TIMING OF INTRODUCTION OF ALLERGENIC FOODS IN INFANTS, AND RISK OF ALLERGIC SENSITISATION

Robert J Boyle[1], Vanessa Garcia-Larsen[2], Despo Ierodiakonou[3], Jo Leonardi-Bee[4], Tim Reeves[5], Jennifer Chivinge[6], Zoe Robinson[6], Natalie Geoghegan[6], Katharine Jarrold[6], Andrew Logan[6], Annabel Groome[6] , Sergio Cunha[7]

[1] Clinical Senior Lecturer, Section of Paediatrics [2] Post-Doctoral Research Associate, Respiratory Epidemiology and Public Health, National Heart and Lung Institute [3] Post-Doctoral Research Associate, Departments of Paediatric and Respiratory Epidemiology and Public Health Group, all at Imperial College London

[4]Associate Professor of Community Health Sciences, University of Nottingham

[5] Research Support Librarian, Faculty of Medicine, Imperial College London

[6] Undergraduate medical students, Imperial College London

[7]Research Associate, Respiratory Epidemiology and Public Health, National Heart and Lung Institute, Imperial College London

Imperial College London

Table of Contents

List of Figures

1. Timing of introduction of allergenic foods and risk of AS – summary of interventions and findings

Key information about each study is shown in the Table of Study Characteristics (Table 1), and summarised below.

1.1. Studies identified

We identified 17 intervention studies which reported the association between timing of introduction of allergenic food(s) and risk of AS. Of these, 14 were randomised control trials, 1 quasi-randomised trial and 2 controlled clinical trials. Six studies used a multifaceted intervention.

1.2. Populations

The majority of studies (n=11) were carried out in European populations, other studies were undertaken in North America (n=2) and Asia-Pacific region (n=4). Overall ~3500 participants were allocated to intervention arms, and ~3500 participants to control arms.

1.3. Interventions and comparators

Current UK Government advice is for the introduction of allergenic food into the infant diet to be delayed until 6 months of age or later. In this report we describe intervention studies of two types:

'Standard' intervention trials where comparisons have been made between giving no advice about introduction of allergenic foods (intervention), with advice to deliberately delay introduction of allergenic foods (control).

'Early' intervention trials in which comparisons have been made between deliberate early introduction of allergenic food(s) (intervention), with either no advice about introduction, or advice to delay introduction of allergenic foods (control).

For our purposes in both types of study the early or unrestricted introduction of allergenic foods is considered as being the 'intervention', and the delayed or standard introduction of allergenic foods as being the 'control'. The reason for this is so that, where appropriate, both types of study can be incorporated into the same meta-analysis.

Cow's milk was used in the intervention group in 12 studies (as early intervention in 4 and standard in 8); egg in 9 studies (early intervention in 4 and standard in 5); fish in 7 studies (early intervention in 1 and standard in 6); soya in 6 studies all as standard; peanut in 4 studies (early intervention in 2 and standard in 2); wheat in 3 studies (early intervention in 1 and standard in 2); other nuts (tree nuts) in 3 studies all as standard; sesame in 1 study as early intervention.

1.4. Outcome assessment methods used

In 14 studies the outcome was defined using skin prick test and in 8 using specific IgE (not mutually exclusively). We included all available data, and pooled data for SPT and sIgE in meta-analyses. Where both measurements were available from the same study we prioritised SPT, and where there were sufficient studies in a meta- analysis we undertook stratified analysis according to the method used for assessing allergic sensitisation. The antigens measured were egg (n=10), cow's milk (n=8), aeroallergens (n= 3) and peanut (n=3) (not mutually exclusively).

1.5. Risk of bias assessment

Overall risk of bias was considered high in 5 studies (33%), due to a combination of attrition bias (n=3) and selection bias (n=2). Four studies had low overall risk of bias. Two studies were considered at high risk of bias due to conflict of interest.

1.6. Key findings

i. Analyses were dominated by studies of multiple interventions – either multifactorial interventions designed to prevent allergic disease, or in one case a multiple allergenic food intervention.

ii. We found no evidence that timing of introduction of cow's milk, soya, egg, peanut, tree nuts, fish, wheat, or 'any allergenic food' is associated with AS.

iii. We found no clear evidence for a relationship between timing of allergenic food introduction and AS to the same food.

Table 1 Characteristics of intervention trials evaluating timing of allergenic food introduction in infants and AS

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Bellach, 2016 (1)	RCT	184/ 199	Pasteurised egg white powder versus rice powder 3 times per week from 4-6 months to 12 months	**HEAP Study.** Infants aged 4-6 months with specific IgE to egg <0.35 kU/L	Germany	Normal	1	sIgE-Egg
de Jong, 2002 (2)	RCT	758/ 775	Cow's milk formula ≥3 times in the first 3 days, versus protein-free placebo formula.	**BOKAAL Study**. Healthy term newborns whose mother intended to breastfeed for ≥6 weeks.	Netherlands	Normal	5	sIgE-Any; sIgE-CM; sIgE-Egg
Du Toit, 2015 (3, 4)	RCT	319/ 321	6g peanut protein per week, divided between 3 meals, from 4-11 months to 5 years, versus peanut avoidance.	**Learning Early About Peanut allergy (LEAP) Study**. Infants aged 4-11 months with severe eczema and/or egg allergy and peanut SPT <4mm. Mean 7.8 months.	UK	High	5, 6	sIgE and SPT to Peanut
Becker, 2004 (5); Chan-Yeung, 2000/5 (6); (7); Carlsten 2013(8)	RCT	268/ 281	**MULTIFACETED**. Standard care versus BF ≥4 months, allergenic food exclusion during pregnancy/lactation, delayed solid (≥6 months) and allergenic food (milk, seafood, peanut ≥12 months) and environmental control.	**Canadian Asthma Primary Prevention study (CAPPS).** Children with family history of atopic disease.	Canada	High	1, 7, 15	SPT-aero; SPT-CM; SPT-Egg; SPT-Peanut
Halmerbauer, 2002/3 (9, 10)	RCT	347/ 349	**MULTIFACETED**. Standard care versus e BF ≥ 3 months, delayed solid (≥6 months) and allergenic food (milk, egg, fish, nuts ≥1 year), and environmental control.	**Study on the Prevention of Allergy in Children in Europe (SPACE)**. ≥1 parent with a positive allergy history plus aeroallergen sensitisation.	UK, Germany, Austria	High	1	sIgE and SPT to Any Allergen, CM and Egg

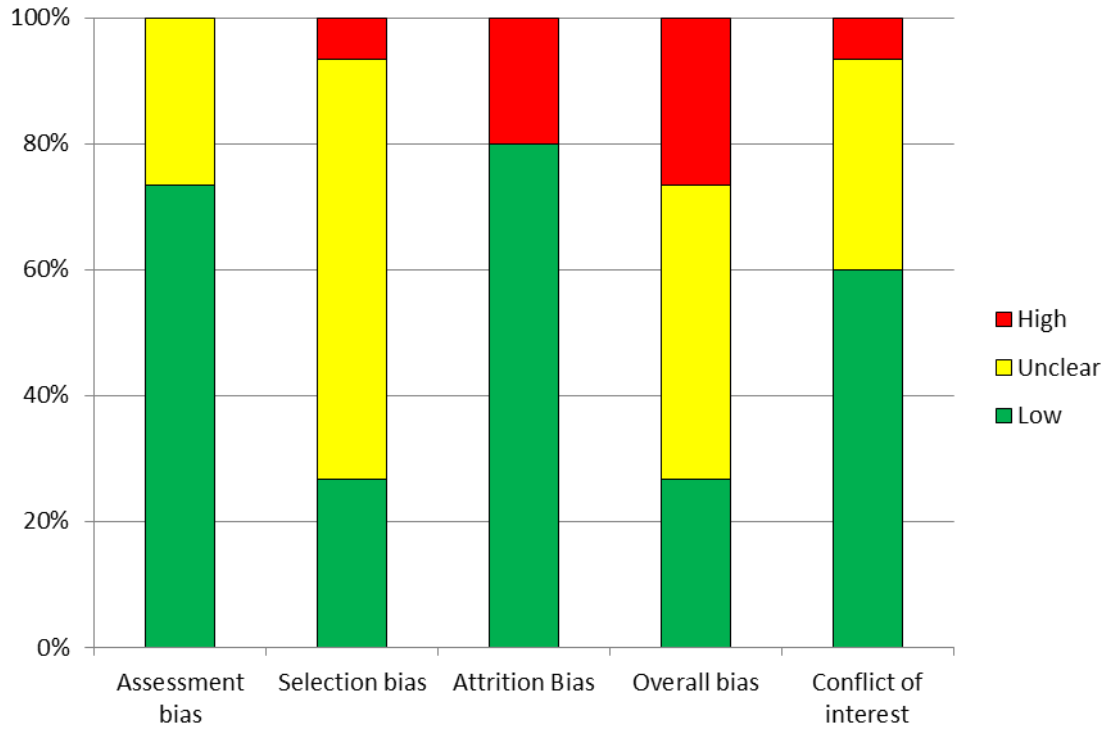
Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Hide, 1994/6 (11, 12) Arshad, 1992/ 2003/7 (13-15) Scott, 2012 (16)	RCT	68/ 71	**MULTIFACETED**. Standard care versus cow's milk, egg, wheat, nuts, fish and soya excluded from diet of infant and lactating mother to 9 months, soya hydrolysate if needed, environmental control.	**Isle of Wight Study**. Infants with a first degree relative affected by an allergic disorder plus cord blood IgE>0.5kU/L.	UK	High	1, 8, 18	SPT-CM; SPT-Egg, Total IgE
Kjellman, 1979 (17)	RCT	25/ 23	Cow's milk versus soya formula as needed until 9 months. Study formula introduced at median 1.5 months age.	Infants with biparental history of atopic disease.	Sweden	High	4	SPT-Any; sIgE-CM, Total IgE
Lowe, 2011 (18)	RCT	206/ 208	Cow's milk versus soya formula, as needed from birth. Introduced at median 4 months.	**Melbourne Atopy Cohort Study (MACS).** Infants with a first degree relative with eczema, asthma, AR or food allergy.	Australia	High	7	SPT-Any, SPT-CM
Burr, 1993 (19); Merrett, 1988 (20); Miskelly, 1988 (21)	RCT	238/ 249	Cow's milk versus soya formula as needed from birth to 6 months. Milk intake restricted during pregnancy & lactation in soya group.	Infants recruited in South Wales with history of asthma, eczema or hayfever in at least one family member	UK	High	1, 7	SPT-Any
Palmer, 2013 (22)	RCT	49/ 37	1 teaspoon per day of pasteurized raw whole egg powder, versus rice flour powder, given daily from randomization at 4 months to 8 months age.	Singleton term infants with symptoms of moderate-to-severe eczema.	Australia	High	1	SPT or sIgE to Egg

