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

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1. Timing of introduction of allergenic foods and risk of ARC – 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 13 intervention studies which reported the association between timing of introduction of allergenic food(s) and risk of AR. Of these, 10 were randomised control trials, and 3 controlled clinical trials. Three studies used a multifaceted intervention, where early or late introduction of allergenic food(s) was part of an intervention package including more than 2 separate dietary interventions.

1.2. Populations

The majority of studies (n=6) were carried out in European populations. Other studies were from North America (n=6) and Asia-Pacific region (n=1). Overall over 3000 participants were allocated to intervention arms, and over 3000 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 groups in all studies (as early intervention in 3 and standard in 9); soya in 8 studies (early intervention in 1 and standard in 7); egg in 2

studies (standard); fish in 1 study (standard); peanut in 3 studies (early intervention in 1 and standard in 2); wheat in 2 studies (standard); other nuts (tree nuts) in 1 as standard.

1.4. Outcome assessment methods used

Outcome assessment was based on examination by a study doctor (n=1), parent report of clinical symptoms (n=4) or parental report of doctor diagnosed AR (n=7) or parent report not otherwise specified (n=1). All included studies reported allergic rhinitis, and no studies were identified which reported allergic conjunctivitis. Hence we refer to AR rather than ARC throughout this report.

Five studies reported AR at age 0-4, ten studies at ages 5-14, one at age 15 and over (not mutually exclusive, several studies examined the association at various age points).

1.5. Risk of bias assessment

Overall risk of bias was considered high in 6 studies (46%), due to a combination of high risk for assessment bias (n=2), attrition bias (n=3) and selection bias (n=2). Two studies had low overall risk of bias. One study was considered as having high risk of conflict of interest.

1.6. Key findings

i. Data came largely from studies comparing cow's milk with soya milk formula in infants, or from multifaceted intervention trials. For most comparisons data were relatively sparse, and the data did not allow us to confidently exclude potential beneficial or harmful effects.
ii. High or extreme heterogeneity was found in several meta-analyses – mainly related to a single study which reported significantly reduced AR with soya introduction prior to 9 months and egg avoidance until after 9 months, compared with cow's milk introduction prior to 9 months. Other studies found no significant association.

iii. Overall we found no evidence for an association between timing of allergenic food introduction and risk of AR, and an absence of any evidence regarding allergic conjunctivitis.

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

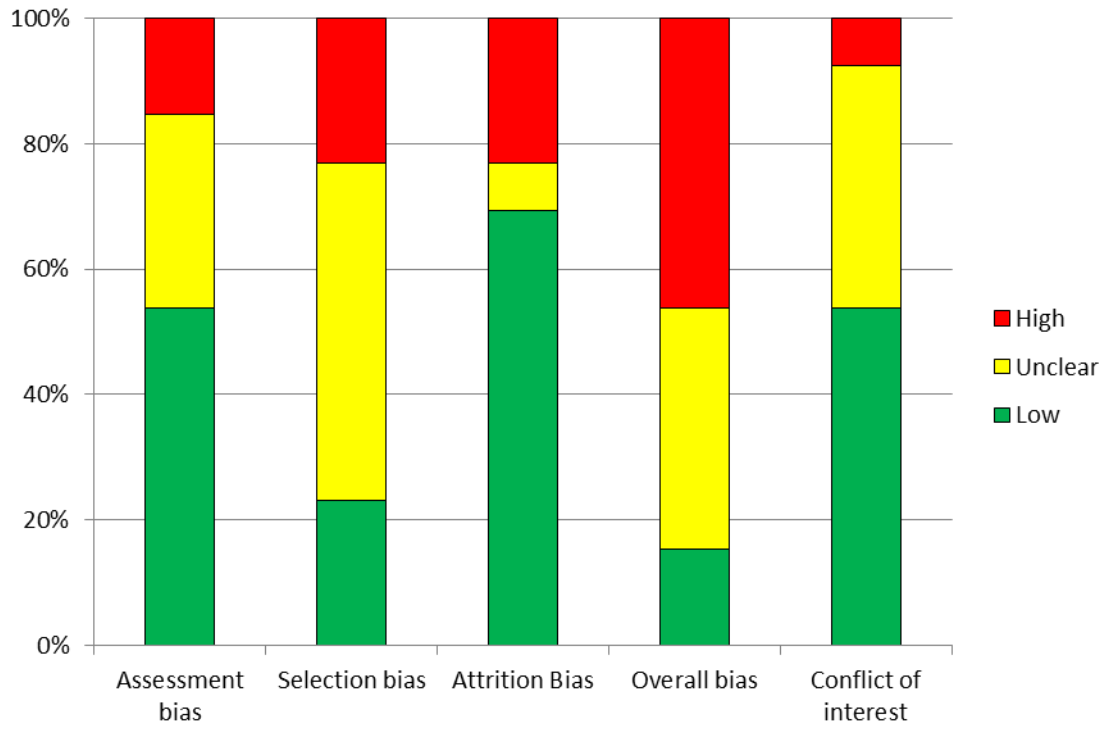
Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
de Jong, 2002 (1)	RCT	758/ 775	Cow's milk formula ≥3 times in the first 3 days, versus protein-free placebo formula.	**BOKAAL Study**. Healthy term newborns whose mother intended to breastfeed for ≥6 weeks.	Netherlands	Normal	5	ISAAC
Becker, 2004 (2); Chan-Yeung, 2000/5 (3); (4); Carlsten 2013(5)	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	7	DD allergic rhinitis
Brown, 1969 (6)	RCT	196/ 183	Cow's milk versus soya based diet as needed, from birth until introduction of complementary foods. 46% in control group introduced cow's milk, versus 95% in cow's milk group	**MONTEFIORE Study**. Mothers in a Health Insurance Plan in Greater New York.	USA	Normal	2.3	DD allergic rhinitis
Johnstone, 1966 (7)	RCT	120/ 115	Cow's milk formula as needed during first 9 months, versus soya formula and egg avoidance to 9 months.	Family member with hay fever, asthma, atopic eczema	USA	High	10	DD allergic rhinitis
Kjellman, 1979 (8)	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	DD allergic rhinitis
Lowe, 2011 (9)	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	DD allergic rhinitis

