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ALLERGEN IMMUNOTHERAPY FOR IgE-MEDIATED FOOD ALLERGY

A SYSTEMATIC REVIEW AND META-ANALYSIS

Supplementary materials

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Appendix 3.1 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 3.2

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 (+).	cross-over 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 up-dosing 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 FAQ-LQ-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).

Table S1 Continued

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
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)	DBP-CRCT	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.

Table S1 Continued

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
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 (+), DBP-CFC (+)	RCT (DB-PCRT 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

Table S1 Continued

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
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 and started the 6-month egg-containing diet. / Hx (+), SPT (+) and sIgE (+), DBPCFC (+). None of the children had previously consumed baked eggs.	DBP-CRT	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).

Table S1 Continued

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
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 DB-PCFC 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.

Table S1 Continued

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
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 (+).	DBP-CRT	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 increment was 12-fold in the AG vs 8% in CG (P =0.13).			24 SRs occurred in the AG and 8 in the CG, (respiratory/ ENT disorders, p 0.9; gastrointestinal disorders<.001). No anaphilaxis. No child interrupted treatment because of an AE, and none received epinephrine or was seen at the emergency department or hospital.	Local AEs were reported for 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 (+)	DBP-CRT	SLIT (sublingual-discharge technique) vs placebo	hazelnut	A biologically standardized hazelnut extract, graded in 5 strengths (FO, 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.

Table S1 Continued

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
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 a weekly 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 DB-PCFC 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%).

Table S1 Continued

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
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.

Table S1 Continued

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
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.

Table S1 Continued

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
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.

Table S1 Continued

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
Kim, 2011, USA	18 children (aged 1 - 11 yrs) were randomized into: AG (n =11) and CG (n=7). / Hx (+), sIgE > 7 kU/L	DBP-CRT	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- DBP-CFC, 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.

Table S1 Continued

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
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.

Table S1 Continued

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
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).

Table S1 Continued

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
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, multi-centre 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 was performed 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.

Table S1 Continued

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
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	

Table S1 Continued

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
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

Table S1 Continued

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
Salmivesi, 2012, Finland	28 children (aged 6-14 yrs) randomized into 2 groups: AG (n=18) and CG (n=10) / Hx (+), SPT (+), sIgE (+), DBPCFC (+)	DBP-CRT	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 (+)	DBP-CRT	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)

Table S1 Continued

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
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 (+), DB-PCFC (+) [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

Table S1 Continued

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
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).	DBP-CRT	(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 sustained unresponsiveness 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

Table S1 Continued

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
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 (+)	DBP-CRCT	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.

Table S1 Continued

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
Martinez-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 DBP-CFC (+).	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.

Table S1 Continued

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
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

Table S1 Continued

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
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 3.3

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 3.4

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 onfounding	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 3.5

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	2.23
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	0.62
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	38.33
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	4.59
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	2.15
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	2.25
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	2.32
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	38.47
Paino 2010	0.048	0.003	0.746	0 / 15	10 / 15	2.21
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	2.24
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	2.31
Varshney 2011	0.061	0.004	0.910	0 / 9	16 / 19	2.28
	0.171	0.114	0.258	15 / 207	272 / 344	

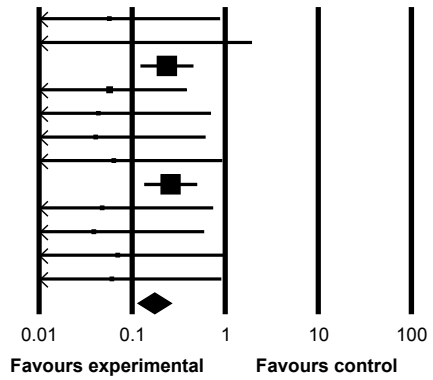

Figure S1 Subgroup analysis RR of food allergy after OIT (only LRB and URB studies) (random-effects model). Heterogeneity: τ^2 = 0.000; χ^2 = 10.882, df = 11 (P<0.453); I^2 =0%; Test for overall effect: Z = -8.451 (P<0.0001)

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37	46.04
Fleischer 2013	0.214	0.073	0.632	3 / 20	14 / 20	39.93
Kim 2011	0.065	0.004	0.957	0 / 7	11 / 11	14.03
	0.312	0.099	0.978	8 / 46	39 / 68	

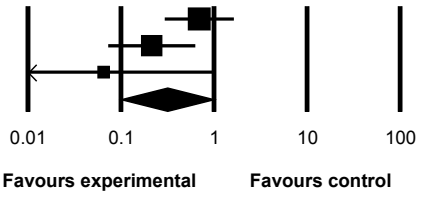

Figure S2 Subgroup analysis RR of food allergy after SLIT (only LRB and URB studies) (random-effects model). Heterogeneity: τ^2 = 0.547; χ^2 = 4.623, df = 2 (P<0.099); I^2 =57%; Test for overall effect: Z = -1.998 (P<0.046)