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Perkin, 2016 (23)	RCT	652/ 651	Sequential introduction of six allergenic foods - cow's milk, peanut, egg, wheat, sesame and fish from age 3 months, versus avoidance to ≥6 months.	**Early Acquisition of Tolerance (EAT) Study.** Children exclusively breastfed at 3 months and gestation over 37 weeks.	UK	Normal	3	SPT-Food; SPT-CM; SPT-Egg; SPT-Peanut
Shao, 2006 (24)	RCT	23/ 23	**MULTIFACETED**. Standard advice versus eBF for 4 months, allergenic food exclusion during lactation, delayed solid (4 months) and allergenic food (fish/prawn ≥6 months; egg/nuts ≥12 months), pHF if necessary.	Chinese babies with parental history of allergic disease, with specific food allergies according to + SPT	China	High	1.5	sIgE or SPT to any food
Tan, 2016 (25)	RCT	165/ 154	Pasteurised whole egg powder (350mg egg protein) daily versus rice powder from the time of solid food introduction until 8 months age.	BEAT Study. Infants with a first degree relative with allergic disease, and egg SPT <2mm at age 4 months.	Australia	High	1	SPT-Egg
Zeiger, 1989/92/94 (26-28)	RCT	~185 / 103	**MULTIFACETED**. Standard care versus infants cow's milk/ wheat/soy/egg/peanut/fish avoidance to ≥1 year & maternal allergenic food avoidance during pregnancy/ lactation.	Infants covered by Kaiser Permanente Health Plan, with an allergic parent.	USA	High	2, 4, 7	SPT-Aero
Juvonen, 1996 (29); Juvonen, 1999 (30)	qRCT	~43/ 58	Cow's milk formula versus breast milk for first 3 days of life.	Healthy term infants.	Sweden	Normal	1	Total IgE, sIgE-CM, sIgE-Egg

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Lindfors, 1988 (31) Lindfors, 1992 (32)	CCT	112/ 104	Cow's milk formula given as first meal and increased to ≤60 ml every 4 hours, until breastfeeding started; versus breastfed from birth.	Healthy low birth weight infants with gestational age 37-42 weeks.	Sweden	Normal	1.5, 5	SPT-Aero; SPT-Food; SPT-CM; SPT-Egg
Matthew, 1977 (12)	CCT	35/ 27	**MULTIFACETED**. Standard care in cow's milk formula fed infants, versus BF for ≥6 months, soya in place of cow's milk, delayed solid (≥3 months) and allergenic (cow's milk, fish and egg ≥6 months), environmental control	Included mothers with a convincing history of asthma, AR, and eczema from Queen Charlotte's Hospital	UK	High	1	SPT-Any, SPT-CM

BF breastfeeding; eBF exclusive breastfeeding; RCT randomised clinical trial, qRCT quasi-randomised controlled trial, CCT controlled clinical trial; SPT skin prick test, BHR bronchial hyperresponsiveness, FEV_1 forced expiratory volume in one second; Physician assessment refers to assessment by a study physician , DD refers to community diagnosis

Figure 1 Risk of bias in intervention studies of timing of allergenic food introduction and risk of AS



2. Timing of cow's milk introduction and risk of AS

2.1. Short term early cow's milk introduction and AS

Figures 2 to 8 show data from studies of short term early cow's milk introduction (where the intervention period was limited to the first week of life, and did not extend beyond this) and risk of AS. Data are generally sparse, but there is no statistically significant association seen with AS-Any, AS to specific foods, or to aeroallergens.

Figure 2 Short term early cow's milk introduction and risk of AS-Any

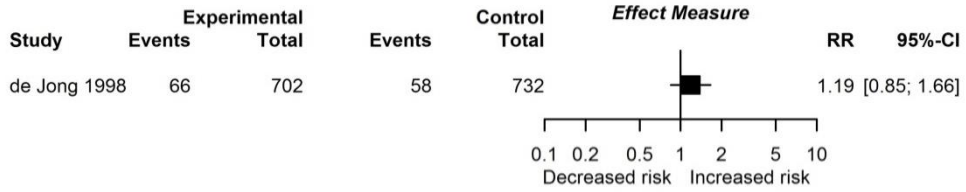


Figure 3 Short term early cow's milk introduction and risk of AS-Food CCT

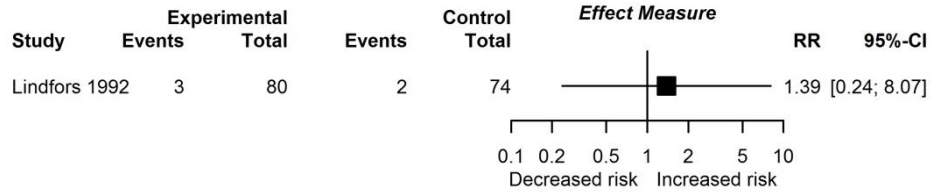


Figure 4 Short term early cow's milk introduction and risk of AS-CM

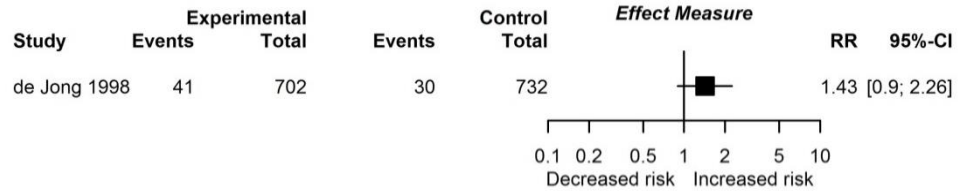


Figure 5 Short term early cow's milk introduction and risk of AS-CM CCT

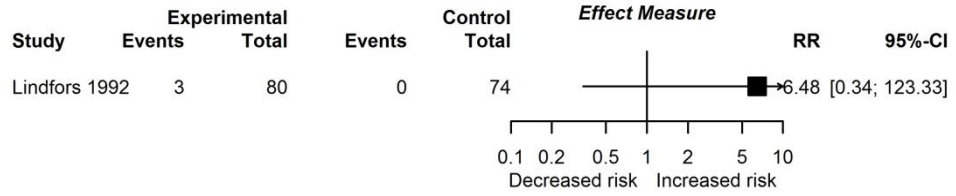


Figure 6 Short term early cow's milk introduction and risk of AS-Egg

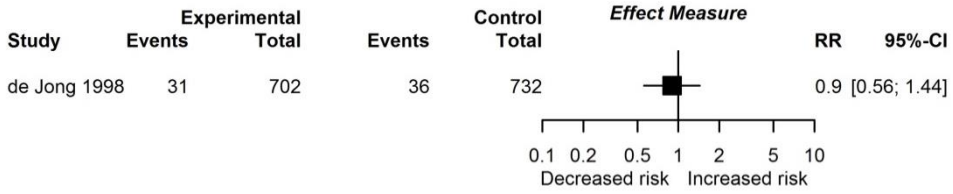


Figure 7 Short term early cow's milk introduction and risk of AS-Egg CCT

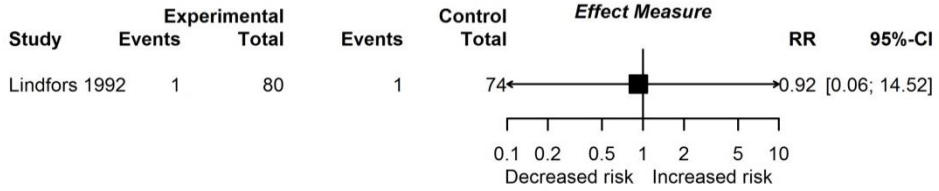
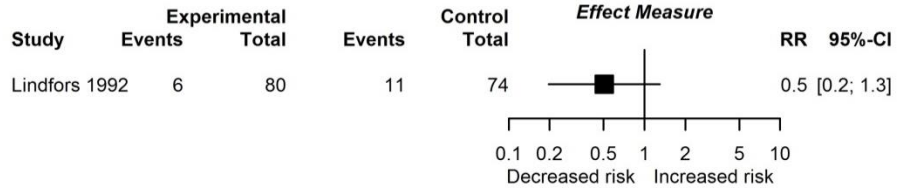


Figure 8 Short term early cow's milk introduction and risk of AS-Aero CCT



2.2. Longer term early cow's milk introduction and AS

Figures 9 to 14 show data from studies of longer term early cow's milk introduction (where the intervention period was not restricted to the first week of life) and risk of AS. No significant association was seen between early and late cow's milk introduction and AS-Any, AS to any food or specific foods, or AS to aeroallergen. Subgroup analysis of AS-CM suggests a significant difference between multifaceted and single intervention studies, but in neither group is there a statistically significant effect of the intervention on AS-CM (Table 2).

