |   |   |   |
| Fuentes-Aparicio, 2013, Spain |   | X |   |   |   |   |   |   | X |   |  |   | X | X | X | X |   |   | X | X |   | X | X |
| Kim, 2011, USA |   |   | X |   |   |   |   |   |   | X |  | X |   | X | X |   |   |   | X |   |   |   |   |
| Lee, 2013, Korea | X |   |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X | X |   |   | X | X |
| Longo, 2008, Italy | X |   |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X | X |   |   | X | X |
| Martorell, 2011, Spain  | X |   |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X | X |   |   |   | X |
| Meglio, 2013, Italy |   | X |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X | X |   |   |   | X |
| Morisset, 2007, France^ | X | X |   |   |   |   |   |   | X |   |  |   | X | X | X |   | X |   | X |   |   | X | X |
| Pajno, 2010, Italy | X |   |   |   |   |   |   |   | X  |   |  | X  |   | X  | X  |   |  | X  | X  |   |   |  X | X  |
| Patriarca, 1998, Italy | X | X |   |   |   | X | X |   | X |   |  |   | X | X | X |   |   | X | X |   |   |   | X |
| Salmivesi, 2012, Finland | X |   |   |   |   |   |   |   | X |   |  | X |   | X | X | X |   |   | X | X |   | X | X |
| Skripak, 2008, USA | X |   |   |   |   |   |   |   | X |   |  | X |   |   | X |   |   | X | X |   |   | X | X |
| Staden, 2007, Germany | X | X |   |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X |  | X |   | X | X |
| Tang, 2015, Australia |   |   | X |   |   |   |   |   | X¥ |   |  | X |   | X | X |   |   | X | X | X |   | X | X |
| Varshney, 2011, USA |   |   | X |   |   |   |   |   | X |   |  | X |   | X | X |   |   |   | X |   |   | X | X |
| **CCT (n=6)** |
| García-Ara, 2013, Spain | X |   |   |   |   |   |   |   | X |   |  |   | X | X | X | X |   |   | X |   |   | X | X |
| Martınez-Botas, 2015, Spain | X |  |  |  |  |  |  |  | X |  |  |  | X | X | X |  |  | X | X | X |  | X | X |
| Mansouri, 2007, Iran | X |   |   |   |   |   |   |   |  X |   |  |   |  X | X | X |   |   | X | X |   |   | X | X |
| Patriarca, 2003, Italy | X | X | X |   | X | X | X | X\*\* | X |   |  |   | X | X | X |   |   | X | X |   |   | X | X |
| Patriarca, 2007, Italy | X | X |  |   |  | X | X | X§ |  | X\*  |  |   | X | X | X |   |   | X | X |   |   | X | X |
| Syed, 2014, USA  |   |   | X |   |   |   |   |   | X |   |  |   | X | X | X |   |   | X |   | X |   | NR | NR |

***AE****, adverse event;* ***AIT****, allergen specific immunotherapy;* ***DR-QoL****, disease related quality of life;* ***LR****, local reaction;* ***NR****, not reported;* ***OIT****, oral immunotherapy;* ***OFC***, open food challenge; ***SLIT****, sublingual immunotherapy;* ***SR****, systemic reaction.*

ⱡ sublingual-discharge technique

\*sublingual-swallow technique

\*\* orange, corn, bean, lettuce

§ wheat, bean

¥ AIT and probiotics

^ one report that included two independent randomized controlled trials on cows’ milk and hens’ eggs

**Supplementary materials: Appendices**

Appendix 1: Search strategy

Appendix 2: Table S1. Detailed characteristics of included studies

Appendix 3: Table S2. Risk of bias assessment of RCTs

Appendix 4: Table S3. Risk of bias assessment of CCTs

Appendix 5: Additional forest plots (Figures S1 – S28)

Appendix 6: PRISMA checklist

**Appendix 1: Search strategy**

**Search strategy 1**

(MEDLINE, EMBASE)

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

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. Specific immunotherapy.mp.

22. Or/19-21

23. exp Intervention Studies/

24. Intervention Studies.mp.

25. Experimental stud\*.mp.

26. exp Clinical Trial/

27. Trial.mp.

28. Clinical Trial.mp.

29. exp Controlled Clinical Trial/

30. Controlled Clinical Trial.mp.

31. Randomi?ed Controlled Trial.mp.

32. Quasi-randomi?ed trial.mp.

33. Non-randomi?ed trial.mp.

34. exp Placebos/

35. Placebos.mp.

36. exp Random Allocation/

37. Random Allocation.mp.

38. exp Double-Blind Method/

39. Double-Blind Method.mp.

40. Double-Blind design.mp.

41. exp Single-Blind Method/

42. Single-Blind Method.mp.

43. Single-Blind design.mp.

44. Triple-Blind Method.mp.

45. Random\*.mp.

46. Exp.Case series/

47. (Case$ and series).tw.

48. Cost:.mp.

49. Cost effective:.mp.

50. Cost utility:.mp.

51. Exp Health care Costs/

52. (Costs and Costs Analysis).mp.

53. Economic evaluation\*.mp.

54. ((cost effective\* adj1 analys\*) or cost minimi?ation analys\* or cost benefit analys\* or cost utility analys\* or cost consequence analys\* or finances).mp.

55. Or/23-54

56. 8 and 22 and 55

**Search strategy 2**

(Cochrane Library, TRIP, CINAHL, ISI Web of Science, BIOSIS)

(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)

AND

(Intervention stud\* or experimental stud\* or trial or clinical trial\* or controlled clinical trial or randomi\* controlled trial or random allocation or single blind method or double blind method or triple blind method or random\* or case series or economic evaluation\* or cost effective\* analys\* or cost minimization analys\* or cost benefit analys\* or cost utility analys\* or cost consequence analys\* or finances)