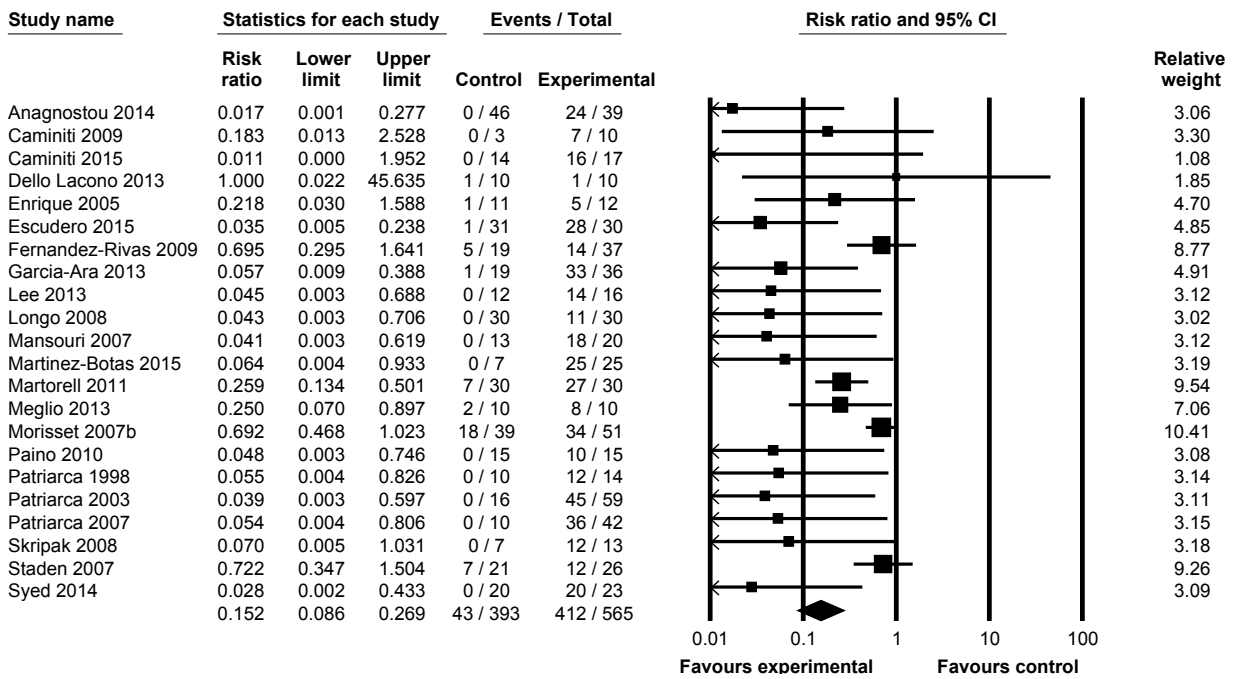

Figure S3 Sensitivity analysis RR of food allergy after OIT or SLIT (diagnosis of food allergy confirmed by DBPCFC) (random-effects model). Heterogeneity: $\tau^2 = 0.773$; $\chi^2 = 55.513$, df = 21 (P<0.0001); $I^2 = 62\%$; Test for overall effect: Z = -6.480 (P<0.0001)

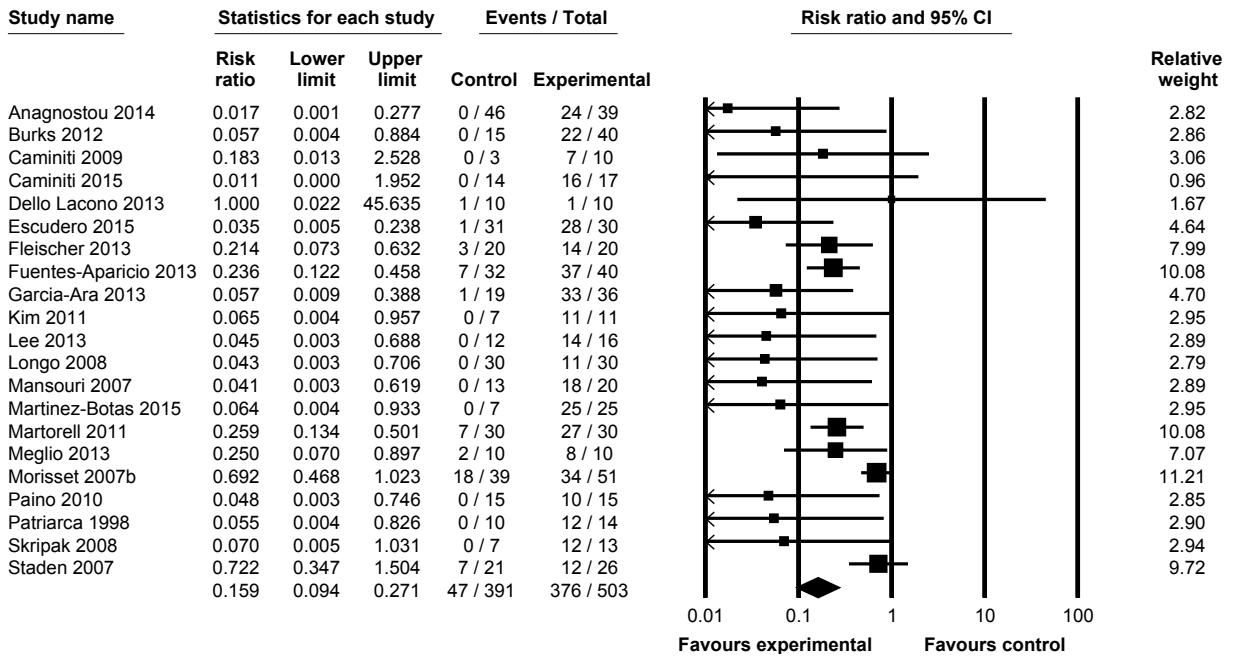

Figure S4 Risk ratios (RR) of persisting food allergy as assessed by DBPCFC in OIT or SLIT v. controls (Children's studies). Heterogeneity: $\tau^2 = 0.617$; $\chi^2 = 51.024$, df = 20 (P<0.0001); $I^2 = 61\%$; Test for overall effect: Z = -6.773 (P<0.0001)

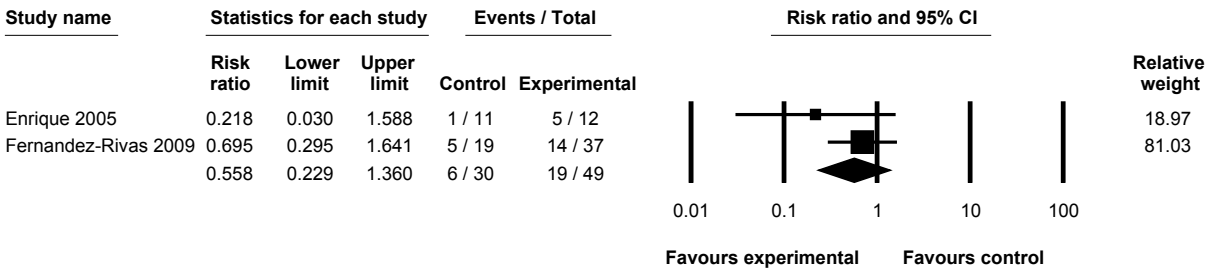

Figure S5 Risk ratios (RR) of persisting food allergy as assessed by DBPCFC in SLIT v. controls (Adult studies) (random-effects model). Heterogeneity: $\tau^2 = 0.063$; $\chi^2 = 1.104$, df = 1 (P<0.293); I^2 =9%; Test for overall effect: Z = -1.283 (P<0.200)