Figure 9 Early cow's milk introduction and risk of AS-Any

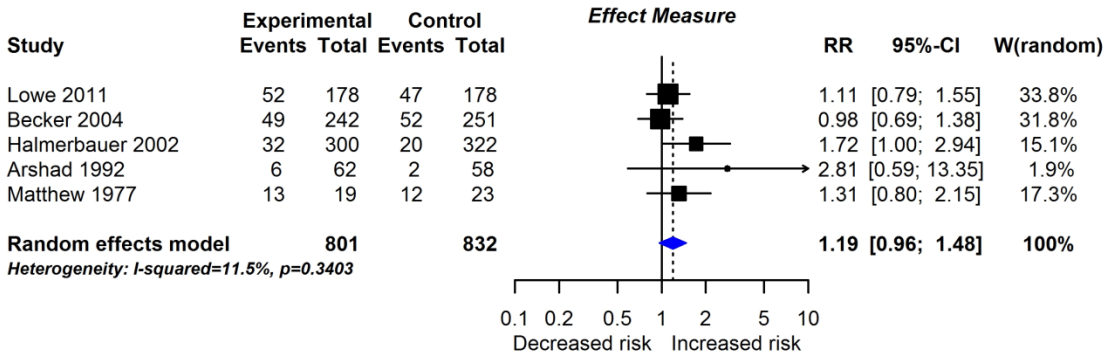
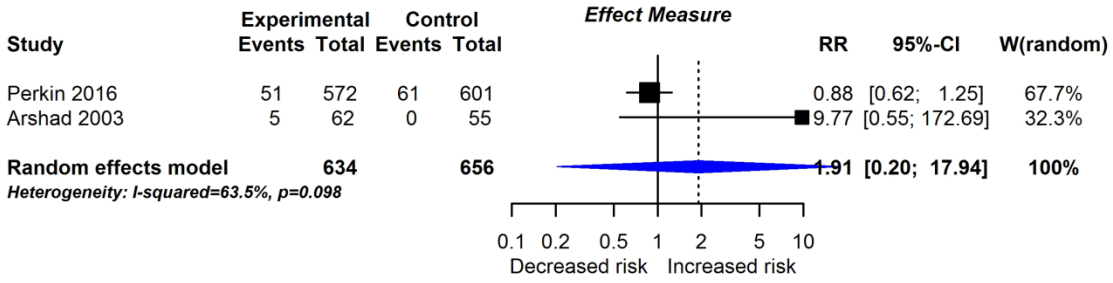


Figure 10 Early cow's milk introduction and risk of AS-Food



Note – both studies included advice regarding timing of cow's milk introduction, but both studies also included other dietary and/or non-dietary interventions.

Figure 11 Early cow's milk introduction and the risk of AS-CM

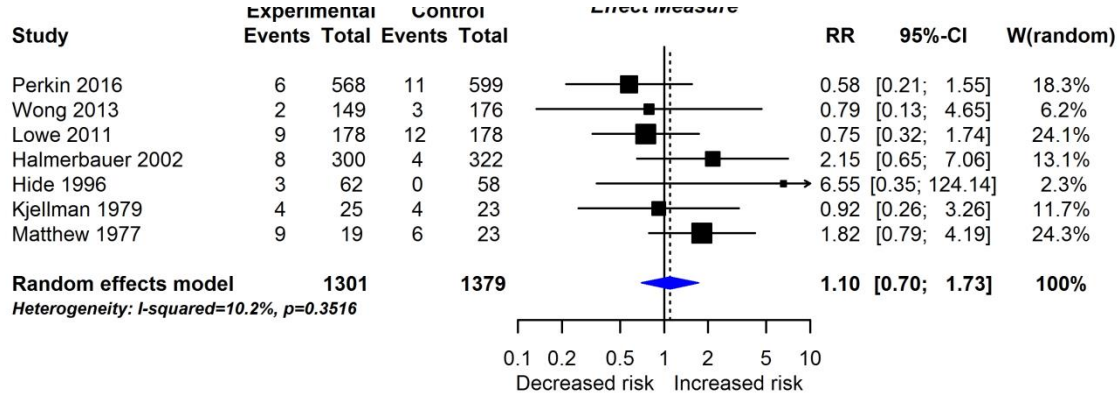


Figure 12 Early cow's milk introduction and risk of AS-Egg

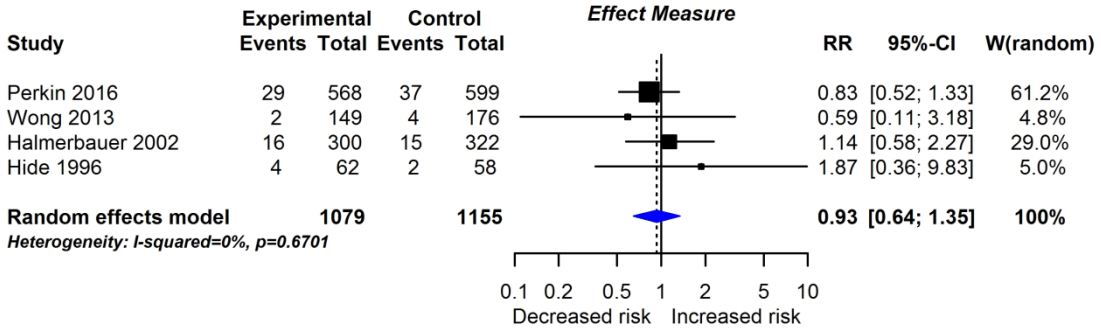


Figure 13 Early cow's milk introduction and risk of AS-Peanut

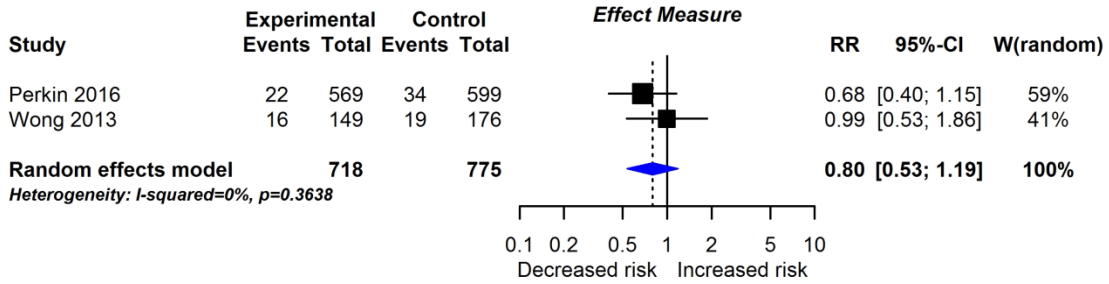


Table 2 Subgroup analyses of early cow's milk introduction and risk of AS-CM

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Method of assessment – Mixed sIgE/SPT	1	2.15 [0.65-7.06]	-	
Method of assessment - sIgE	1	0.92 [0.26-3.26]	-	0.51
Method of assessment - SPT	5	1.01 [0.56-1.81]	24.1	
Study design – RCT	7	1.10 [0.70-1.73]	10.2	-
Study design – qRCT	-	-	-	
Intervention – early introduction	1	0.58 [0.21-1.55]	-	0.16
Intervention – 'standard' introduction	6	1.26 [0.79-2.01]	0	
Risk of disease – High	6	1.26 [0.79-2.01]	0	0.16
Risk of disease – Low/Normal	1	0.58 [0.21-1.55]	-	
Intervention – multifaceted	4	1.82 [0.97-3.39]	0	**0.03**
Intervention – not multifaceted	3	0.72 [0.40-1.27]	0	
Overall risk of bias – High/Unclear	7	1.10 [0.70-1.73]	10.2	-
Overall risk of bias – Low	-	-	-	
Risk of conflict of interest – High/Unclear	2	1.48 [0.74-2.97]	17.1	0.35
Risk of conflict of interest – Low	5	0.95 [0.52-1.75]		

2.3. Data for cow's milk introduction and AS which were not included in meta-analysis

Zeiger 2004 separately reported no significant difference in AS to cow's milk, egg, peanut, any food or any aeroallergen at age 4, but no data were shown that could be included in meta-analysis. **Chan_Yeung 2005** separately reported no significant difference in AS to any allergen at age 2 and age 7 in the same study as Becker 2004 (CAPPS). **Matthew 1977** found no significant difference in total IgE between intervention and control group at one year of age – mean IgE level 6.0 (sd 3.4; n=16) intervention, 7.6 (sd 4.4; n=11) control P=0.30. **Arshad 1992** reported no significant difference in total IgE level at age 8, between standard (geometric mean 91.7 units) compared with delayed (geometric mean 103.6 units) allergenic food introduction, in a multifaceted trial (P=0.71). **Kjellman 1979** and **Juvonen 1999** measured total IgE at 3.5 years and 1 year respectively, and found no significant difference in IgE level between infants allocated to early versus late CM introduction. Juvonen 1999 reported no significant difference between groups in AS-CM or AS-Egg at 1 year, but did not present data that could be included in meta-analysis. **Burr 1993** measured AS-Any using SPT at age 1 and age 7, but did not report the outcome by treatment allocation.