**Appendix 2: Table S1. Detailed characteristics of included studies (n=31)**

| **Study** | **Partecipants characteristics/ diagnostic criteria** | **Design** | **Active group vs comparator** | **Food allergen(s)** | **Immunotherapy Protocol** | **Clinical outcomes** |
| --- | --- | --- | --- | --- | --- | --- |
| **OD** | **OT** | **DR-QoL** | **Adverse events / medication use** |
| **SRs** | **LRs** |
| **RCT (n =25)** |
| Anagnostou, 2014, UK | 99 pts (aged 7–16 yrs) of both sexes; [pt allocation: OIT (n =49); CG (n=50); pts under intervention: OIT (n =49); CG (n=47)]; pts analyzed: OIT (n=39); CG (n=46)] / Hx (+), SPT (+) to peanuts, and DBPCFC(+). | crossover RCT | OIT vs routine care (food avoidance) | peanut | *1st phase:* the AG underwent 26 wks of peanut OIT, and the CG 26 wks of peanut avoidance. At the end of the 1st phase (26 wks) all pts were assessed by DBPCFC.  *2nd phase:* pts in the CG still allergic to peanuts were offered peanut OIT, with a subsequent further DBPCFC. The OIT was given in daily doses of characterised light roast peanut flour. First, there was a gradual updosing phase with 2 wk increments to protein doses of 800 mg/day, and subsequently a maintenance period where the highest tolerated dose (with a target of 800 mg/day) was taken daily to complete a total of 26 wks OIT.Doses were: 2 mg, 5 mg, 12·5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg of peanut protein. Dose increments took place in clinical setting. The same dose was then given at home daily for 2–3 wks. | 1st phase: OD [= negative peanut DBPCFC (1.4g protein) at 6 mo]: 62% (24 of 39 pts; 95% CI 45–78) in the AG and none of the CG (0 of 46; 95% CI 0–9; p<0·001). 84% (95% CI 70–93)of AG tolerated daily ingestion of 0.8g protein (~ 5 peanuts). Median increase in peanut threshold after OIT: 1345 mg (range 45–1400; p<0·001) or 25.5 times (range 1·82–280; p<0·001). After the 2nd phase, 54% (95% CI 35–72) tolerated 1400 mg challenge (~10 peanuts) and 91% (95%CI 79–98) tolerated daily ingestion of 800 mg protein. |  | Statistically significant improvement after OIT (median change: 1·61; p<0·001) in DR -QoL score assessed by FAQLQ-PF. | Wheeze after 0·41% of doses (21 pts). I.m. E was used after 0·01% of doses (1 pt). Overall, 4 pts withdrew for frequent AEs: 2 in the AG in the 1st phase and 2 in the 2nd phase. | GI Sx were, collectively, the most common (31 pts nausea; 31 pts vomiting; 1 diarrhoea), then oral pruritus after 6.3% of doses (76 pts). |
| Burks, 2012, USA | 55 children (aged 5- 11 yrs, median age 7yrs) randomized in: AG (n= 40) and placebo group (n=15) / Hx (+); sIgE level > 5 kU/l (≥ 6 yrs), or > 12 kU/l (<5 yr old) | DBPCRCT | OIT vs placebo | egg (DEW) | Dose escalation (clinical research setting), build-up, and maintenance phases until the challenge at 10 mo (5g of DEW) were in DBPCRT. Open label thereafter. Placebo then discontinued, OIT group on maintenance until 22 mo.Children who successfully passed the 10g OFC at 22 mo discontinued OIT and avoided all egg consumption until 10 g (+whole cooked egg) OFC at 24 mo, to test for sustained uresponsiveness. Children who passed this OFC at 24 mo were placed on a diet with ad libitum egg consumption and were evaluated for continuation of sustained unresponsiveness at 30 mo and 36 mo. [Dose escalation: 1st dose 0.1 mg DEW doubled every 30 minutes up to 50 mg. The maximum tolerated single dose (minimum dose of 3 mg of DEW) was the starting dose for the build-up phase to be ingested daily at home. For pts whose maximal Day 1 dose was less than 50 mg, doses were doubled every 2 weeks up to 50 mg. After 50 mg, dosing was increased to 75 mg, and then dosing increased by 25% until 2 g of DEW was reached. The dose achieved at 10 mo was considered the maintenance dose. Pts who did not reach 306 mg by 10 mo were discontinued from dosing but were included in the endpoint analysis. After reaching their highest build-up dose (maximum 2 g), pts continued this dose daily for at least 2 mo before the month 10 OFC and egg OIT pts continued maintenance dosing through 22 mo. Per protocol, subjects not reaching a maintenance dose of 2 g by 10 mo were allowed to escalate to 2 g after the 10 month OFC.] | After 10 mo of therapy, none of the children who received placebo and 55% of those who received OIT passed the OFC and were considered to be desensitized. After 22 mo, 75% of children in the OIT group were desensitized.  | In the OIT group, 28% (11 of 40 children) passed the OFC at 24 mo and were considered to have sustained unresponsiveness. At 30 mo and 36 mo, all children who had passed the OFC at 24 mo were consuming HE. |   |   | AEs, 25.0% of 11,860 doses of OIT with egg and 3.9% of 4018 doses of placebo.Respiratory & skin AEs: 3.2% of 4018 placebo doses, 12.2% of 11860 OIT doses.Oral or pharyngeal AEs: 78% of OIT doses, 20% of placebo doses (p<0.001). After 10 mo, the rate of Sx in the OIT group decreased to 8.3% of 15,815 doses. |
| Caminiti, 2009, Italy | 13 children (8 male, aged 5- 10 yrs, mean age 8yrs): AG (n=10); placebo (soy formula, n=3) / Hx (+), SPT(+), SpIgE(+), DBPCFC (+) | RCT (DBPCRT for 6 pts; open fashion 7 pts) | OIT vs placebo | cow‘ s milk | The desensitization schedule started with one drop of whole CM diluted 1:25 every week, then doubled weekly until the 18th week to achieve an intake of 200 ml in ≈ 4 mo.All doses were administered at the clinic under medical supervision. | In the AG, 7 children achieved the maximum dose of 200 ml of milk; in 2 pts OD failed, because of severe AEs; 1 pt achieved a partial OD (64 ml of milk). The 3 control children receiving placebo still showed a positive OFC at the end of the study. |   |   | 1 child in the double-blind group stopped the OD as with 4 ml of CM had severe anaphylaxis (with shock) treated with i.m. E; AH; i.v. CS and gradually recovered.1 pt in the open group with 4 ml of CM had R, A, generalized U, and laryngeal edema; he received i.m. E and CS; oral AH; inhaled salbutamol and promptly recovered.1 pt achieved a partial tolerance because with the dose of 64 ml she developed U, angioedema, cough; i.m. AH and CS were introduced. | 1 pt in the double-blind group and 2 pts in the open study group had throat pruritis, gritty eyes, watery eyes, abdominal pain, transient erythema (face and hands); no medication has been taken |
| Caminiti, 2015, Italy  | 31 children of both sexes (aged 4-11 yrs) randomized to OIT with DEW (n= 17) or placebo (n =14). Of the 17 active pts (1 dropout), 16 achieved OD andstarted the 6-month egg-containing diet. / Hx (+), SPT (+) and sIgE (+), DBPCFC (+). None of the children had previously consumed baked eggs. | DBPCRT | OIT vs placebo | egg (DEW) |  The OIT procedure consisted of weekly administration, at the hospital clinic, of increasing dosages of DEW, diluted in sterile saline, starting with 0.1 mg. The dose was doubled every wk until wk 16, to achieve a cumulative dose of 4 g in approximately 4 mo. The placebo (corn flour, indistinguishable from active) was administered following the same protocol. |  Of the 17 active pts (1 dropout), 16 achieved OD and started the 6-month egg-containing diet.  | After 3-month of HE avoidance, 31% of the 16 pts that have achieved OD and performed the 6-month egg-containing diet remained tolerant. In the control group, only 1 passed the final OFC.  |   | During OD 1 pt failed OIT for SR (U, throat pruritus, R, A, vomiting). During HE-containing diet: 1 pt presented U, abdominal pain after exercise (1 cooked HE) and another wheezing and cough during upper respiratory infection (1 cooked HE). Both were tolerant after 3 mo of HE containing diet discontinuation  | During OD 1 pt presented erythema of face and hands (1.5 mg DEW) and another abdominal pain and diarrhea (3 mg DEW).  |