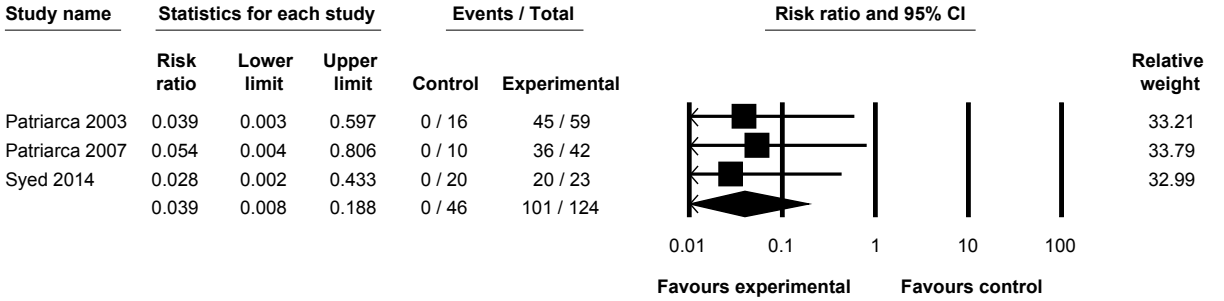

Figure S6 Risk ratios (RR) of persisting food allergy as assessed by DBPCFC in OIT v. controls (Mixed population studies). Heterogeneity: $\tau^2 = 0.000$; $\chi^2 = 0.110$, df = 2 (P<0.946); I^2 =0%; Test for overall effect: Z = -4.042 (P<0.0001)

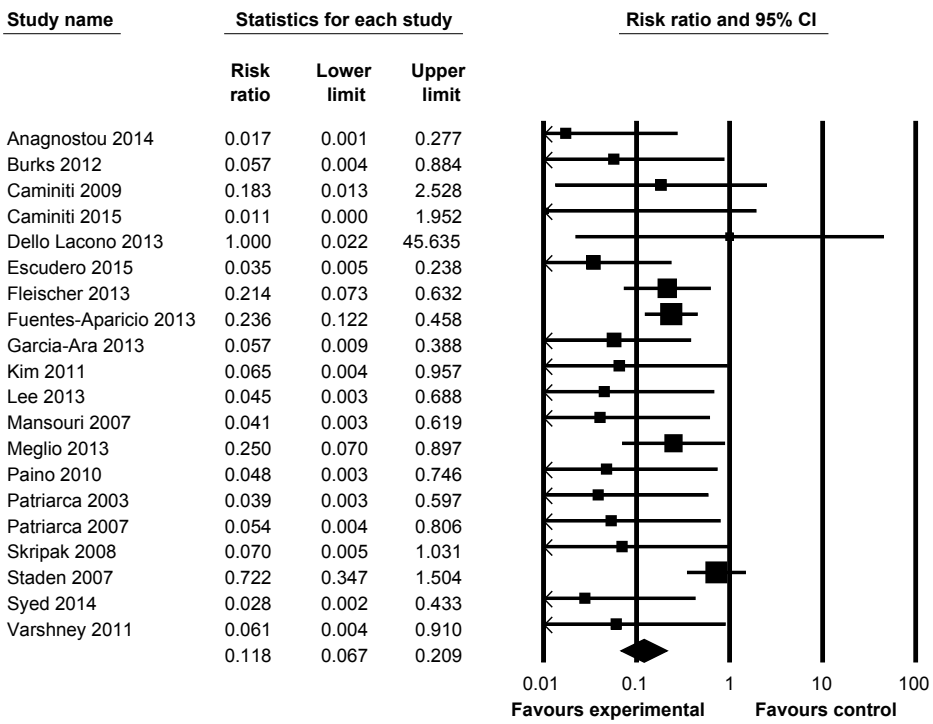

Figure S7 Risk ratios (RR) of persisting food allergy as assessed by DBPCFC in OIT or SLIT v. controls (AIT protocol: Conventional). Heterogeneity: $\tau^2 = 0.530$; $\chi^2 = 32.445$, df = 19 (P<0.028); I^2 =41%; Test for overall effect: Z = -7.363 (P<0.0001)

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Enrique 2005	0.218	0.030	1.588	1 / 11	5 / 12	8.84
Fernandez-Rivas 2009	0.695	0.295	1.641	5 / 19	14 / 37	21.41
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	5.20
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	5.53
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	24.71
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	28.89
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	5.42
	0.325	0.162	0.650	31 / 146	128 / 199	

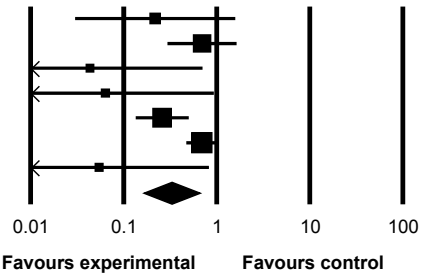

Figure S8 Risk ratios (RR) of persisting food allergy as assessed by DBPCFC in OIT or SLIT v. controls (AIT protocol: Rush) (random-effects model). Heterogeneity: τ^2 = 0.395; χ^2 = 15.479, df = 6 (P<0.017); I^2 =61%;Test for overall effect: Z = -3.174 (P<0.002)

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Caminiti 2009	0.183	0.013	2.528	0 / 3	7 / 10	5.76
Garcia-Ara 2013	0.057	0.009	0.388	1 / 19	33 / 36	8.81
Lee 2013	0.045	0.003	0.688	0 / 12	14 / 16	5.45
Longo 2008	0.043	0.003	0.706	0 / 30	11 / 30	5.27
Mansouri 2007	0.041	0.003	0.619	0 / 13	18 / 20	5.45
Martinez-Botas 2015	0.064	0.004	0.933	0 / 7	25 / 25	5.57
Martorell 2011	0.259	0.134	0.501	7 / 30	27 / 30	18.50
Paino 2010	0.048	0.003	0.746	0 / 15	10 / 15	5.37
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	5.47
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	5.42
Patriarca 2007	0.054	0.004	0.806	0 / 10	36 / 42	5.49
Skripak 2008	0.070	0.005	1.031	0 / 7	12 / 13	5.56
Staden 2007	0.722	0.347	1.504	7 / 21	12 / 26	17.87
	0.119	0.057	0.249	15 / 193	262 / 336	

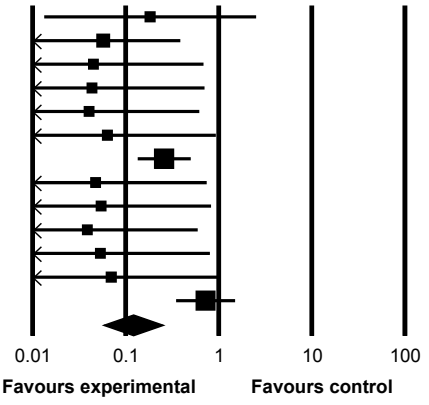

Figure S9 RR of CMA as assessed by DBPCFC in OIT vs. controls (random-effects model). Heterogeneity: τ^2 = 0.647; χ^2 = 22.521, df = 12 (P<0.032); I^2 =47%; Test for overall effect: Z = -5.672 (P<0.0001)