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Burr, 1993 (10); Merrett, 1988 (11); Miskelly, 1988 (12)	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	Parental report
Du Toit, 2016 (13)(14)	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	6	Parental report of seasonal rhinitis
Hide, 1994/6 (16, 17) Arshad, 1992/ 2003/7 (18-20) Scott, 2012 (21)	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>O.5kU/L.	UK	High	1, 8, 18	DD allergic rhinitis
Zeiger, 1989/92/94 (22-24)	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	Parental report
Gruskay, 1982 (25)	CCT	249/ 79	Cow's milk formula versus soya formula as needed, from birth to 9 months. Introduced at median 5 month.	Infants with a positive family history of allergy, fed a formula milk from <4 months age.	USA	High	3, 5	DD allergic rhinitis

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Lindfors, 1988 (26) Lindfors, 1992 (27)	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	DD allergic rhinitis
Halpern, 1973 (28)	CCT	~ 359/ 359/ 359	Allocated by paediatrician at birth to feed by breast, cow's milk or soya milk.	Caucasian infants with a family history of allergic disease.	USA	High	5	Physician assessment

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 AR



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

2.1. Short term early cow's milk introduction and risk of AR

Figures 2 and 3 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 AR. Data are sparse, but there is no statistically significant association seen.

Figure 2 Short term early cow's milk introduction and risk of AR age 5-14

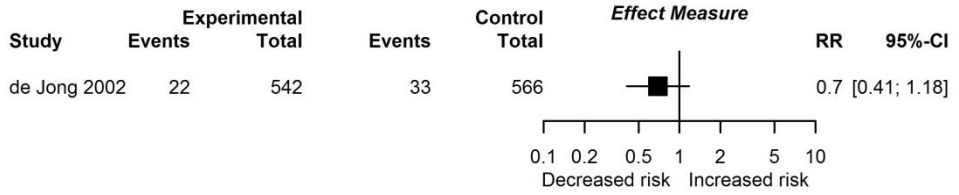
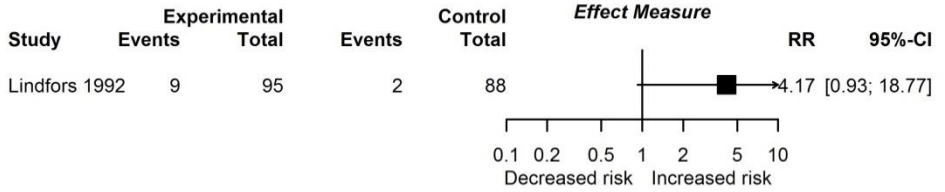


Figure 3 Short term early cow's milk introduction and risk of AR age 5-14 CCT



2.2. Longer term early cow's milk introduction and risk of AR

Figures 4 to 8 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 AR. In general data do not show evidence of an association. One multifaceted study found increased atopic AR (but not all AR) at age 5-14 with early cow's milk introduction, however this was not supported by other analyses of AR. 'Atopic' AR is defined as AR associated with a positive skin prick or specific IgE test to a common environmental allergen. Heterogeneity was moderate to very high in analysis of AR at age ≤4 and 5-14 respectively (Figures 4 and 6), and this statistical heterogeneity was partly explained by the positive findings in the study of Johnstone 1966. Subgroup analysis of these findings did not identify important subgroup differences, although these were limited by small study numbers. Sensitivity analyses excluding the study of Johnstone found reduced statistical heterogeneity, and no significant effect – for Figure 4 RR 1.31 (0.95, 1.82; I^2=50%); for Figure 6 RR 0.98 (0.82, 1.18; I^2=21%).