| Dello Iacono, 2013, Italy | 20 children (aged 5 - 11 yrs, median age 7. 7yrs; male 50%) were enrolled: OIT (n =10); routine care (n = 10) / Inclusion criteria: i) ≥ 1 anaphylactic reaction after accidental egg exposure within 12 mo of pre-enrolment; (ii) previous SPT/IgE positive for egg (iii) a positive DBPCFC at ≤0.9 ml of raw egg emulsion. | open RCT | OIT vs routine care (food avoidance) | (raw) egg | Initial day escalation phase: 1 drop of undiluted raw HE emulsion (0.015 ml) flavoured with vanilla and cacao in day hospital; Day 2-7 at home 1 drop. Build-up phase: OIT continued at home with gradually increasing doses mixed by the parents in the child’s breakfast (cow’s milk, soymilk, fruit juice or other) and 5 doubling doses in day hospital up to 40 ml (maintenance dose) over about 6 mo. | After 6 mo of OIT, no child could tolerate 40 ml of raw HE emulsion in a single dose as none reached the final dose of the protocol; 9/10 (90%) achieved partial OD (10-40ml), and 1/10 (10%) was able to ingest only 5 ml. None control pts achieved tolerance.The median maximal tolerated dose was 20 ml (range: 5–30 ml) in AG and 0.45ml (range: 0.225–1.8) in CG (p<0.0001). |   |   |   | All children in AG had AEs (53 AEs), none required E. In CG, 5 AEs in 4/10 pts. AG vs CG 23/53 vs 0/5 skin / respiratory, 21/53 vs 5/5 oral/GI. In the AG relative risk of incurring an AE: 4.96 (95% CI = 3.30–7.45). However, no significant differences in the severity of AEs between AG vs CG. |
| Dupont, 2010, France | 19 children [aged 10 months to 7.7 yrs (mean ± SD , 3.82 ± 2 yrs)] were randomized: OIT (n =10); placebo (n = 9) / Inclusion criteria: Hx (+), SPT (+) and / or sIgE (+), OFC (+). | DBPCRT | EPIT vs placebo | cow‘ s milk | Treatment consisted of three 48-hour applications of the epicutaneous devices (EDS) per wk (Viaskin; DBV Technologies SA, Paris, France) for 3 mons to the interscapular area. Active EDS contained 1 mg skimmed CM powder. Placebo contained 1 mg glucose.  | EPIT treatment tended to increase the cumulative tolerated dose during OFC (CTD) in the AG [ from a mean ± SD of 1.77 ± 2.98 mL at day 0 to 23.61 ± 28.61 mL at day 90 (P = .18)] but not in the CG (4.36 ± 5.87 mL at day 0 vs 5.44 ± 5.88 mL at day 90). The mean CTD incrementwas 12-fold in the AG vs 8% in CG (P =0.13). |  |  | 24 SRs occurred in the AG and 8 in the CG, (respiratory/ENTdisorders, p 0.9; gastrointestinaldisorders<.001). No anaphilaxis. No child interrupted treatment becauseof an AE, and none received epinephrine or was seen at the emergencydepartment or hospital. | Local AEs were reportedfor 4 children in the AG and 2 in the CG (p<.001).  |
| Enrique, 2005, Spain | 23 adults (aged 18 to 60, mean age 29.4) randomized into: AG (n=12) and placebo group (n=11); Hx(+), SPT(+), SpIgE(+), DBPCFC (+) | DBPCRT | SLIT (sublingual-dischargetechnique) vs placebo | hazelnut | A biologically standardized hazelnut extract, graded in 5 strengths (F0, F1, F2, F3, FA) in glycerosaline solution was used. Rush build-up phase All doses were administrated in a hospital setting (309 doses) and was completed in 4 days; doses were administered at 15 minute. Maximum dose (4th day) contained 188.15 µg of Cor a 1 and 121.9 µg of Cor a 8 (equal to 25 drops from the most concentrated vial). After the build-up phase, all pts followed the same daily maintenance schedule consisting of 5 drops of the maximum concentration performed at home (1157 doses). Total doses administered 1466. | Mean hazelnut quantity provoking objective Sx increased from 2.29 g to 11.56 g (P=0.02) into AG vs 3.49g to 4.14g (placebo; NS). Almost 50% of pts into AG reached the highest dose (20 g); 9% in the CG. |   |   | SRs 0.2% (3 AEs/ 1466 doses); they occurred during build-up phase and only AH were used; 1 facial U occurred in the CG and 2 AEs in 1 pt of the AG (skin pruritis and delayed U). | LRs: immediate oral itching were observed in 7.4% (109 reactions/ 1466 doses); during build-up phase, 4 pts in the AG: abdominal pain several hours after the ingestion on 1 occasion each. All LRs during maintenance phase were also oral itching, and all were in the same pt. |
| Escudero, 2015, Spain | 61 pts [63 % male (73% in AG and 52% in CG) aged 5- 17 yrs, (median, 8 yrs; IQR, 6 yrs)] randomized into: OIT group (n=30) and CG (n=31) / Hx (+), SPT(+), SpIgE(+), DBPCFC (+) | RCT | OIT vs routine care | egg | Initial day dose escalation phase: in 1 day administration of 0.08, 0.2, 0.3, 0.5, 1, 2, 5, 9, 17, 35, 70 and 140 mg of EW protein (cumulative dose 280 mg) at intervals of 20 minutes. Build-up phase: increasing doses of 0.02, 0.3, 3, 14, 68, 188, 352, 1404 mg and 2808 mg of EW protein on aweekly basis. Maintenance phase, consisting in eating at least one undercooked egg (fried egg, scrambled or undercooked omelette) compulsory every 48 hours. Moreover, during this phase, the pt could freely take any other foodstuffs containing raw, cooked or heated egg (i.e. candies, sauces and ice cream).After 3 mo of AIT, children who completed egg-OIT avoided egg for 1 month. At 4 mo, both groups underwent a DBPCFC. OITG pts who passed this challenge were instructed to add egg to their diet ad libitum. |   | At 4 mo, 37% (11/30) of AG pts passed the DBPCFC, vs 3% (1/31) in CG (95% CI for the difference in the response rate, 14 to 51%; P = 0.003). The AG pts (n=14) who did not pass DBPCFC at 4 mo increased their threshold mean dose from 100.8 mg EW protein (SD, 96.3 mg) at baseline to 481.3 mg (SD, 417.5 mg) at 4 mo (P = 0.002). The latter was significantly higher than in CG (mean 256.2 mg, SD 425.3 mg) (P = 0.02). CG pts showed a non-significant increase in their threshold from baseline (mean 218.3 mg, SD 405.5 mg) to 4 mo (mean 256.2 mg, SD 425.3 mg) (P = 0.41). |   | E treatment only in 1 pt during build-up phase (0.04% of all AEs) |  145 AEs during OIT in 70% (21/30) of pts. [n (%)]: 21 (14.5%) in the initial-day dose escalation phase; 79 (54.5%) in build-up phase; and 45 (31%), in maintenance phase. They were overall mild unless 1 case. Symptom type [n (%)]: Generalized U (0.3%); R 32 (1.3%); Respiratory Distress 5 (0.2%); GI 97 (4%). |
| Fernandez-Rivas, 2009, Spain | 56 adult pts (aged 18-65 yrs) randomised into: active group [(n=37) (a Pru p 3 quantified peach extract)] or placebo group [(n=19) (similar solution without peach allergen)] / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | DBPCRT | SLIT vs placebo  | peach | The treatment was administered sublingually (sublingual-swallow technique) and comprised 4 vials containing 0.4, 2, 10 and 50 µg/ml of Pru p 3 or placebo. Rush build-up phase in hospital (Total daily dose of Pru p 3 in μg): 1st day – 3 doses (0.22 μg) of Pru p 3; 2nd day – 3 doses (1.12 μg); 3rd day – 3 doses (5.60 μg); 4th day – 3 doses (28.0 μg); 5th day – 1 dose (50 μg). Home maintenance (6 mo) Monday, Wednesday and Friday 1 dose of Pru p 3 peach extract (10.0 μg); pts visited the clinics once a month. | DBPCFC with peach (after 6 mo): the AG tolerated a significantly higher amount of peach (3 to 9 fold, needed to induce LR or SR, respectively); inter group differences at T6mo for SR were almost significant (Log Rank test, P=0.06). No significant changes were observed within CG. |   |   | Active group: 16 SRs: 14 in the build-up phase (6 pts skin AEs, 1 RC, 7 GI complaints)]; 2 during the hospital maintenance wk [1 RC and 1 GI complaints]. All SRs were mild and subsided either spontaneously or with oral AH, antacids and/or omeprazole. Placebo group: 3 SRs 1 in the build-up phase (cutaneous itching), and 2 in the first maintenance wk (1 angioedema and 1 diarrhea) | From a total of 1480 AEs recorded, 1356 were assessed by the investigators as probably and/ or possibly related to the treatment: 1344 in the AG, and 12 in the PG (P <.0001).No serious AEs were reported during the trial.AG: LRs 98.8% (n=1328); mostly during build-up phase and the 1st maintenance wk (P=0.014); 94.9% (n=1260) located on the oropharynx, others GI complaints. |