Study name	Risk ratio	Lower limit	Upper limit	Control	Experimental	Relative weight
Burks 2012	0.057	0.004	0.884	0 / 15	22 / 40	5.11
Caminiti 2015	0.011	0.000	1.952	0 / 14	16 / 17	1.72
Dello Lacono 2013	1.000	0.022	45.635	1 / 10	1 / 10	2.99
Escudero 2015	0.035	0.005	0.238	1 / 31	28 / 30	8.23
Fuentes-Aparicio 2013	0.236	0.122	0.458	7 / 32	37 / 40	17.57
Meglio 2013	0.250	0.070	0.897	2 / 10	8 / 10	12.44
Morisset 2007b	0.692	0.468	1.023	18 / 39	34 / 51	19.48
Patriarca 1998	0.055	0.004	0.826	0 / 10	12 / 14	5.18
Patriarca 2003	0.039	0.003	0.597	0 / 16	45 / 59	5.13
Patriarca 2007	0.054	0.004	0.806	0 / 10	36 / 42	5.19
Staden 2007	0.722	0.347	1.504	7 / 21	12 / 26	16.97
	0.218	0.107	0.445	36 / 208	251 / 339	

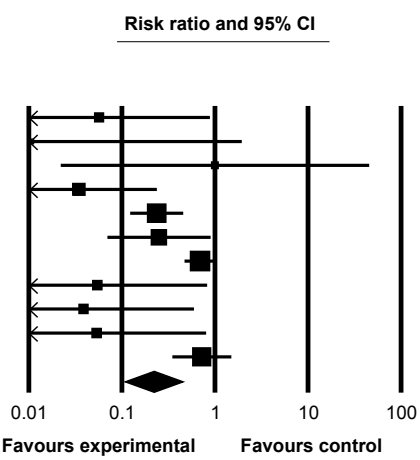

Figure S10 RR of HE allergy as assessed by DBPCFC in OIT vs. controls (random-effects model). Heterogeneity: τ^2 = 0.642; χ^2 = 29.618, df = 10 (P<0.001); I^2 =66%; Test for overall effect: Z = -4.182 (P<0.0001)

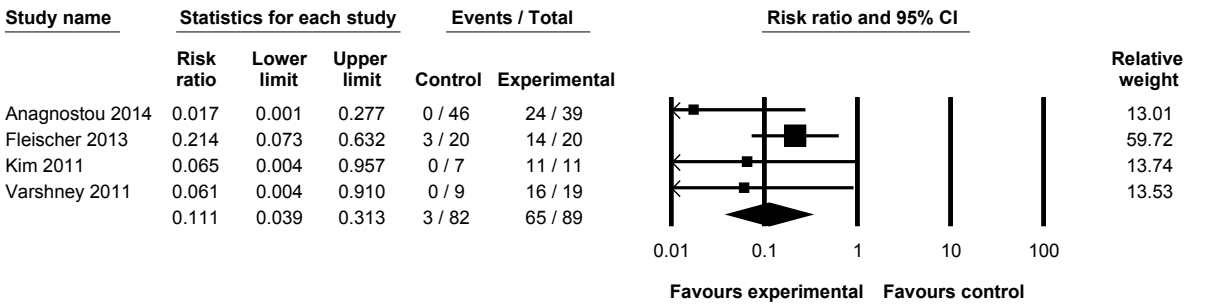

Figure S11 RR of peanut allergy as assessed by DBPCFC in OIT/SLIT vs. controls (random-effects model). Heterogeneity: τ^2 = 0.166; χ^2 = 3.405, df = 3 (P<0.333); I^2 =12%; Test for overall effect: Z = -4.154 (P<0.0001)

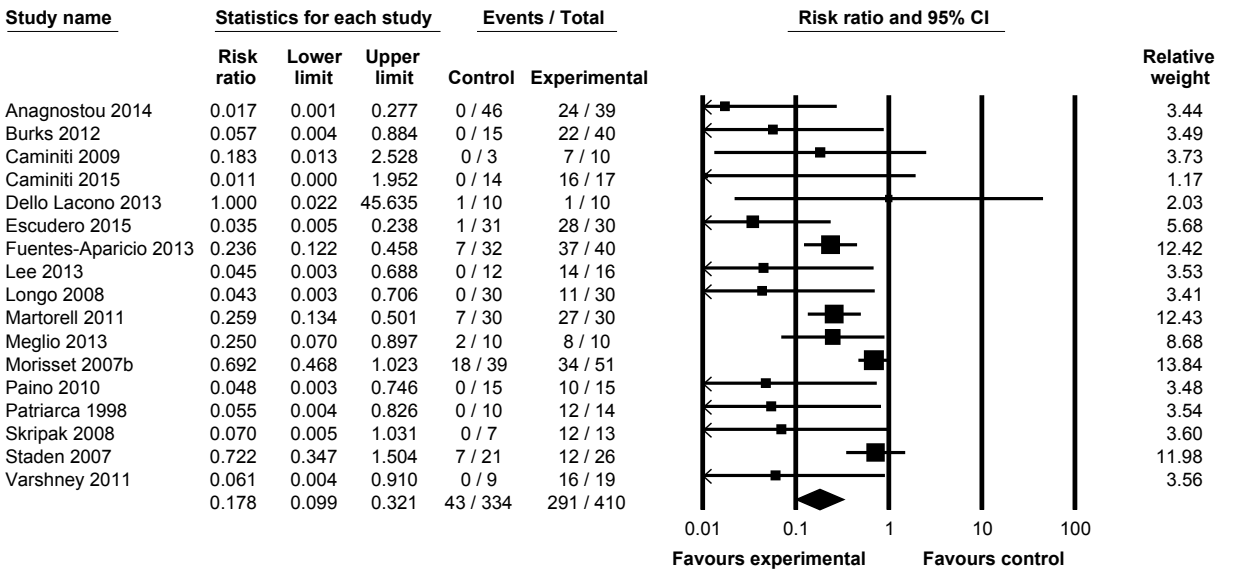

Figure S12 Sensitivity analysis RR of food allergy after OIT (only RCTs) (random-effects model). Heterogeneity: τ^2 = 0.608; χ^2 = 42.676, df = 16 (P<0.0001); I^2 =62%; Test for overall effect: Z = -5.760 (P<0.0001)