Figure 4 Early cow's milk introduction and risk of AR at age ≤ 4 years

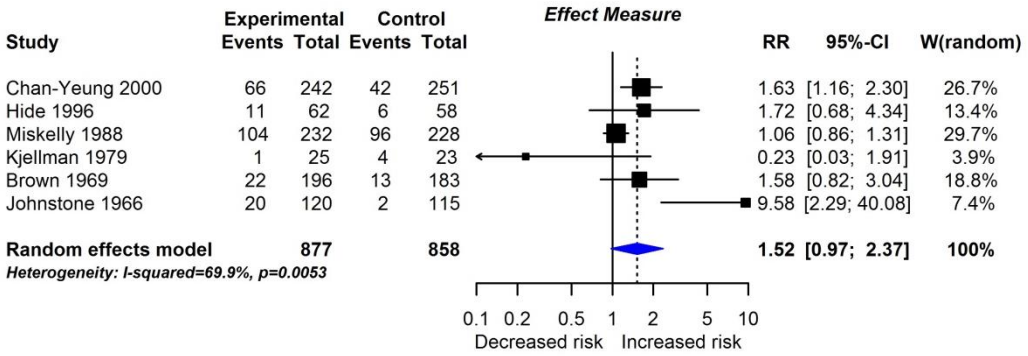


Figure 5 Early cow's milk introduction and risk of recurrent AR at age ≤ 4 CCT

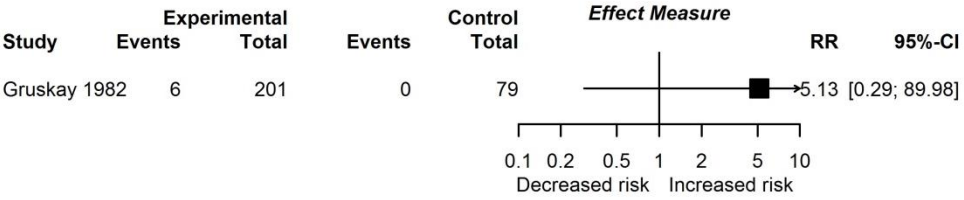


Figure 6 Early cow's milk introduction and the risk of AR at age 5-14 years

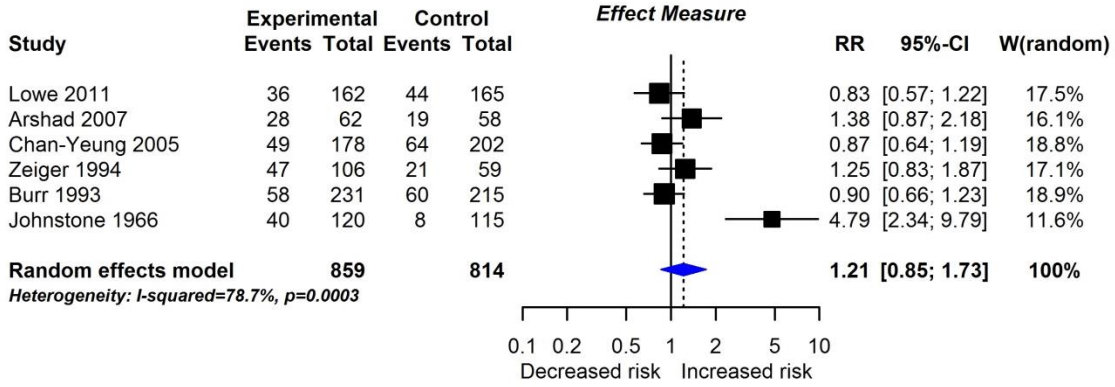


Figure 7 Early cow's milk introduction and risk of atopic AR at age 5-14 years

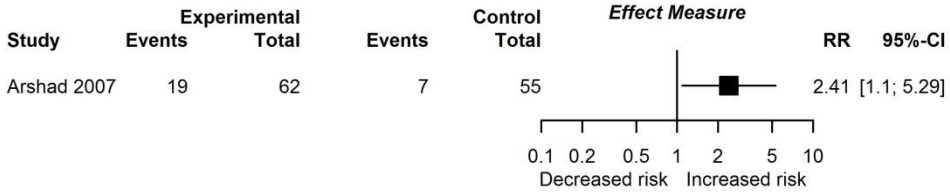


Figure 8 Early cow's milk introduction and risk of AR at age 5-14 CCT

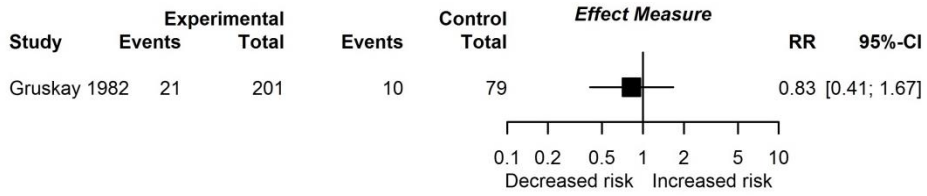


Table 2 Subgroup analyses of early cow's milk introduction and risk of AR at age ≤ 4 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Study design – RCT	6	1.52 [0.97-2.37]	69.9	-
Study design – qRCT	-	-	-	
Intervention – early introduction	-	-	-	-
Intervention – 'standard' introduction	6	1.52 [0.97-2.37]	69.9	
Risk of disease – High	5	1.53 [0.89-2.62]	75.1	0.94
Risk of disease – Low/Normal	1	1.58 [0.82-3.04]	-	
Intervention – multifaceted	2	1.64 [1.19-2.26]	0	0.87
Intervention – not multifaceted	4	1.52 [0.66-3.53]	76.8	
Overall risk of bias – High/Unclear	5	1.54 [0.79-3.00]	70.8	0.89
Overall risk of bias – Low	1	1.63 [1.16-2.30]	-	
Risk of conflict of interest – High/Unclear	4	1.52 [0.66-3.53]	76.8	0.87
Risk of conflict of interest – Low	2	1.63 [1.19-2.26]	0	

Table 3 Subgroup analyses of early cow's milk introduction and risk of AR at age 5-14 years

	Number of studies	RR [95% CI]	I^2 (%)	P-value for between groups difference
Study design – RCT	6	1.21 [0.85-1.73]	78.7	-
Study design – qRCT	-	-	-	
Intervention – early introduction	-	-	-	-
Intervention – 'standard' introduction	6	1.21 [0.85-1.73]	78.7	
Risk of disease – High	6	1.21 [0.85-1.73]	78.7	-
Risk of disease – Low/Normal	-	-	-	
Intervention – multifaceted	3	1.10 [0.82-1.48]	41.6	0.55
Intervention – not multifaceted	3	1.43 [0.64-3.18]	90.2	
Overall risk of bias – High/Unclear	5	1.33 [0.86-2.07]	49.7	0.12
Overall risk of bias – Low	1	0.87 [0.64, 1.19]	-	