2.4. Conclusions: cow's milk introduction and AS

Overall 12 studies reported this association. Statistical heterogeneity was generally low to moderate. No study and no meta-analysis found any significant association between early cow's milk introduction and AS or total IgE. Overall there was no evidence to suggest a relationship between timing of introduction of cow's milk to the infant diet, and AS risk.

Overall we found no evidence that early cow's milk introduction influences risk of AS.

3. Timing of soya introduction and risk of AS

Figures 14 to 16 show data from studies of soya milk introduction and risk of AS. In general data are relatively sparse and do not show evidence of an association.

Figure 14 Early soya milk introduction and risk of AS-Any

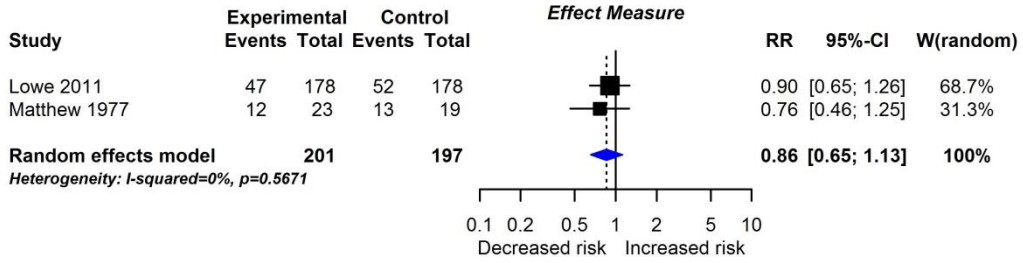


Figure 15 Early soya milk introduction and risk of AS-CM

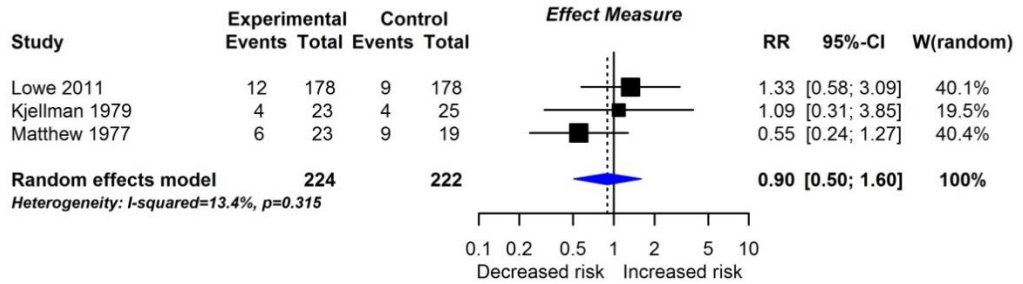
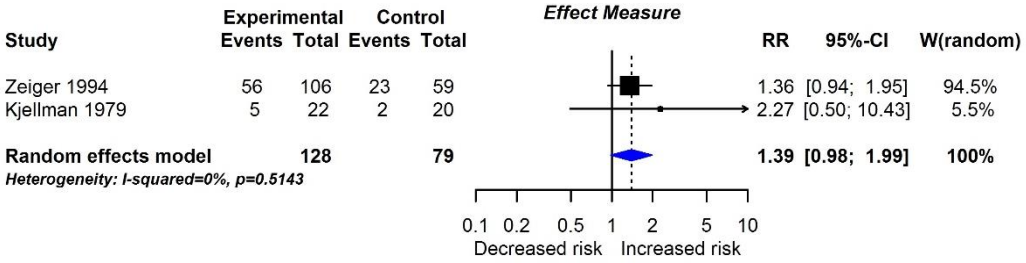


Figure 16 Early soya milk introduction and risk of AS-Aero



3.1. Data for soya introduction and AS which were not included in meta-analysis

Zeiger 1994 separately reported no significant difference in AS to cow's milk, egg, peanut, any food or any aeroallergen at age 4 in relation to timing of soya introduction, but no data were shown that could be included in meta-analysis. **Matthew 1977** found no significant difference in total IgE between intervention and control group at one year of age – mean IgE level 6.0 (sd 3.4; n=16) intervention, 7.6 (sd 4.4; n=11) control P=0.30. **Kjellman 1979** measured total IgE at 3.5 years, and found no significant difference in IgE level between infants allocated to early versus late soya introduction. **Burr 1993** measured AS-Any using SPT at age 1 and age 7, but did not report the outcome by treatment allocation.

3.2. Conclusions: soya introduction and AS

Overall 5 studies reported this association, and neither individual studies nor meta-analyses found evidence of a relationship between timing of soya introduction and AS.

Overall we found no evidence that early soya introduction influences risk of AS.

4. Timing of egg introduction and risk of AS

Figures 17 to 21 show data from studies of egg introduction and risk of AS. Data are mainly derived from studies of multiple interventions (either multifaceted interventions, or early introduction of multiple foods), with just one trial of simple egg introduction reported (Palmer). Pooled data from three multifaceted intervention studies found increased AS-Any associated with early egg introduction (Figure 17). This was not seen in analysis of AS to any food, or to individual foods including egg (Figure 20). Sensitivity analysis of AS-Egg excluding the 'standard' studies showed similar findings to those shown in Figure 10 – RR 0.77 95% CI 0.53, 1.11 I^2=37%.