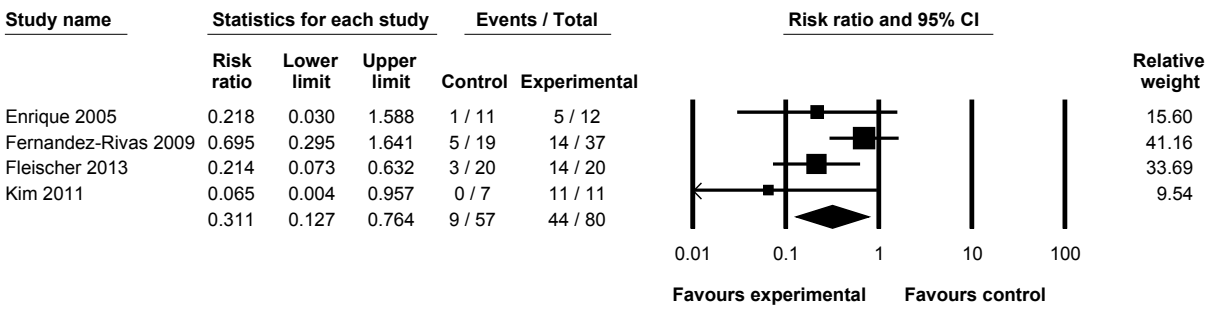

Figure S13 Sensitivity analysis RR of food allergy after SLIT (only RCTs) (random-effects model). Heterogeneity: τ^2 = 0.317; χ^2 = 4.931, df = 3 (P<0.177); I^2 =39%; Test for overall effect: Z = -2.548 (P<0.0001)

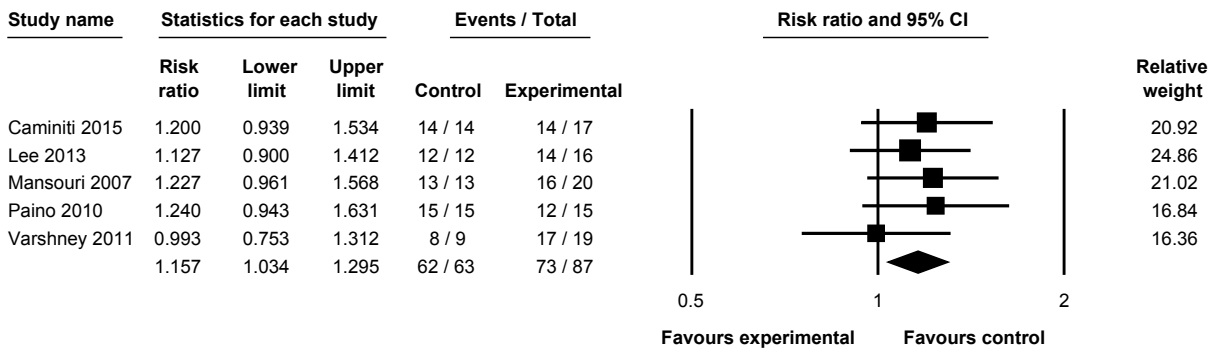

Figure S14 Safety data – absence of systemic reactions during OIT for food allergy (random-effects model). Heterogeneity: τ^2 = 0.000; χ^2 = 1.761, df = 4 (P<0.780); I^2 =0%; Test for overall effect: Z = 2.542 (P<0.011)

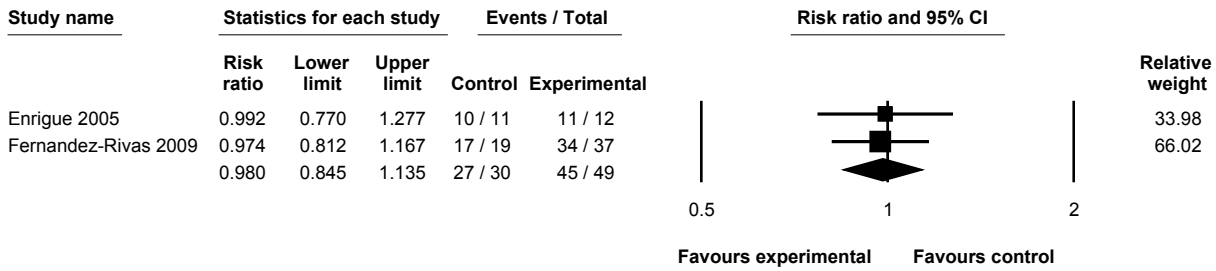

Figure S15 Safety data – absence of systemic reactions during SLIT for food allergy (random-effects model). Heterogeneity: τ^2 = 0.000; χ^2 = 0.013, df = 1 (P<0.908); I^2 =0%; Test for overall effect: Z = -0.271 (P<0.786)

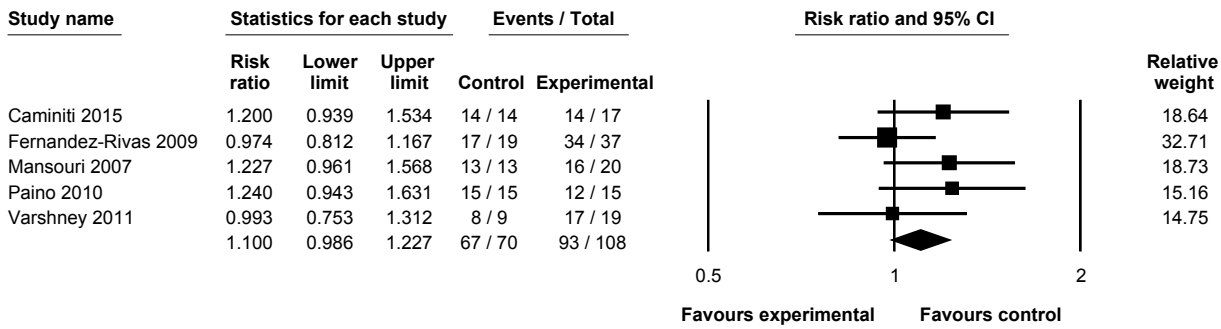

Figure S16 Safety data – absence of systemic reactions during OIT or SLIT for food allergy (only LRB and URB studies). Heterogeneity: τ^2 = 0.001; χ^2 = 4.235, df = 4 (P<0.375); I^2 =5%; Test for overall effect: Z = 1.713 (P<0.087)