| Fleischer, 2012, USA | 40 subjects (male 68%) aged 12 to 37 yrs (median age, 15yrs) randomized into AG (n= 20) or placebo (n =20). / Hx(+),peanut SPT (+) (wheal diameter >3mm) or detectable peanut-sIgE (>0.35 kUA/L), DBPCFC (+) (objective allergic Sx at a cumulative dose of <2 g of peanut powder). | DBPCRT, multicentre trial | SLIT vs placebo  | peanut | Phase 1 Build-up phase: Dosing started at 0.000165 µg of peanut protein or placebo escalation through 660 µg occurred every 2 wks, 660µg attained at 12 wks. 3 doses attempted at a minimal interval of 30 minutes. If pts failed 3- dose escalations after 3 consecutive biweekly attempts, 1- or 2-dose biweekly escalations were allowed subsequently.After each observed dose, pts continued the same daily dose at home for 2 wks. After 660 µg was achieved, single dose increases occurred, followed by 2 wks of maintenance therapy of 1,386 µg/d. Pts took a minimum dose of 165µg and a maximum maintenance dose of 1386 µg of peanut protein or placebo (420µl) at home on a daily basis for the maintenance period until the wk 44.Unblinding 5-g DBPCFC. After unblinding, pts receiving active peanut SLIT continued on maintenance dosing with a 10-g OFC after approximately 1 yr of maintenance therapy.Phase 2 Placebo pts crossed over to active peanut SLIT and were escalated to a maximum maintenance dose of 3696mg (1120µl). A 5g crossover OFC was performed after 44 wks of SLIT. | Week 44 Unblinding OFC). Pts successfully consuming 5 g or at least 10-fold more peanut powder than the baseline OFC threshold were considered responders: 70% (n=14) in the AG vs 15% in the CG (p<0.001).The median successfully consumed dose (SCD) at Week 44 was significantly higher than the baseline OFC for AG pts (371 vs 21 mg, respectively; P <.01) but not for CG pts (146 vs 71 mg, respectively; P =.14). However, the median SCD after 44 wks of therapy was not significantly different between treatment groups (P=0.16).All Week 44 responders still being followed were Week 68 responders. The median SCD increased to 996 mg, and this was significantly higher than at Wk 44 (P =.05) and baseline (P =.009) |   |   | Only 1 out of 127 AEs required E and oral antihistamine. | Only 127 (1.1%) of 11,854 total doses required treatment during the 1st phase: 125 (1.1%), oral AH only; 1 (0.01%), albuterol only. |
| Fuentes-Aparicio, 2013, Spain | 72 pts (aged 4-15 yrs) randomly assigned to OIT (n = 40) or elimination diet (n = 32) / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | RCT | OIT vs routine care (food avoidance) | egg [powdered pasteurised egg] | On the 1st day, fractionated doses of powdered pasteurized egg mixed with juice or milkshakes were administered until reaching 31 mg of egg, beginning with 1 mg and continuing with 3, 9, and 18 mg at 30 min intervals. On the 2nd day, 30 mg in one single dose was administered, with the treatment continuing at home at this same dosage. Subsequently, weekly increases were made in the clinic until 10 g of powdered egg, the equivalent of one egg, was reached.The procedure’s average duration was 10 wks (range 4-28 wks). Then, 2 eggs/week were administrated at home. A month after finishing the treatment the pts were contacted by telephone and if they had good OD they were recommended a normal (non egg-free) diet. The pts had follow-ups at the clinic 6 and 12 mo after achieving OD. An OFC with raw egg white in the OIT group after 6 mo from the end of OIT.  | 37 out of 40 children finished the OIT, 2 pts were withdrawn from the study due to repeated GI Sx doses. Another pt was withdrawn with 500 mg due to suspected and later confirmed eosinophilic oesophagitis. No withdrawals in the CG. After 6 mo from the end of OIT, 32 pts (92.5%) in the AG passed OFC with raw egg white vs 21.8% in the CG (natural resolution). |  |   | 3 pts out of 40 in the AG were withdrawn from the protocol for persistent GI Sx. During OIT, 21 pts (52.5%) presented AEs. In 13 (61.90%), the AEs were moderate- severe, resulting in doses having to be repeated, and in 5 cases E was needed. During the OFC, AEs were severe in 9 (33.4%) and in 10 (40%) and E used in 6 (22.3%) and 7 (28%) in the AG and CG, respectively.  | During OIT, in 8 pts in the OIT group the AEs were mild and required no treatment. During the OFC, AEs were mild in 6 (22.3%) and 4 pts (16%) and moderate in 12 (44.5%) and in 11 (44%) in the AG and CG, respectively.  |
| Kim, 2011, USA | 18 children (aged 1 - 11 yrs) were randomized into: AG(n =11) and CG (n=7). / Hx (+), sIgE > 7 kU/L | DBPCRT | SLIT vs placebo  | peanut | All observed dosing was performed in the hospital. AG received dilutions of crude peanut extract (1:20 wt/vol) dissolved in 0.2% phenol and 50% to 55% glycerinated saline (max peanut concentration 5000 μg/ml. CG received a glycerinated saline solution + phenol with caramel coloring (doses 1 to 8 pumps (50 μL per pump).The first day the starting dose was 0.25 μg of peanut protein (1 pump of 1:1000 dilution). Subjects then returned for 13 biweekly observed dose-escalation visits. After each observed dose escalation, pts continued the same dose daily at home for 2 wks. When the maintenance dose reached 2000- μg of peanut protein (8 pumps of 1:1 stock dilution) , pts continued daily maintenance dosing at home for approximately 6 mo. | At the 12- month- DBPCFC, in AG, all 11 pts had a significant increase in reaction threshold after safely ingesting a median cumulative dose of 1710 mg of peanut protein (a 20-fold greater amount of peanut protein and approximately equivalent to 6-7 peanuts). In CG, the 7 pts only safely ingested a median cumulative dose of 85 mg (<1 peanut), (OD: AG vs CG, p=0.011)  |   |   | One (0.02%) pt had mild wheezing which required albuterol. No E required for whole study.  | AEs were reported with 11.5% of peanut doses and 8.6% of placebo doses. Skin Sx: 0.6% in AG, 6.5% in CG. In AG most of the Sx were transient oropharyngeal itching (9.3%), whereas skin itching was most common in CG (6.5%). Of the 4182 active peanut doses, 11 (0.26%) home doses required AH.No placebo doses required AH or albuterol treatment. |
| Lee, 2013, Korea | 31 infants (7 to 12 mo old) randomly assigned to OIT (n = 16) or elimination diet (n =15) and evaluated 6 mo later. 26 pts concluded the study [OIT (n =14); routine care (n=12)] / Hx (+), SPT (+) to CM, and DBPCFC(+).  | RCT | OIT vs routine care (food avoidance) | cow‘ s milk | The initial build-up phase took place in the hospital, with a rapid increase in CM dosage every 30 minutes from 0.5 ml to a maximum of 2 mL of CM. Thereafter, pts began home dosing with 2 mL of CM. Doses were increased at home every wk or decreased based on the frequency and severity of AEs (minimum duration: 22 wks) up to 200 ml. Families connected to the 2 groups were contacted by regular clinic visits and instructed to phone the study physicians in the event of any AEs. | 14 of 16 pts receiving OIT could accept daily doses of 200 mL of CM, whereas all but 3 dropout pts receiving the elimination diet still showed allergic Sx at the follow-up OFC. |   |   | Only 2 pts, both in the OIT group, presented severe AEs during the initial build-up phase, which resulted in their early withdrawal.  | 12 of 14 pts (85.7%) in the OIT group presented Sx with at least 1 dose. These Sx never occurred after the pts reached 50 mL of CM. All Sx were mild and local AEs, mainly in the form of immediate rash around the month, increased pruritus, or single wheals. In the CG, 3 of 12 pts (25.0%) had mild AEs, probably caused by accidental exposure to CM, and easily recovered without treatment or after the use of oral AH. |