Figure 17 Early egg introduction and risk of AS-Any

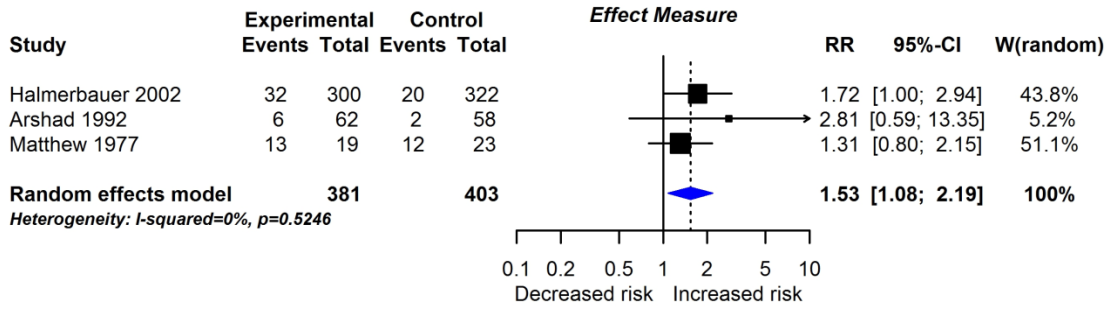


Figure 18 Early egg introduction and risk of AS-Food

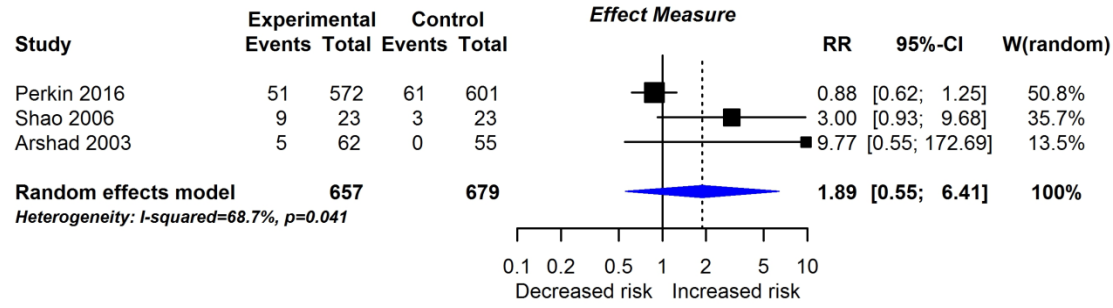


Figure 19 Early egg introduction and risk of AS-CM

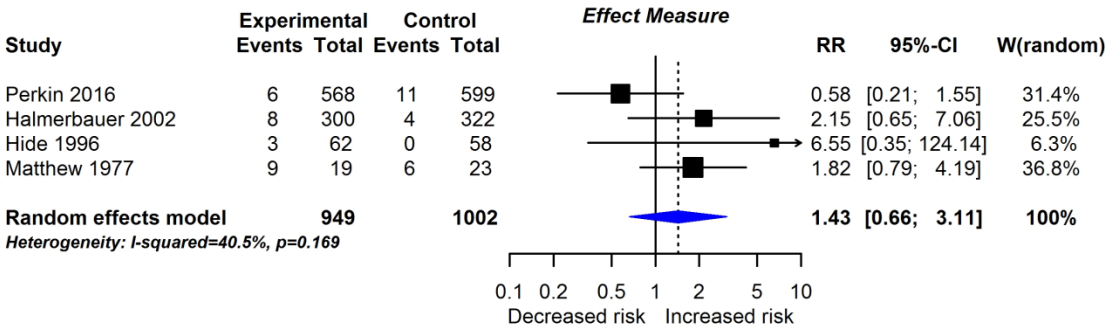


Figure 20 Early egg introduction and risk of AS-Egg

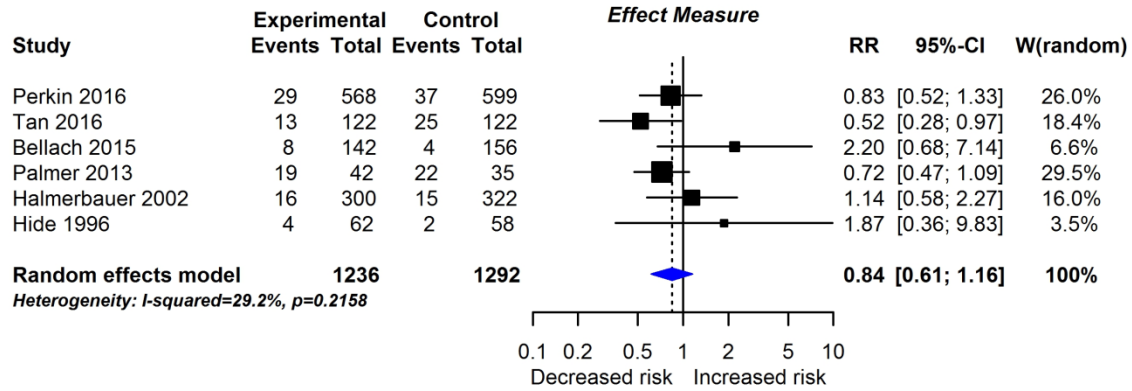
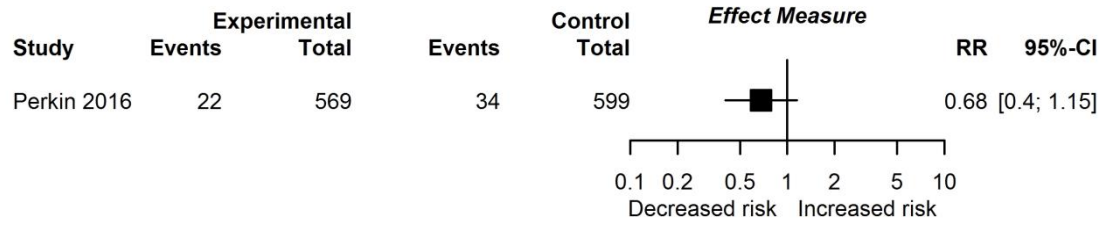


Figure 21 Early egg introduction and risk of AS-Peanut



4.1. Data for egg introduction and AS which were not included in meta-analysis

Zeiger 1994 separately reported no significant difference in AS to cow's milk, egg, peanut, any food or any aeroallergen at age 4, but no data were shown that could be included in meta-analysis. **Matthew 1977** found no significant difference in total IgE between intervention and control group at one year of age – mean IgE level 6.0 (sd 3.4; n=16) intervention, 7.6 (sd 4.4; n=11) control P=0.30. **Arshad 1992** reported no significant difference in total IgE level at age 8, between standard (geometric mean 91.7 units) compared with delayed (geometric mean 103.6 units) allergenic food introduction, in a multifaceted trial (P=0.71). In the study of **Palmer 2013** the authors reported no significant difference in AS to egg measured as median specific IgE to egg (P=0.88).

4.2. Conclusions: egg introduction and AS

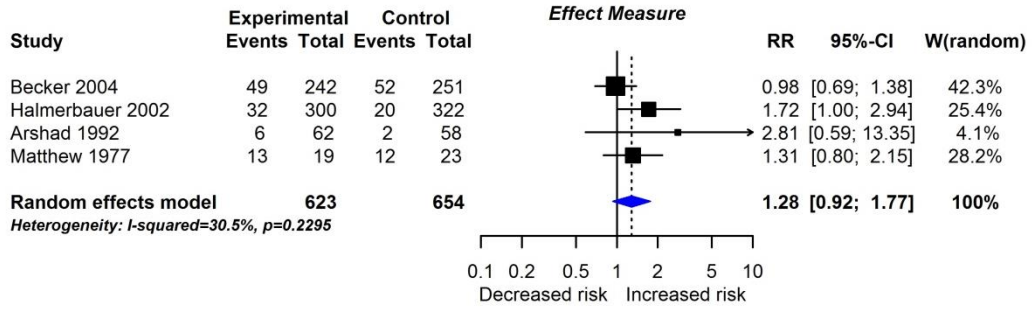
Overall 9studies reported this outcome. Almost all meta-analyses showed no evidence of any association between timing of egg introduction and AS-Any, AS-Food, AS-CM, AS-Egg, AS-Peanut or AS-Aero.

Overall we found no evidence that earlier egg introduction influences risk of AS. For studies of AS-Egg introduction of egg before 3, 4-6, 4-8 and at the time of weaning were evaluated in trials of 'early' egg introduction; and delayed introduction of egg to after 9-12 months was evaluated in the trials of 'standard' egg introduction.

5. Timing of nut, wheat and fish introduction and risk of AS

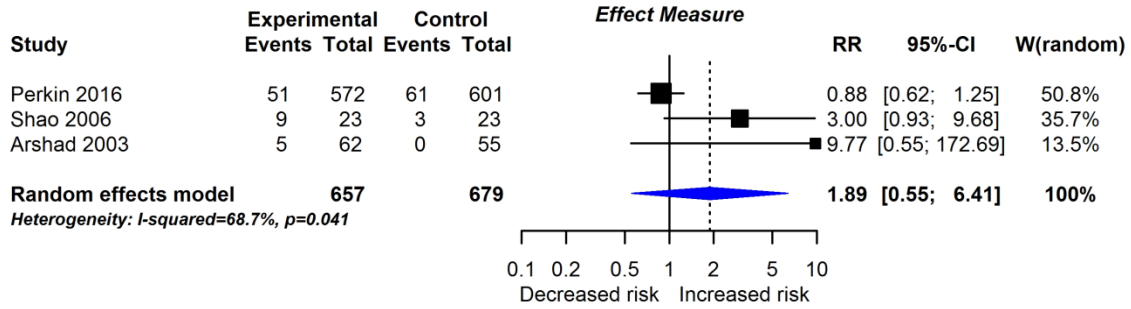
Figures 22 to 27 show data from studies of nut (peanut and/or tree nut), wheat and fish introduction and risk of AS. Data are exclusively derived from studies of multiple interventions (either multifaceted interventions, or early introduction of multiple foods). Findings were not suggestive of a relationship between early nut introduction and risk of AS.

Figure 22 Early nut, wheat and fish introduction and risk of AS-Any



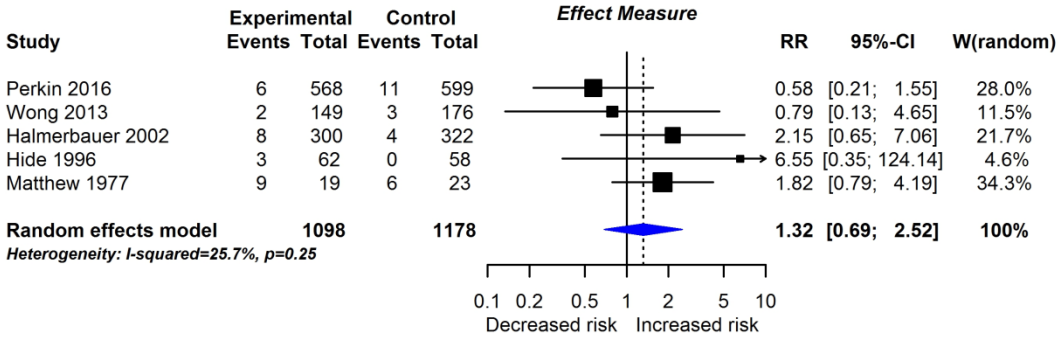
The study of Arshad 1992 included advice regarding nut, wheat and fish introduction; Becker 2004 and Halmerbauer 2002 nut and fish; Matthew 1977 included advice regarding fish introduction, but not nut or wheat.