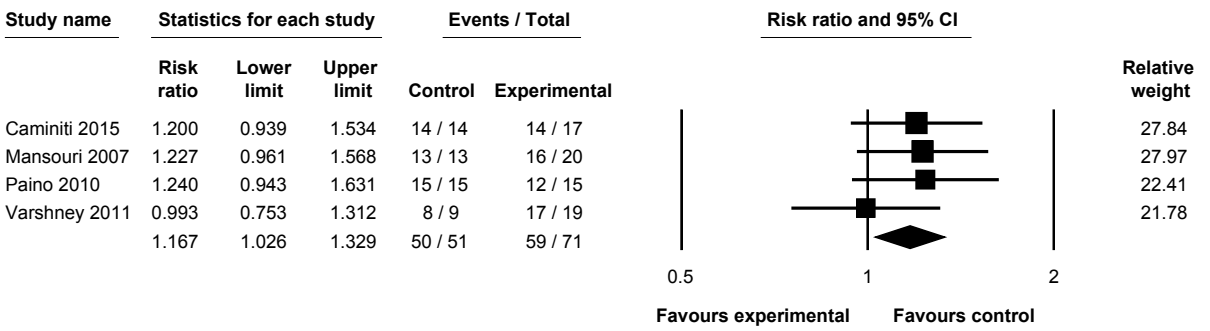

Figure S17 Safety data – absence of systemic reactions during OIT for food allergy (only LRB and URB studies) (random-effects model). Heterogeneity: $\tau^2 = 0.000$; $\chi^2 = 1.691$, df = 3 (P<0.639); I^2 =0%; Test for overall effect: Z = 2.341 (P<0.019)

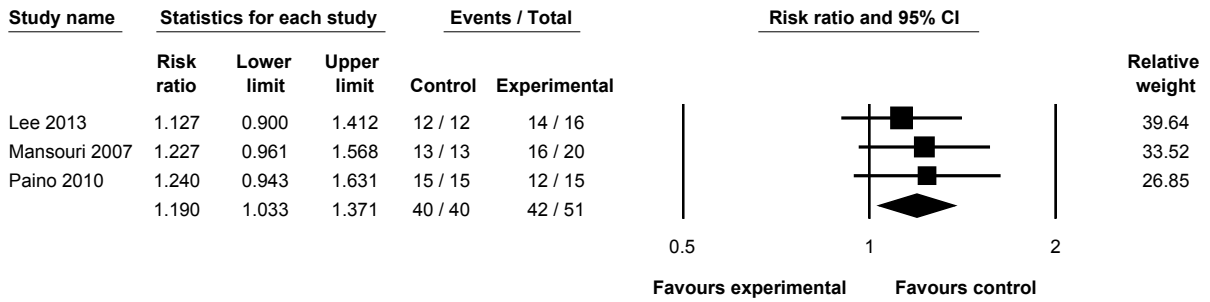

Figure S18 Safety data – absence of systemic reactions during OIT for CMA (random-effects model). Heterogeneity: $\tau^2 = 0.000$; $\chi 2 = 0.369$, df = 2 (P<0.831); I^2 =0%; Test for overall effect: Z = 2.402 (P<0.016)

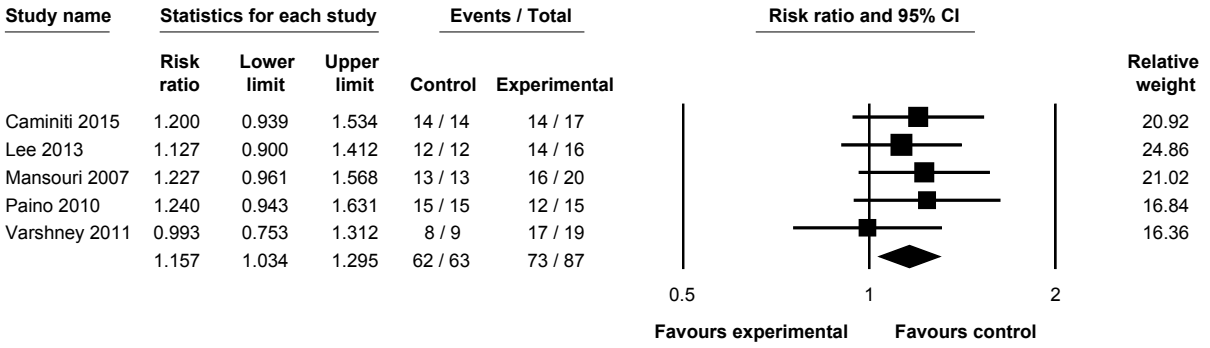

Figure S19 Safety data – absence of systemic reactions during OIT for food allergy. RR, risk ratio (Children's studies). Heterogeneity: $\tau^2 = 0.000$; $\chi^2 = 1.761$, df = 4 (P<0.780); I^2 =0%; Test for overall effect: Z = 2.549 (P<0.011)

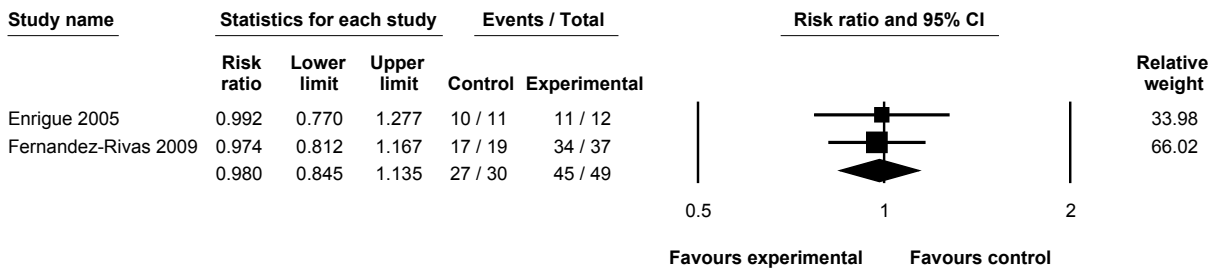

Figure S20 Safety data – absence of systemic reactions during SLIT for food allergy. RR, risk ratio (Adults studies). Heterogeneity: τ^2 = 0.000; χ^2 = 0.013, df = 1 (P<0.908); I^2 =0%; Test for overall effect: Z = -0.271 (P<0.786)