| Longo, 2008, Italy | 60 children randomized in OIT group (n=30, mean age 7.9 yrs) and milk –free diet (n=30, mean age 8.1 yrs); Hx of severe CM-induced SRs (+), SPT(+), sIgE (+), DBPCFC (+).  | RCT | OIT vs routine care (food avoidance) | cow‘ s milk | OIT had 2 phases: the 1st (rush phase) took place in the hospital for 10 days. 1st day: 6 doses of diluted milk at 1-hour intervals; second, third, and fourth day: 4 doses of diluted milk at 2-hour intervals; and then 3 daily doses at 2-hour intervals, increasing the concentration of the solution each day to reach whole milk (up to 20 ml, cumulative dose 49 ml pure CM in the 10th day). All children were given AH daily (oxatomide, 1 mg/kg per day). After discharging from hospital children followed a slow increasing phase (increasing by 1 ml every second day) personalized for each pt, on the basis of the frequency and severity of AEs and confidence of parents; when home dosing reached 150 ml of whole milk in a single dose, the pts were asked to eat other dairy products. AH continued at home as well until they reached 150 ml of milk, and then reduced within 4 wks. OIT was considered to have failed if the child did not reach at least 5 ml of undiluted milk in a single dose after 1 yr or if pts were stopped for AEs. | After 1 yr of OIT, in the AG: 11 (36%) pts achieved a daily intake of CM > 150 mL, many of them with the addition of different dairy products, enough to permit an unrestricted diet; 16 (54%) were able to take a limited amount of CM (5 to 150 mL), and 3 (10%) were not able to continue in the study because of AEs. In CG, no subject after a yr reached spontaneous tolerance to CM (positive DBPCFC). [Efficacy of OIT, AG vs CG: P < .001] |  |   | In the rush phase: i.m. E 4 times in 4 children, nebulized E in 18 children and more than once in 7 pts for recurring respiratory Sx.Slow (home) dosing: 2 pts required treatment in the emergency department (oral CS, AH, and i.m. E (1 case). | In AG, almost all pts presented with 1 or more allergic Sx, mainly cutaneous (U and angioedema) or abdominal. In CG, 6 (20%) pts had mild AEs (accidental exposure). |
| Martorell, 2011, Spain | 60 children (aged 24-36 mo) randomized into: OIT group (n =30) or CG (n=30)/ Hx (+), SPT(+), sIgE (+), DBPCFC (+). | parallel-group, multicentre RCT | OIT vs routine care (food avoidance) | cow‘ s milk | *Day 1* in hospital: doses hourly; milk doses (ml): A) dilution 1/100: 1,2,3,4,8; B) Dilution 1/10: 1.6 ml. *Day 2* in hospital: milk doses (ml): A) dilution 1/10, doses hourly: 1.6, 3.2; 6;12 ml and B) pure milk: 2.5 ml;*Dose maintained* at home, with elevation once a week in hospital (total 16 wks) from 4 up to 200ml of pure CM.*At the end of the study,* OD was offered to the pts in the AG who had not achieved tolerance | After 1-yr follow-up period, 90% of pts in AG were desensitized. 1 pt abandoned the study as a result of moving house before reaching the maximum dose. Another pt abandoned the study due to poor tolerance of the OD protocol (U, RC, cough and wheezing on reaching the 2.5 ml dose), while partial OD was achieved in another pt (35mL of milk) In the CG, after 12 mo of follow-up, DBPCFC wasperformed in 23 /30 pts and proved negative in 3 (23%, natural tolerance) |  |   | None | 24 pts in AG (80%) [14 moderate (47%) and 10 mild (33%) reaction]. The most common manifestations were U-angioedema, followed by cough. |
| Meglio, 2013, Italy | 20 children (median age 8.4 ys) allergy randomized into: OIT group (n=10) or control group (n =10). / Hx (+), SPT(+), sIgE (+), DBPCFC (+) unless convincing history of life-treatening AEs after minimal amount of HE | open RCT | OIT vs routine care (food avoidance) | egg | Initial day escalation phase: Started from 1 drop (mixed raw egg white and yolk) diluted 1:100 with water, corresponding to 0.27 mg of HE proteins. This dose was administered in hospital; the following by parents at home. Build-up phase: The HE doses were doubled every 8 days until day 80. Subsequently, the HE doses were doubled every 16 days to achieve a total daily intake of 25 ml in 6 mo. Children underwent 0.25 mg/kg/day cetirizine per os during the study. | 8/10 children (80%) in the AG achieved the daily intake of 25 ml over a 6-month period (p < 0.01, in comparison to CG). 1 child (10%) could tolerate up to 2 ml/day while another child (10%) failed the desensitisation. 2 children (20%) in the CG could tolerate HE after 6 mo since the enrollment spontaneously |  |   |   | 3 of 10 pts in AG reached the full dose without any AEs. 6/10 children during the OIT presented some mild Sx, which started shortly after ingesting HE, persisted for <2 h and resolved spontaneously. 1/10 child had U and pruritus around 3 ml of raw HE and the treatment was stopped.  |
| Morisset, 2007, France | CMA: 57 pts (mean age 2.2 ± 1 yrs, range 13 mo - 6.5 yrs) randomized to AG (n=27) and CG (n=30) for 6 mo;HE allergy: AG (n=49, mean age 3.5 yrs); CG (n=35, mean age 3.6 yrs) ) / Hx (+), SPT(+), sIgE (+), DBPCFC (+) | RCT | OIT vs routine care (food avoidance) | cow´s milk and hen´s egg |  OD protocol using whole pasteurized milk: 1st wk from 1 ml (day 1 ) to 20 ml (day 5-7); 2nd wk 50 ml/day; 3rd wk 100 ml/day; 4th wk 100 ml/day and introduction of cream desserts, yoghurts or cream cheese; 5th and 6th wk 250 ml/day and dairy products; 7th wk and thereafter: routine amounts, not quantified.OD protocol with hard-boiled eggs: 1st wk 1 g of egg yolk once a day, every day; 2nd wk 1 g of yolk and 1 g EW once a day, every day;3rd wk 2 g of yolk and 2 g of EW once a day, every other day; 4th wk 4 g of yolk and 4 g of EW once a day, every other day; 2nd month: introduction of biscuits and crackers, etc; 3rd month: introduction of flans, cream desserts | CM: A SBPCFC (up to 200 ml of milk) was positive in 11.1% (3/27) of those following OD vs 40% (12/32) in CG (p<0.025) after 6 mo. HE: A SBPCFC (up to 7 mg of raw egg white) was positive in 30.6% (15/49) of those following OD vs 48.6% (17/35) in CG (p<0.1) after 6 mo.  |   |   | Unclear reporting  |
| Pajno, 2010, Italy | 30 children (aged 4 - 10 yrs) randomized in: AG (milk, n=15); and CG (soy, n=15) / Hx (+), SPT (+), sIgE (+), DBPCFC (+)  | Randomised single-blind controlled study | OIT vs placebo  | cow´s milk | Fresh CM or soy formula was administered at the clinic at weekly intervals at increasing doses. The initial dose started from 1 drop of whole milk diluted 1:25. The dose was doubled every week at the clinic until week 18 to achieve an intake of 200 ml. | 10 pts in the AG achieved full tolerance to CM (200 ml) and in 1 pt partial tolerance (100 mL) [10/13 tolerance on protocol, 10/15 on intention to treat] |  |   | In 2 pts SRs (requiriring epinephine) occurred and then stopped OIT. | 7 pts had mild AEs (abdominal pain, throat pruritis, gritty eyes) . They were transient (and only in 1 case AH were given) |
| Patriarca, 1998, Italy | OIT group: n=14; 4-14 yrs old, median age 5.5 yrs; 6/14 male (43%).1 female entered 3 times when desensitized to milk, egg, fish. Hence 24 pts in trial from 22 individuals.Controls: (n=10) aged 5-13 yrs (median 7.5yrs); 6/10 male (60%) / Hx (+), SPT (+), sIgE (+), DBPCFC (+) (unless one who had Hx positive for life threatening reaction) | RCT | OIT vs routine care (food avoidance) | CM [OIT:n =6 (43%); CG: n=5 (50%)];Egg [OIT n =5 (36%); CG: n=4 (40%)];Fish [OIT: n =2 (14%); CG: n=1 (10%)];Apple [OIT: n = 1 (7%); CG: n=0 (0%)] | *Initial day escalation phase:* Pure Milk 10 drops 10 ml; days 1-12, 4 drops increased to 12/day;Pure shaken Egg 10 drops egg in 100 ml water; days 1-20 4 drops to 36 drops x 3;Fish (boiled cod)10 ml 6% fish extract in 90 ml water; days 1 to 24 4 drops to 108 drops;Apple (pure apple mix)1 ml apple mixed in 9 ml water; days 1 to 34 1 drop x 2 to 6 drops x4;*Build-up phase:*Pure Milk 13 to 104 drops 1 drop milk to 30 ml x4;Pure shaken Egg 21 to 90 1 drop to 30 ml x 3;Fish (boiled cod)25 to 120 15 drops 6% extract to 200 g boiled fish/day;Apple (pure apple mix) 35 to 109 1 drop apple mix to 1 apple a day;*Maintenance phase* (4 mo): Pure Milk 100 ml 2-3x/week;Pure shaken Egg 1 egg 2-3 x/week;Fish (boiled cod) 200 g boiled/week; Apple (pure apple mix) 1- 2x/week. | In OIT group, 12/14 (86%) successfully able to eat any foods without problems in 3-6 yr- long follow-up; 2 failures due to attendance.In CG all DBPCFC at 6 mo were positive, as well as SPT and sIgE at 6 mo (OD, AG vs CG, P<0.0001) |   |   | None | In AG: 6/14 U, 2 asthma, 1 angioedema, 2 abdominal pain, 4 none; all AEs were mild and easily controlled by AH |