Figure 23 Early nut, wheat and fish introduction and risk of AS-Food



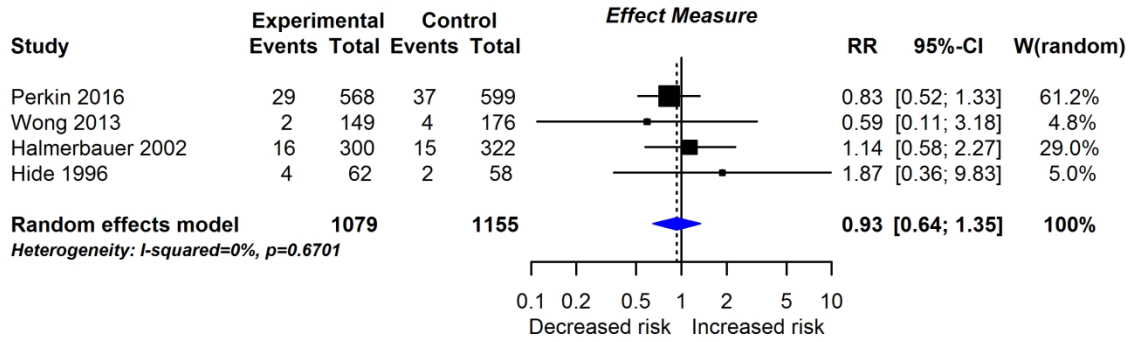
The studies of Perkin and Arshad 2003, but not Shao 2006, included advice regarding wheat introduction. Meta-analysis of these two studies showed no evidence for an effect on AS-Food.

Figure 24 Early nut, wheat and fish introduction and risk of AS-CM



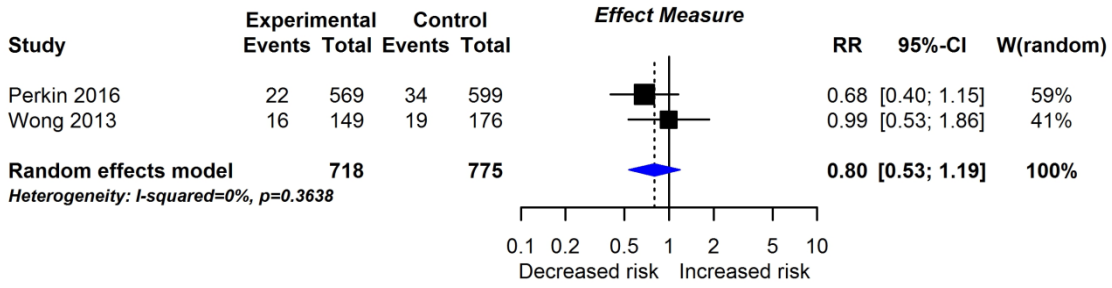
The studies of Perkin 2016 and Hide 1996 included advice regarding nut, wheat and fish introduction; Wong 2013 and Halmerbauer 2002 nut and fish; Matthew 1977 included advice regarding fish introduction, but not nut or wheat.

Figure 25 Early nut, wheat and fish introduction and risk of AS-Egg



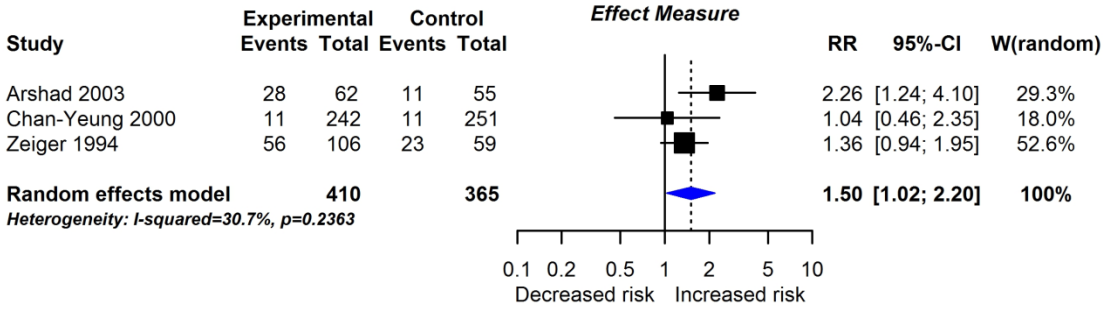
The studies of Perkin 2016 and Hide 1996, but not the others, included advice regarding wheat introduction. Meta-analysis of these two studies alone showed no evidence for an effect on AS-Egg.

Figure 26 Early nut, wheat and fish introduction and risk of AS-Peanut



The study of Perkin 2016, but not Wong 2013, included advice regarding wheat introduction.

Figure 27 Early nut, wheat and fish introduction and risk of AS-Aero



The studies of Arshad 2003 and Zeiger 1994, but not Chan-Yeung 2000, included advice regarding wheat introduction.

5.1. Data for nut introduction and AS which were not included in meta-analysis

Zeiger 1994 separately reported no significant difference in AS to cow's milk, egg, peanut, any food or any aeroallergen at age 4, but no data were shown that could be included in meta-analysis. **Chan_Yeung 2005** separately reported no significant difference in AS to any allergen at age 2 and age 7 in the same study as Becker 2004 (CAPPS). **Arshad 1992** reported no significant difference in total IgE level at age 8, between standard (geometric mean 91.7 units) compared with delayed (geometric mean 103.6 units) allergenic food introduction, in a multifaceted trial (P=0.71). In the study of **du Toit 2015** the authors reported significantly lower allergic sensitisation to peanut in the early peanut intervention group 'SPT wheal size and sIgE level to peanut were significantly lower in the intervention than control group at all study timepoints including 5 years P<0.001'. Similar findings were reported at 6 years.

5.2. Conclusions: nut introduction and AS

Overall 8 studies reported this outcome. In 7 studies there was no evidence of association, but in one study with direct early feeding of peanut and a very high treatment compliance rate there was reduced AS-Peanut – no numerical data were reported.

Overall we found no consistent evidence that early nut, wheat or fish introduction reduces risk of AS-Peanut.

6. Timing of 'any allergenic food' introduction and risk of AS

It is possible that any effect of early allergenic food introduction is not allergen-specific. To assess evidence for this, we also undertook analysis of RCT/qRCT evidence that timing of 'any allergenic food' (AF) introduction is related to risk of AS. These analyses were stratified by the intervention, and studies which compared early introduction of one allergenic food with another eg cow's milk versus soya milk) were not included in these analyses (Brown 1969, Johnstone 1966, Arshad 1992, Kjellman 1979, Lowe 2011, Merrett 1988, Zhou 2014, Gruskay 1982). Figures 28 to 33 show data from studies of AF introduction and risk of AS. Findings are similar to those of previous analyses in this report, and do not contribute significant added information.