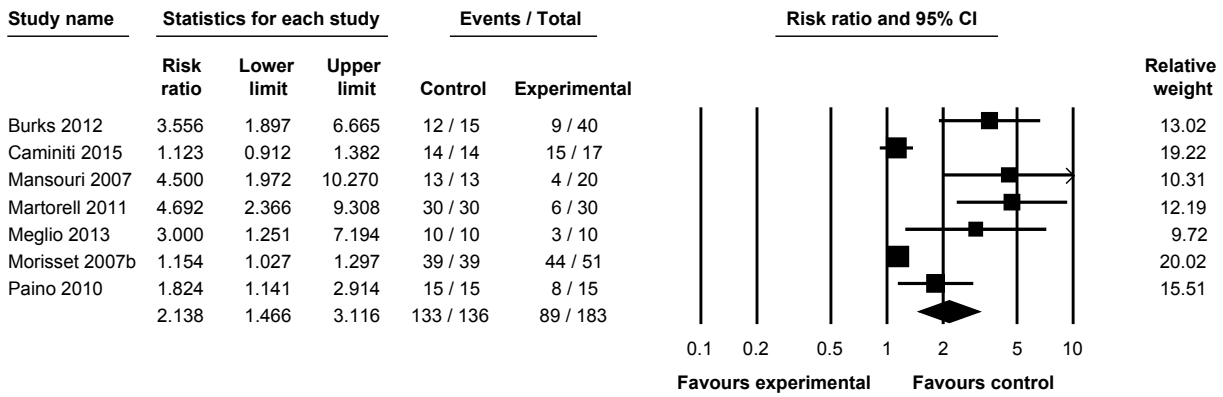

Figure S21 Sensitivity analysis. Safety data – absence of local reactions during OIT for food allergy (random-effects model). Heterogeneity: τ^2 = 0.181; χ^2 = 43.261, df = 6 (P<0.0001); I^2 =86%; Test for overall effect: Z = 3.952 (P<0.0001)

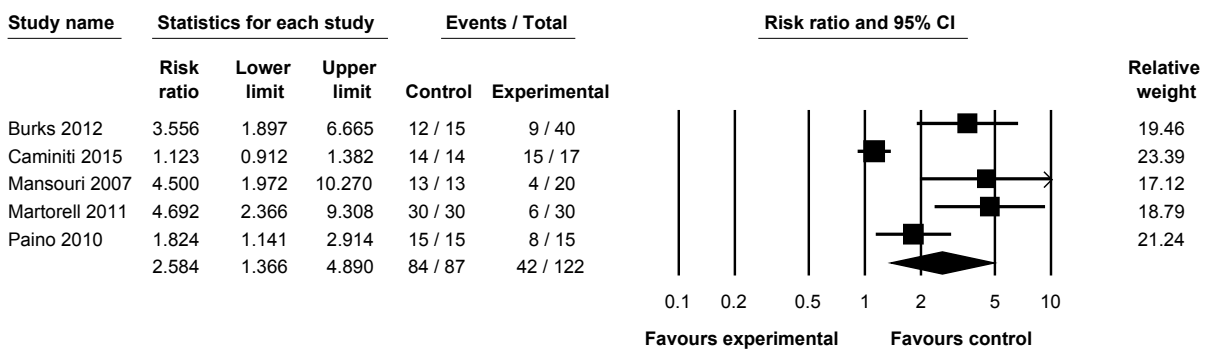

Figure S22 Safety data – absence of local reactions during OIT for food allergy (only LRB and URB studies) (random-effects model). Heterogeneity: τ^2 = 0.441; χ^2 = 32.816, df = 4 (P<0.0001); I^2 =88%; Test for overall effect: Z = 2.918 (P<0.004)

Study name	Risk ratio	Lower limit	Upper limit	Events / Total: Control	Events / Total: Experimental	Relative weight
Burks 2012	3.556	1.897	6.665	12 / 15	9 / 40	13.52
Caminiti 2015	1.123	0.912	1.382	14 / 14	15 / 17	20.48
Lee 2013	6.000	1.576	22.844	9 / 12	2 / 16	5.76
Martorell 2011	4.692	2.366	9.308	30 / 30	6 / 30	12.61
Meglio 2013	3.000	1.251	7.194	10 / 10	3 / 10	9.95
Morisset 2007b	1.154	1.027	1.297	39 / 39	44 / 51	21.41
Paino 2010	1.824	1.141	2.914	15 / 15	8 / 15	16.27
	2.077	1.429	3.019	129 / 135	87 / 179	

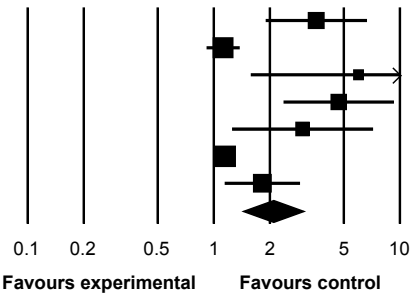

Figure S23 Safety data – absence of local reactions during OIT for food allergy (only RCTs) (random-effects model). Heterogeneity: $\tau^2 = 0.166$; $\chi^2 = 39.390$, df = 6 (P<0.0001); I^2 =85%; Test for overall effect: Z = 3.832 (P<0.0001)

Study name	Risk ratio	Lower limit	Upper limit	Events / Total: Control	Events / Total: Experimental	Relative weight
Lee 2013	6.000	1.576	22.844	9 / 12	2 / 16	14.08
Mansouri 2007	4.500	1.972	10.270	13 / 13	4 / 20	24.04
Martorell 2011	4.692	2.366	9.308	30 / 30	6 / 30	27.80
Paino 2010	1.824	1.141	2.914	15 / 15	8 / 15	34.09
	3.484	1.887	6.434	67 / 70	20 / 81	

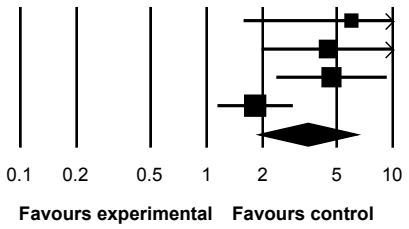

Figure S24 Safety data – absence of local reactions during OIT for CMA (random-effects model). Heterogeneity: $\tau^2 = 0.230$; $\chi^2 = 7.886$, df = 3 (P<0.048); I^2 =62%; Test for overall effect: Z = 3.990 (P<0.0001)