| Salmivesi, 2012, Finland | 28 children (aged 6-14 yrs) randomized into 2 groups: AG (n=18) and CG (n=10) / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | DBPCRT | OIT vs placebo  | cow‘ s milk | Build up phase The 1st dose (0.06 mg) and 8 later doses were given in the outpt clinic. The amount of milk protein (pasteurized 2.5% fresh milk) increased daily doubled every wk, from 0.06 to 6400 mg. The final dose of 6400 mg was given at home on day 162, and control visit was held within 2 wks, all other dose increases were performed at home according to a prospective, daily schedule. Mantainance phase Then the AG pts who had completed the OIT protocol totally or partially, continued daily CM use, either 200 mL or CM products (6400 mg milk protein ) or a lower amount reached during OIT. All 10 children in the CG successfully completed an open-lable OIT by an identical protocol placebo (oat milk, rice milk or soy milk, depending on the allergy status of the child) | 24 (86%) pts completed the protocol: 16/18 in AG and 8/10 in CG.After OIT: 14 children tolerated 6400 mg, and other two 960 and 1920 mg | Before OIT none, after open label OIT all children in the previous placebo group tolerated 200 ml milk. |   | During the OD period, in the AG: wheezing in 5 pts (19.2%) but no emergency rooms were needed. Follow-up 3.0-3.5 yrs later: one child had stopped using diary products because of severe eczema and severe A; 1 anaphylactic reaction took place when CM avoidance was restored. | AG: subjective abdominal and oral Sx; CG: subjective abdominal and oral Sx |
| Skripak, 2008, USA | 20 pts (aged 6 to 21 yrs) randomized into: AG (n=13; male 8, mean age and SD 9.3 ± 3.3 from the pediatric clinics) and placebo group (n=7, male 4, mean age and SD 10.2 ± 3.3) / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | DBPCRT | OIT vs placebo  | cow‘ s milk |  *On the first day* of treatment, a dose escalation was initiated in the hospital with 0.4 mg of milk protein (dry non-fat powdered milk); doubling doses were given every 30 minutes to a maximum of 50 mg (cumulative dose, 98.7 mg); pts had to tolerate a minimum dose of 12 mg (cumulative dose, 23.7 mg) to proceed with home dosing. *Build up phase* Home dose was initiated at the highest dose tolerated on the dose escalation day. After 7 to 14 days on a given dose, pts returned to the hospital to receive a dose increase. *Maintenance phase* Once a dose of 5g (equivalent to 15 ml of milk) was achieved, they continued on that dose daily for 13 wks, after which they underwent DBPCFC.  | The median milk threshold dose in both groups was 40 mg at the baseline DBPCFC, after OIT in the AG, 12/13 patient reached OD. Tthe median cumulative dose inducing a reaction was 5140 mg (range 2540-8140); all pts in the PG reacted at 40 mg (OD, AG vs CG: P=0.0003) |   |   | Among 2437 active OIT doses vs 1193 placebo doses, there were 1107 (45.4%) vs 134 (11.2%) total AEs; SRs (GI, lower respiratory tract, and skin Sx) were rare, occurring with a median frequency of 1% of active doses vs. none in the placebo group (P=0.01)Skin AEs 0.9% vs. 0.1% (p=0.1)Respiratory 8.1% vs. 2.3% (p=0.3) | LRs (oral pruritis, abdominal pain) with a median frequency of 16% and 2% of active doses, respectively (P= 0.006 and 0.02, respectively) |
| Staden, 2007, Germany | 45 children (29 male, median age 2.5 yrs, range 0.6-12.9 yrs) randomized in 2 groups: OIT group (CM n=14, HE n=11) and CG (CM: n=10; HE: n=10). / Hx (+), SPT (+), sIgE (+), DBPCFC (+)[47 recruited, 45 reported, 2 lost to follow up or failed to start] | RCT | OIT vs routine care (food avoidance) | cow‘ s milk and hen´s egg | OIT was carried out at home. Induction phase: CM starting dose: 0.02 mg CM protein from 3.5% fresh pasteurized CM; HE - starting dose: 0.006 mg lyophilized HE protein. Build-up phase: Doses were increased according to the individual tolerance to a maximum dose of 8250 mg CM protein (250 ml CM) or 2800 mg HE protein (around ½ HE). Median period to reach the mantainance dose 7 mo. Maintenance phase: a minimum daily maintenance dose of 3300 mg CM protein (100 ml CM) and 1600 mg HE protein (around ¼ HE) plus deliberate intake. Median maintenance phase 9 mo (range 7-15 mo). After OD, the AG received an elimination diet for 2 mo prior to follow-up DBPCFC to evaluate OT. OT for all children was finally evaluated after a median of 21 mo (range 12-47) considering AG and PG. |   | At follow-up DBPCFC 9 of 25 pts (36%) showed permanent tolerance in the AG; 3 of 25 (12%) were tolerant with regular intake and 4 of 25 (16%) were partial responders; in the CG, 7 of 20 pts (35%) were tolerant. Overall, 16/25 (64%) were tolerant (totally or partially in AG, and 7/20 (35%) in CG (P=0.05). |   | In the AG, in 4 pts: generalized U, bronchial obstruction, or angioedema (treated with AH and Cs); in the CG 1 child had severe AEs (vomiting, paleness, circulatory disorder) after accidental exposure; 2 pts during follow-up DBPCFC had bronchial obstruction, generalized U, and circulatory disorders and were equipped with an E self-administration-pen.  | In AG, 21/2 pts (84%) mild Sx |
| Tang, 2015, Australia | 62 pts (aged 1–10 yrs, average 6 yrs) of both sexes; [pt allocation: AG (n =31); placebo (n=31)] / Hx (+), SPT (≥ 8 mm) to peanuts, and sIgE to peanut (≥ 15 kU/L).  | DBPCRT | (OIT + probiotic) vs placebo  | peanut | The AG received Lactobacillus rhamnosus CGMCC 1.3724 (NCC4007; provided by Nestle Health Science, Konolfingen, Switzerland) at a fixed dose of 2 \* 1010 colony-forming units (freeze-dried powder) once daily together with peanut OIT (peanut flour, 50% peanut protein) once daily according for 18 mo. The CG received placebo (maltodextrin) and placebo (maltodextrin, brown food coloring, and peanut essence) once daily. Active and placebo OIT products were similar in taste, color, and smell.The peanut OIT protocol comprised a1-day rush induction phase (8 doses: 0.1 mg - 12 mg of peanut proteins, cumulative final dose 24 mg of peanut proteins),a build-up phase with updosing every 2 wks from 25 mg up to maintenance dose of 2 g of peanut protein (8 mo), and a maintenance phase (10 mo); total OIT was 18 mo. Where the build-up phase was longer than 8 mo (because of AEs) but less than 12 mo, the maintenance phase was adjusted to preserve a total of 18 mo of OIT. For pts taking more than 12 mo to reach maintenance, the total duration of OIT was extended to ensure a minimum of 6 mo of maintenance dosing. | 89.7% of pts receiving PPOIT and 7.1% receiving placebo were desensitized (P < .001).  | PPOIT was effective in inducing possible sustainedunresponsiveness in 82.1% receiving PPOIT and 3.6% receiving placebo (P<.001). The relative RR of achieving possible sustained unresponsiveness with PPOIT was 23 (95% CI, 3.33-158.8), providing an NNT of 1.27 (95% CI, 1.06-1.59) [P < .001]. |   | At least 1 severe AE was reported in 45.2% of pts in AG and 32.3% in CG (P= .3). The total number of severe AEs was greater in AG than in CG (34 and 15, respectively), but this reflected 1 child in the AG who had 13 severe AEs. The number of severe AEs per pt did not differ by group (P = .9). AEs during rush induction and build-up were similarly distributed between groups. However, AEs during the maintenance phase were more common in AG than CG. 10 severe SRs in 7 pts: 3 in the AG and 4 in CG. All but 1 occurred during the Australian pollen season (August-February). | AG- pts reported a greater number of AEs, mostly with maintenance home dosing |
| Varshney, 2011, USA | 28 pts (aged 2-10 yrs) randomized in: AG [n=19, median age 84 mo, range (38-126)] and CG [n=9, age (mo), 69 (28-114)] / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | DBPCRCT | OIT vs placebo  | peanut | Initial day escalation phase: in clinical setting: 0.1 mg peanut protein (as flour) or placebo; dose doubled every 30 minutes until 6 mg or Sx.Build-up phase: in clinical setting 1st day dose from escalation phase day before; every 2 wks dose increased by 50-100% until 75 mg/day tolerated, then 25-33% until maintenance dose of 4g achieved within 44 wks. At home the dosing was resumed if children missed less than 3 daily doses, if from 3 to 5 doses were missing children returned for an observed dose.Maintenance phase: 4 g/day, for 1 mo then returned for DBPCFC at 48 wks.  | 16/19 in AG reached maintenance dose, 9/9 in CG. At DBPCFC all 16/16 in AG ingested 5000 mg (approximately 20 peanuts); while placebo pts (n=9) ingested a median cumulative dose of 280 mg (range, 0-1900 mg) [p<0.001].  |   |   | Pts requiring E: at the initial day escalation, 2 in AG; at home dosing 1 pt in CG (after placebo); at DBPCFC 0/16 and 3/9 needed E in AG and CG, respectively. | At the initial day escalation 9 pts (47%) in AG needed AH. During build up phase1 pts in AG withdrew after mild GI Sx at the 1st escalation dose; after the DBPCFC 1 pt in AG had mild U+R, treated with AH. |