Figure 28 Early AF introduction and risk of AS-Any

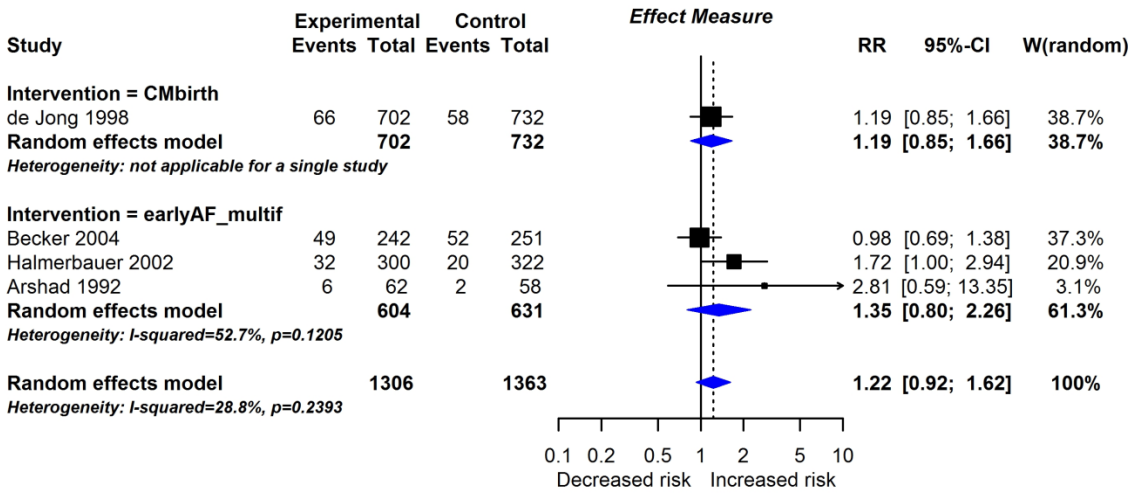


Figure 29 Early AF introduction and risk of AS-Food

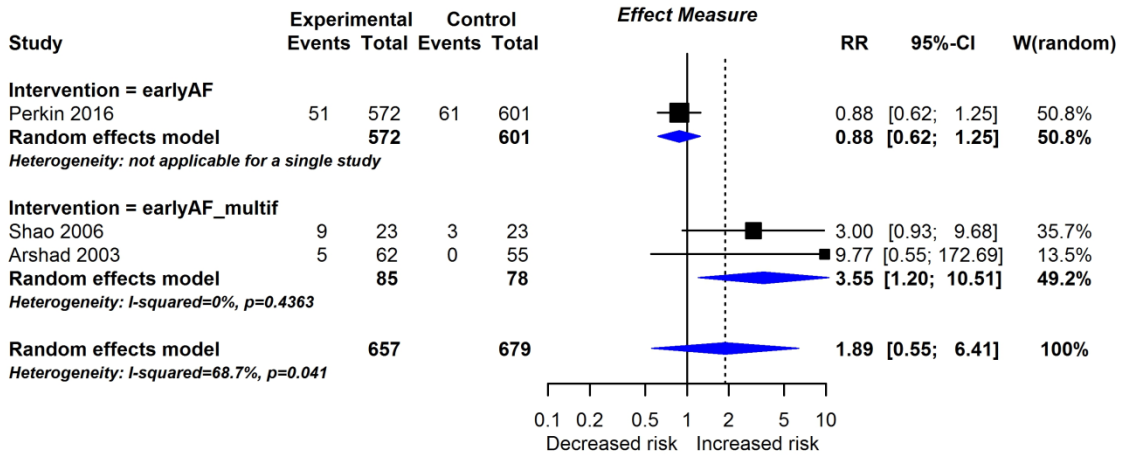


Figure 30 Early AF introduction and risk of AS-CM

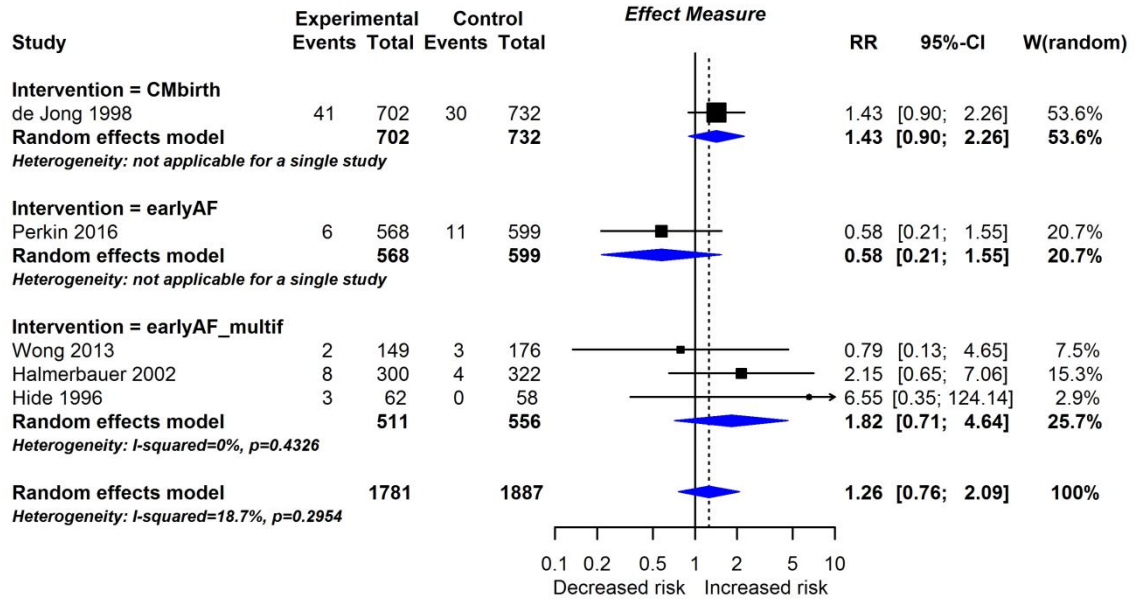


Figure 31 Early AF introduction and risk of AS-Egg

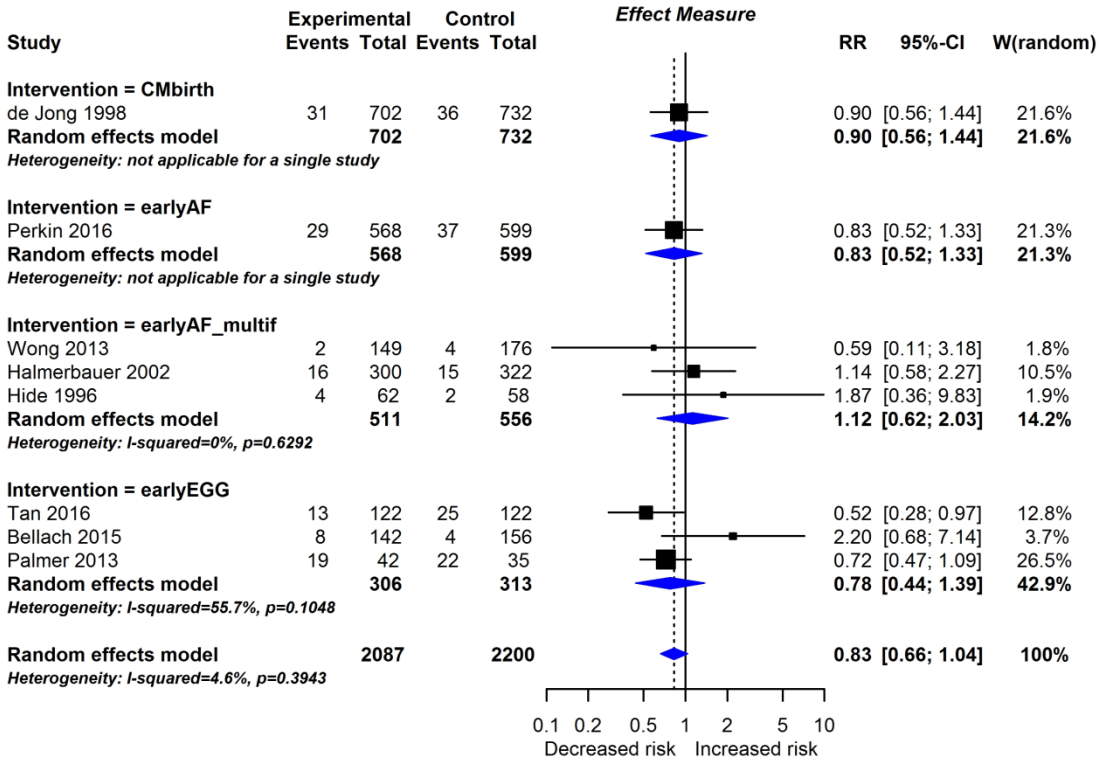


Figure 32 Early AF introduction and risk of AS-Peanut

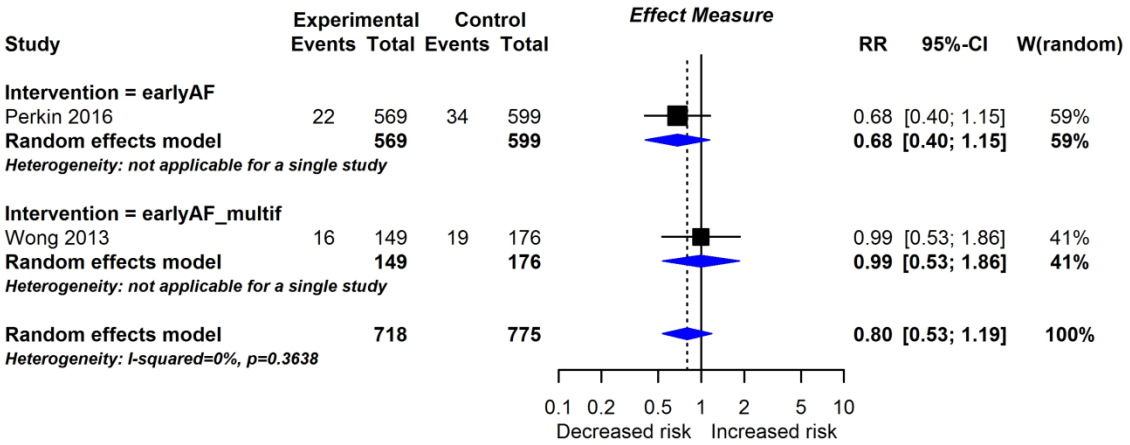
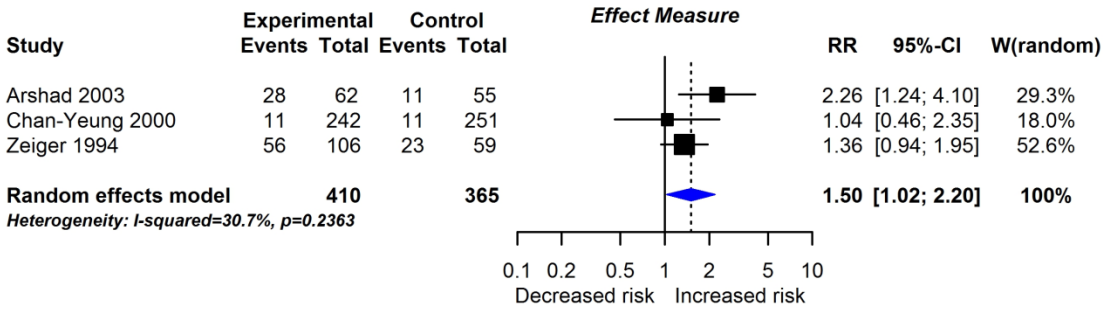


Figure 33 Early AF introduction and risk of AS-Aero



6.1. Conclusions: 'any allergenic food' introduction and AS

Overall 10 studies reported this association. No significant association was found.