Study name	Risk ratio	Lower limit	Upper limit	Events / Total: Control	Events / Total: Experimental	Relative weight
Lee 2013	6.000	1.576	22.844	9 / 12	2 / 16	20.57
Martorell 2011	4.692	2.366	9.308	30 / 30	6 / 30	36.56
Paino 2010	1.824	1.141	2.914	15 / 15	8 / 15	42.87
	3.291	1.498	7.233	54 / 57	16 / 61	

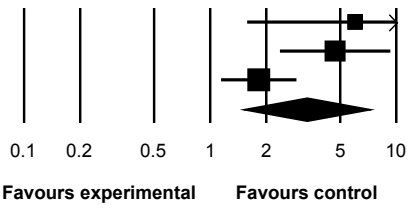

Figure S25 Safety data – absence of local reactions during OIT for CMA (only RCTs) (random-effects model). Heterogeneity: $\tau^2 = 0.319$; $\chi^2 = 6.552$, df = 2 (P<0.038); I^2 =69%; Test for overall effect: Z = 2.966 (P<0.003)

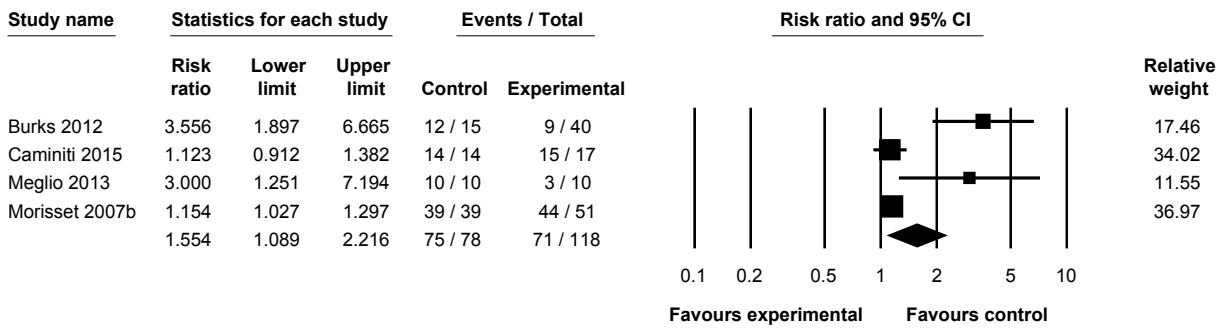

Figure S26 Safety data – absence of local reactions during OIT for HEA (random-effects model). Heterogeneity: $\tau^2 = 0.085$; $\chi^2 = 16.513$, df = 3 (P<0.001); $I^2 = 81\%$;Test for overall effect: Z = 2.432 (P<0.015)

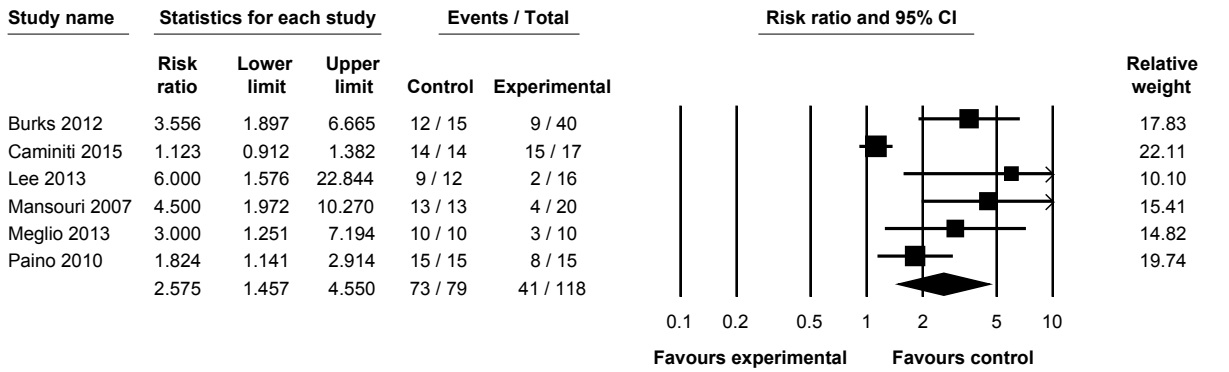

Figure S27 Safety data – absence of local reactions during OIT for food allergy. RR, risk ratio (AIT protocol: Conventional). Heterogeneity: $\tau^2 = 0.370$; $\chi^2 = 28.715$, df = 5 (P<0.0001); $I^2 = 82\%$; Test for overall effect: Z = 3.256 (P<0.001)

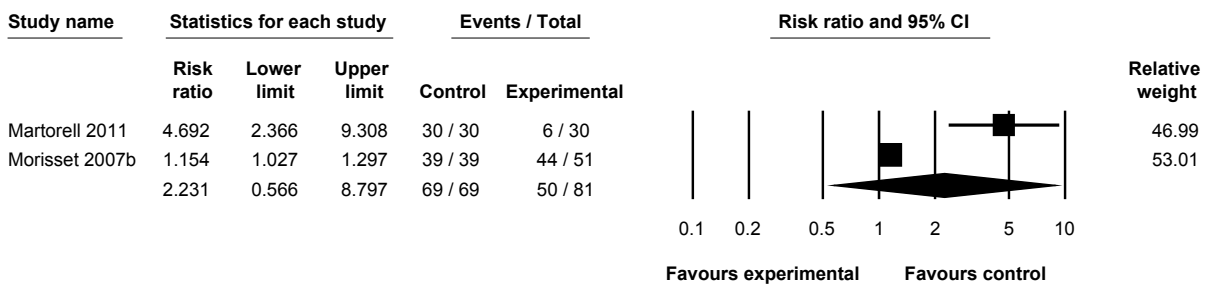

Figure S28 Safety data – absence of local reactions during OIT for food allergy. RR, risk ratio (AIT protocol: Rush) (random-effects model). Heterogeneity: $\tau^2 = 0.921$; $\chi^2 = 15.657$, df = 1 (P<0.0001); $I^2 = 94\%$; Test for overall effect: Z = 1.146 (P<0.252)

Appendix 3.6 PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	65
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.	67
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	68
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	68
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.	69
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.	68-69
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.	68
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	E15-16
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).	68-70
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.	69
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	69
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.	69
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	69
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.	69
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).	69
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	69

Section/topic	#	Checklist item	Reported on page #
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.	69-70
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.	71-72, E17-39
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).	73, E40-41
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.	E17-39
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	74-78
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	73
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression) (see Item 16).	73, 76, E42-51
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).	79
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).	79
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	80
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.	81