| **CCT (n=6)** |
| García-Ara, 2013, Spain | 55 pts allergic to CM [36 boys (63%); median age, 7 yrs; range, 4-14 yrs] confirmed by OFC were assigned to OIT (n= 36) or elimination diet if they refused to undergo OIT after the OFC(n = 19) | CCT | OIT vs routine care (food avoidance) | cow‘ s milk | The initial dose for OIT was the previous dose that elicited Sx in the OFC. The latter started at a dose of 0.005 mL and then doses were doubled until 1 m or an objective clinical reactivity was achieved. Until a dose of 1 mL was achieved, doses were increased at the hospital setting in a daily basis. From there on, doses were increased weekly at the hospital, and pts maintained this dose twice daily at home. Achieving an intake of 200 mL of milk (6 g of proteins) twice a day, which is the usual amount for pts of that age, was considered successful desensitization. In the maintenance phase, follow-up visits were scheduled at 1 month, 6 mo, and 1 yr after finishing induction phase | 33 out of 36 pts in AG were desensitized (200 ml). 3 withdrawals in the OIT group: 1 pt because of psychological stress, and 2 pts because of repeated digestive Sx. Desensitization was achieved in a median of 3 mo (range, 1-12 mo). In the CG only 1 child tolerated milk in OFC 1 yr after finishing induction phase. |  |   | During the induction phase, 27 of 36 (75%) experienced an AEs with 1 or more doses. Pts with higher sIgE levels had more severe AEs. 1 pt had GI Sx and A. 17 AEs treated with oral AH, 2AEs with oral AH and oral CS. AEs took place with increasing doses or with a dose previously tolerated.During the maintenance phase, 5 anaphylaxes were registered. Sx in OFC involved: 1 organ system in : 10 (53 %) controls and 16 (44%) pts in OIT group; 2 organ systems in: 9 (47%) controls and 20 (56%) pts in OIT group.  | Most AEs were mild or moderate.  |
| Martınez-Botas, 2015, Spain | 32 children (aged 4- 7 yrs, median age 4.5 yrs, 68% male) enrolled in: AG (n=25) and CG (n=7 / Hx (+), SPT (+) and DBPCFC(+).  | CCT | OIT vs routine care (food avoidance) | cow's milk | Build- up phase: 1st wk: pts started with 2.5 mL of 1: 10 diluted CM and received several doses every day up to 32 mL of non-diluted CM. In subsequent wks, only one daily dose, increased twice a wk (Monday and Thursday), starting with 48 mL of non-diluted CM and gradually increasing the dose up to 200 mL. Median duration of the OIT protocol: 8 wks. Follow-up: 24 mo of free diet. | 100 % AG pts complete OD (200 ml of CM) after build-up phase and maintained tolerance on a free diet during 24 months of follow-up. CG: none spontaneously tolerant, [OFC (+)] 100 % AG pts complete OD (200 ml of CM) |  |   | None AEs required i.m. E nor hospitalization. | During the build-up phase, 195 doses (23% of the total doses) produced AEs: 13.8% RC, 17.4% cutaneous,33.3% GI, and 48.7% A.6% of the reactions were grade 1, 34% grade 2, 5% grade 3, and 55% grade 4; none grade 5. 88.5% of grade 4 AEs were mild or moderate A, and 69% of them in 5 pts [ classification of Sampson].  |
| Mansouri, 2007 | AG: n=20 [(40% female), mean age 56 mo ( 8 mo-18 yrs)];CG: n=13 [(31% female), mean age 52 mo (4 mo-13 yrs)] / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | quasi RCT (no formal randomisation) | OIT vs routine care (food avoidance) | cow‘ s milk |  Build-up phase: Dose 0.06 mg increased to 6.4 g/day over 6 mo; 1 drop of CM diluted in 25 drops of water 0.06 mg of CM; initial dose given for 7 days, doubled every 7 days for 70 days, then 200 ml undiluted milk a day for 6 mo (Maintenance phase).  |  AG: 18/20 (90%) complee OD (200 ml/day); CG: 0% spontaneous tolerance |  |   |  10% drop out because of severe anaphylactic reactions | 80% mild reactions during OD (nausea, abdominal pain, throat itching, eczema, dyspnea) responded to antihistamine; 10% pts wheezed, slower increase in dose was employed. |
| Patriarca, 2003, Italy | OIT group: 59 pts aged 3-55 yrs, 32 children (54%) <16 yrs (mean age not given); 25/59 male (42%). These 59 pts resulted in 66 ODs as 6 of 59 underwent 13 OD for different foods. CG: n=16 aged 5-29 (No further demographic information). Controls were those pts refusing OIT. Hx (+), SPT (+), sIgE (+), DBPCFC (+) | CCT | OIT vs routine care (food avoidance) | CM n=29 (44%)\*;Egg n=15 (23%)\*;Albumin n=3 (4.5\*%);Fish n=11 (17%)\*;Orange n=2 (3%)\*;Apple n=1 (1.5%)\*;Corn n=1 (1.5%)\*;Beans n=1 (1.5%)\*;Peanut n=1 (1.5%)\*;Lettuce n=1 (1.5%)\*;Peach n=1 (1.5%)\*. | *Escalation phase* Milk Diluted milk (10 drops diluted in 100ml water) days 1-18: 1-18drops/day; pure milk: days 19-136: 1drop milk to 120ml;Egg diluted egg (10drops in 100ml): days 1-33: 1drop to 36 drops x 3 pure egg: day 34 to 139 1drop to 50ml (1 egg);Fish (25g cod boiled in 50ml water): days 1 to 165: 0.000033mg-160g /day;*Maintenance phase:* Milk 120ml (1 glass) 2-3x/wk;Egg 1 egg 2-3x/wk;Fish 160g boiled cod, 2-3x/wk;Other foods 2-3x/wk;OD LENGHT: 136 days (milk); 139 days (egg); 165 days (fish) | OD success rate 45 out of 54 (83%)[ITT 68%] in AG. No pts reached spontaneous tolerance in CG. |   |   | 51.1% of pts in AG experienced AEs (U, angioedema, or abdominal pain) controlled by AH or sodium cromolyn but in 9 pts (16.7%) who stopped OIT due to the occurrence of skin or GI (diarrhea, vomiting and abdominal pain) Sx not controlled by AH or sodium cromolyn. |   |
| Patriarca, 2007, Italy | SLIT group: n=42; 18 girls; aged 3-16 yrs.CG: n=10 (4 girls; aged 5-13 yrs, under strict elimination diet for 18 mo/ Hx (+), SPT (+), sIgE (+), DBPCFC (+) | CCT, (controls refused AIT) | SLIT vs routine care (food avoidance) | CM (n= 18)\*;Egg (n=17)\*;Fish (n=9)\*;Wheat (n=2)\*;Apple (n=1)\*;Bean (n=1)\* | Milk (dilution: 10 drops of milk in 100 ml); from 1 drops/day at the beginning of the protocol and at the end of treatment days 175-177 130 ml/day; maintenance dose: 130 ml of milk at least two or three times a week;Egg [dilution: 1 drop of raw shaken egg (albumin + yolk) in 100 ml of wate]r; 1 drops from days 1-3 till 10 drops days 22-24; then dilution 10 drops of raw shaken egg (albumin + yolk) in 100 ml of water 1 drops in days 25-27 till 50 ml days 166-168; maintenance dose: 1 egg at least two or three times a week;Cooked fish (boiled cod) 0.000033 mg days 1-3 till 100 g days 154-156; maintenance dose: 100 g of boiled cod at least twice a wk. | OD was successful in 31/36 (85.7%) in SLIT group (6 drop out for scarce compliance) [ITT 73%]. No pts reached spontaneous tolerance in CG. |  |   |   | In 11/36 in AG (30.5%) had AEs such as, U, vomiting, worsening of A or of atopic dermatitis, angioedema, and abdominal pain |
| Syed, 2014, USA  | 43 pts in: OIT group (n=23, median age 10.4, range 5–45 yrs, male 60%) controls (n=20, median age 12, range 6–20 yrs, male 40%) / Hx (+), SPT (+), sIgE (+), DBPCFC (+) | CCT | OIT vs routine care (food avoidance) | peanut |  Doses of peanut protein were administered orally, with dose escalation every 2 weeks (as tolerated by the subject) from 0,1 mg up to 4000 mg protein by 24mo. | In the CG, no pt successfully passed the OFC at 24mo (none spontaneous tolerant).In the AG, pts with no reaction to OFC were defined as desensitized at 24mo (n=20) and avoided peanut-containing foods for 3mo.  | At 27mo (after 3 mo of AIT withdrawal), desensitized pts underwent another OFC. Pts who reacted were classified as non-tolerant (NT, n=13) and those who did not have any clinical allergic reaction were operationally defined as “immune tolerant” (IT, n=7). IT pts abstained from OIT and avoided all peanut-containing food for an additional 3mo (total of 6mo of avoidance) and were reassessed for “immune tolerance” with an OFC at 30mo (IT, n=3).  |   | Safety profile not assessed  |