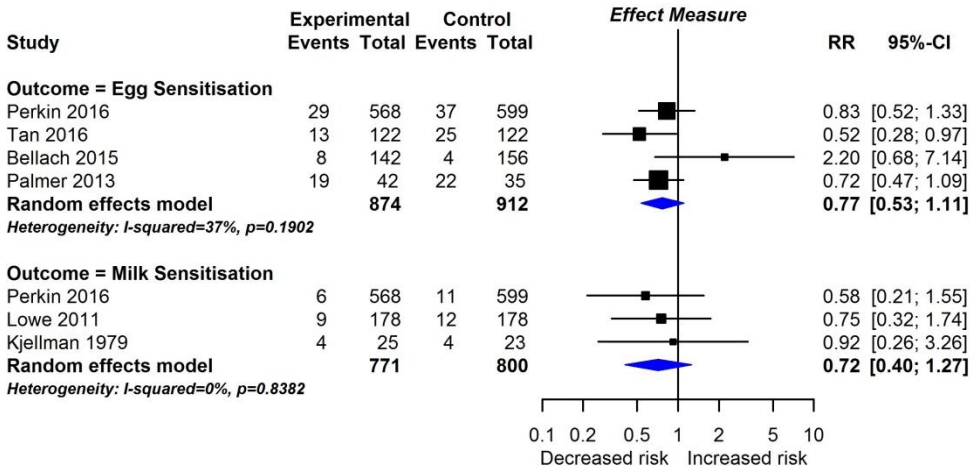
Overall we did not find evidence that early allergenic food introduction influences risk of AS in a non allergen-specific manner.

7. Timing of allergenic food introduction and risk of AS to the same food

In order to evaluate fully the possibility that timing of allergenic food introduction influences risk of AS to the same food, we meta-analysed studies where timing of allergenic food introduction was modified as part of the intervention, and the outcome AS to the intervention food(s) was reported. If the phenomenon of oral tolerance, first described in guinea pigs over 100 years ago, is relevant to humans – then one might expect a similar, allergen-specific effect across all common food allergens.

Figure 34 shows data from studies of AF introduction and risk of AS to the same food. Pooled analysis shows moderate statistical heterogeneity, and no significant association for either milk, egg or both pooled. In the study of **du Toit 2015** the authors reported significantly lower allergic sensitisation to peanut in the early peanut intervention group up to age 5 years (P<0.001) but numerical data were not reported which could be included in meta-analysis.

Figure 34 Early AF introduction and risk of AS to the same food



Overall we did not find consistent evidence that timing of cow's milk, egg or peanut introduction influence risk of AS to the same food.

References

1. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Keil T, Niggemann B, et al. Early introduction of hen's egg during weaning results in frequent allergic reactions: First results from a randomized placebo-controlled trial on hen's egg allergy prevention: Blackwell Publishing Ltd; 2015. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=72028833.

2. de Jong MH, Scharp-Van Der Linden VT, Aalberse R, Heymans HS, Brunekreef B. The effect of brief neonatal exposure to cows' milk on atopic symptoms up to age 5. Archives of Disease in Childhood. 2002;86(5):365-9.

3. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. New England Journal of Medicine. 2015;372(9):803-13.

4. Du Toit G, Sayre PH, Roberts G, Sever ML, Lawson K, Bahnson HT, et al. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. The New England journal of medicine. 2016.

5. Becker A, Watson W, Ferguson A, Dimich-Ward H, Chan-Yeung M. The Canadian asthma primary prevention study: outcomes at 2 years of age. Journal of Allergy & Clinical Immunology. 2004;113(4):650-6.

6. Chan-Yeung M, Manfreda J, Dimich-Ward H, Ferguson A, Watson W, Becker A. A randomized controlled study on the effectiveness of a multifaceted intervention program in the primary prevention of asthma in high-risk infants. Archives of Pediatrics & Adolescent Medicine. 2000;154(7):657-63.

7. Chan-Yeung M, Ferguson A, Watson W, Dimich-Ward H, Rousseau R, Lilley M, et al. The Canadian Childhood Asthma Primary Prevention Study: outcomes at 7 years of age. Journal of Allergy & Clinical Immunology. 2005;116(1):49-55.

8. Carlsten C, Dimich-Ward H, Ferguson A, Watson W, Rousseau R, Dybuncio A, et al. Atopic dermatitis in a high-risk cohort: Natural history, associated allergic outcomes, and risk factors. Annals of Allergy, Asthma and Immunology. 2013;110(1):24-8.

9. Halmerbauer G, Gartner C, Schierl M, Arshad H, Dean T, Koller DY, et al. Study on the Prevention of Allergy in Children in Europe (SPACE): Allergic sensitization at 1

year of age in a controlled trial of allergen avoidance from birth. Pediatric Allergy and Immunology. 2003;14(1):10-7.

10. Halmerbauer G, Gartner C, Schierl M, Arshad H, Dean T, Koller DY, et al. Study on the Prevention of Allergy in Children in Europe (SPACE): Allergic sensitization in children at 1 year of age in a controlled trial of allergen avoidance from birth. Pediatric Allergy and Immunology, Supplement. 2002;13(15):47-54.

11. Hide DW. The Isle of Wight study, an approach to allergy prevention. Pediatric Allergy & Immunology. 1994;5(6 Suppl):61-4.

12. Hide DW, Matthews S, Tariq S, Arshad SH. Allergen avoidance in infancy and allergy at 4 years of age. Allergy. 1996;51(2):89-93.

13. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. Lancet. 1992;339(8808):1493-7.

14. Arshad SH, Bateman B, Matthews SM. Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. Thorax. 2003;58(6):489-93.

15. Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. Journal of Allergy & Clinical Immunology. 2007;119(2):307-13.

16. Scott M, Roberts G, Kurukulaaratchy RJ, Matthews S, Nove A, Arshad SH. Multifaceted allergen avoidance during infancy reduces asthma during childhood with the effect persisting until age 18 years. Thorax. 2012;67(12):1046-51.

17. Kjellman NI, Johansson SG. Soy versus cow's milk in infants with a biparental history of atopic disease: development of atopic disease and immunoglobulins from birth to 4 years of age. Clinical Allergy. 1979;9(4):347-58.

18. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB, et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. Journal of Allergy & Clinical Immunology. 2011;128(2):360-5.e4.

19. Burr ML, Limb ES, Maguire MJ, Amarah L, Eldridge BA, Layzell JC, et al. Infant feeding, wheezing, and allergy: a prospective study. Archives of Disease in Childhood. 1993;68(6):724-8.

20. Merrett TG, Burr ML, Butland BK, Merrett J, Miskelly FG, Vaughan-Williams E. Infant feeding and allergy: 12-month prospective study of 500 babies born into allergic families. Annals of Allergy. 1988;61(6 Pt 2):13-20.

21. Miskelly FG, Burr ML, Vaughan-Williams E, Fehily AM, Butland BK, Merret TG. Infant feeding and allergy. Archives of Disease in Childhood. 1988;63(4):388-93.

22. Palmer DJ, Metcalfe J, Makrides M, Gold MS, Quinn P, West CE, et al. Early regular egg exposure in infants with eczema: A randomized controlled trial. Journal of Allergy & Clinical Immunology. 2013;132(2):387-92.e1.

23. Perkin M, Logan K, Lack G. A randomized controlled trial of early introduction of allergenic foods to induce tolerance in infants. Food Standards Agency, 2015.

24. Shao J, Sheng J, Dong W, Li YZ, Yu SC. [Effects of feeding intervention on development of eczema in atopy high-risk infants: an 18-month follow-up study]. Zhonghua Erke Zazhi. 2006;44(9):684-7.

25. Tan JWL, Valerio C, Barnes EH, Van Asperen PP, Kakakios AM, Campbell DE. Early introduction of dietary egg reduces egg sensitization at 12 months of age in infants at risk of allergic disease. Journal of Allergy and Clinical Immunology. 2016;137(2 SUPPL. 1):AB398.

26. Zeiger RS, Heller S, Mellon MH, Halsey JF, Hamburger RN, Sampson HA. Genetic and environmental factors affecting the development of atopy through age 4 in children of atopic parents: A prospective randomized study of food allergen avoidance. Pediatric Allergy and Immunology. 1992;3(3):110-27.

27. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: A randomized study. Journal of Allergy and Clinical Immunology. 1989;84(1):72-89.

28. Zeiger RS. Dietary manipulations in infants and their mothers and the natural course of atopic disease. Pediatric Allergy & Immunology. 1994;5(6 Suppl):33-43.

29. Juvonen P, Mansson M, Andersson C, Jakobsson I. Allergy development and macromolecular absorption in infants with different feeding regimens during the first three days of life. A three-year prospective follow-up. Acta Paediatrica. 1996;85(9):1047-52.

30. Juvonen P, Mansson M, Kjellman NI, Bjorksten B, Jakobsson I. Development of immunoglobulin G and immunoglobulin E antibodies to cow's milk proteins and

ovalbumin after a temporary neonatal exposure to hydrolyzed and whole cow's milk proteins. Pediatric Allergy & Immunology. 1999;10(3):191-8.

31. Lindfors A, Enocksson E. Development of atopic disease after early administration of cow milk formula. Allergy. 1988;43(1):11-6.

32. Lindfors AT, Danielsson L, Enocksson E, Johansson SG, Westin S. Allergic symptoms up to 4-6 years of age in children given cow milk neonatally. A prospective study. Allergy. 1992;47(3):207-11.

33. Matthew DJ, Taylor B, Norman AP, Turner MW. Prevention of eczema. Lancet. 1977;1(8007):321-4.