\* values referred only to the active group

***A****, asthma;* ***AG****, active group;* ***AH****, Antihistamines;* ***CCT****, controlled clinical trials;* ***CG****, control group;* ***CM****, Cows’ milk;* ***CS****, Corticosteroids;* ***DBPCF****, Double blind placebo controlled food challenge;* ***DEW****, Dehydrated egg white;* ***E****, epinephrine;* ***EPIT****, Epicutaneous immunotherapy;* ***FAQL,PB****, Food Allergy Quality of Life – Parental Burden Questionnaire;* ***GI****, gastrointestinal;* ***HE****, Hens’ egg;* ***Hx****, Clinical History;* ***i.m.****, intramuscular;* ***LRs****, Local reactions;* ***mo****, month;* ***NS****, not statistically significant;* ***nsLTPs****, nonspecific Lipid Transfer Proteins;* ***OD****, Oral desensitization;* ***OFC****, oral food challenge;* ***OFS****, oropharyngeal symptoms;* ***OIT****, Oral immunotherapy; ;* ***PPOIT****, probiotic + peanut OIT;* ***Pt****, participant;* ***R****, rhinitis;* ***RC****, rhinoconjunctivitis;* ***RCT****, randomized controlled trial;* ***RR****, risk rate;* ***SCD****, median successfully consumed dose;* ***sIgE****, specific IgE;* ***SLIT****, Sublingual immunotherapy;* ***SPT****, Skin Prick Test;* ***SRs****, Systemic reactions; SU, Sustained unresponsiveness;* ***Sx****, symptoms;* ***U****, urticaria;* ***wk****, week.*

**Appendix 3: Table S2 Critical appraisal of included RCTs (n=25) assessed by the Cochrane Risk of Bias tool**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study****(Author, year, country)**  | **Adequate sequence generation**  | **Allocation concealment**  | **Blinding/ patient-related outcomes**  | **Incomplete outcome data addressed?**  | **Free of selecting reporting**  | **Free of other bias\***  | **Overall risk of bias** |
| Anagnostou, 2014, UK | Low | High | High | Low | Low | Low | High |
| Burks, 2012, USA | Low | Low | Low  | Low | Low | Low | Low |
| Caminiti, 2009, Italy | High  | High | Low | Low | Low | High  | High  |
| Caminiti, 2015, Italy  | Low | Low | Low | Low | Low | Low | Low |
| Dello Iacono, 2013, Italy | Low | High | High | Unclear  | Unclear  | Unclear  | High  |
| Dupont, 2010, France | Unclear | Unclear | Unclear | Low | Low | Low | Unclear |
| Enrique, 2005, Spain | Unclear  | Unclear  | Low | Low | Low | High  | High  |
| Escudero, 2015, Spain | Low | High | High | Low | Low | Low |  high  |
| Fernandez-Rivas, 2009, Spain | Unclear | Low | Low | Low | Low | Low  | Unclear |
| Fleischer, 2013, USA | Low | Low | Low | Low | Low | Low | Low |
| Fuentes-Aparicio, 2013, Spain | Unclear  | Unclear  | Unclear  | Low | Low | Low | Unclear  |
| Kim, 2011, USA | Unclear  | Low | Low | Low | Low | Low | Low |
| Lee, 2013, Korea | Low | High | High | Low | Low | Low | High  |
| Longo, 2008, Italy | Low | Low | Low | Low | Low | Low | Low |
| Martorell, 2011, Spain | Low | Unclear  | Unclear  | Low | Low | Low | Unclear  |
| Meglio, 2013, Italy | Low |  High | High | Low | Low | Low | High  |
| Morisset, 2007, France | High | Unclear | Unclear  | Unclear  | Low | High  | High |
| Pajno, 2010, Italy | Low | Low | Low | Low | Low | Low | Low |
| Patriarca, 1998, Italy | Unclear  | High | Low | Unclear  | Low | High | High |
| Salmivesi, 2012, Finland | Unclear  | Low | Low | High | High | High | High |
| Skripak, 2008, USA | Unclear  | Low | Low | Low | Low | Low | Unclear |
| Staden, 2007 | High | High | Low | Unclear  | Low | High  | High  |
| Tang, 2015, Australia | Low | Low | Low | Low | Low | Low | Low |
| Varshney, 2011, USA | Low | Low | Low | Low | Low | Low | Low |

**Appendix 4: Table S3. Consensus ACROBAT-NRSI judgments between two reviewers by domain of bias for CCTs (n=6)**

|  |  |  |
| --- | --- | --- |
| **Study** | **Domain** | **Overall****RoB****bias due to judgment** |
| **Bias due to judgment****confounding** | **Bias in****selection of****participants** | **Bias in****measurement of****interventions** | **Bias due to****departures from****intended****interventions** | **Bias due****to****missing****data** | **Bias in****measurement****of outcomes** | **Bias in****selection of****reported****results** |
| Garcia-Ara, 2013 | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Martınez-Botas, 2015 | Moderate | Moderate | Low | Low | Low | Low | Low | Moderate |
| Mansouri, 2007 | Moderate | Moderate | Low | Low | Unclear | Low | Low | Moderate |
| Patriarca, 2003 | Moderate | Moderate | Low | Low | Moderate | Low | Low | Moderate |
| Patriarca, 2007 | Moderate | Moderate | Low | Low | Moderate | Low | Low | Moderate |
| Syed, 2014 | Moderate | Moderate | Low | Low | Moderate | Low | Low | Moderate |

**Appendix 6**

**PRISMA statement for the Allergy submission for copublication of “Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis”**

| *Section/topic* | *#* | *Checklist item* | *Reported on page #* |
| --- | --- | --- | --- |
| **TITLE** |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known.  | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | 3 |
| **METHODS** |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | 5 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 4,5 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | 4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 28-31, Appendix1 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | 5 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 5 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 4,5 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 5 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 4,5 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | 4,5 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | 4,5 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 5 |
| *RESULTS* |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 6; Table 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 6,7; Table 1; Appendix 2:Table S1; 32-72 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12). | 6; Appendix 3 and 4; Table S2 and S3; 73-74 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot. | 6-10 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6-10 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see Item 16). | Appendix 5: Figures S1-S28; 75-102 |
| *DISCUSSION* |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers). | 10 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). | 10 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 10,11 |
| *FUNDING* |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 11 |

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