Risk of conflict of interest – High/Unclear	2	2.37 [0.59-9.44]	91.2	0.19
Risk of conflict of interest – Low	4	0.94 [0.78-1.13]	10.9	

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

The study of **Johnstone 1966** reported perennial rhinitis (shown in Figures 4 and 6), and also reported the outcome 'hayfever'. Johnstone found no significant difference between groups in risk of hayfever at age 3 (RR 1.44 95% CI 0.24, 8.45 for early cow's milk introduction) or at age 10 (RR 1.76 95% CI 0.91, 3.38). The study by **Zeiger 1994** (22) reported AR in graphical form in a further 225 participants, so could not be included in meta-analysis. There was no significant difference between groups, with ~30% in both the intervention and the control groups developing AR by 4 years. The CCT of **Halpern 1973** did not report outcome data that could be included in meta-analysis, but reported 'the incidence of allergy was remarkably similar in the 3 dietary groups. The kind of milk fed to the infant did not influence the development of allergy.'

2.4. Conclusions: cow's milk introduction and AR

Overall 12 studies reported this association – 10 RCT and 2 CCT. We found no evidence for an association between timing of cow's milk introduction and risk of AR.

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

3. Timing of soya introduction and risk of AR

Figures 9 to 12 show data from studies of soya introduction and risk of AR. All studies used soya in the form of soya milk. In general data are relatively sparse and do not show evidence of an association. Most studies were a comparison of cow's milk versus soya milk based infant formula. Statistical heterogeneity was very high to extreme in analysis of AR at age ≤4 and 5-14 respectively (Figures 9 and 11), and this statistical heterogeneity was partly explained by the positive findings in the study of Johnstone 1966. However analyses remained non-significant after exclusion of Johnstone 1966.

Figure 9 Early soya milk introduction and risk of AR at age ≤ 4 years

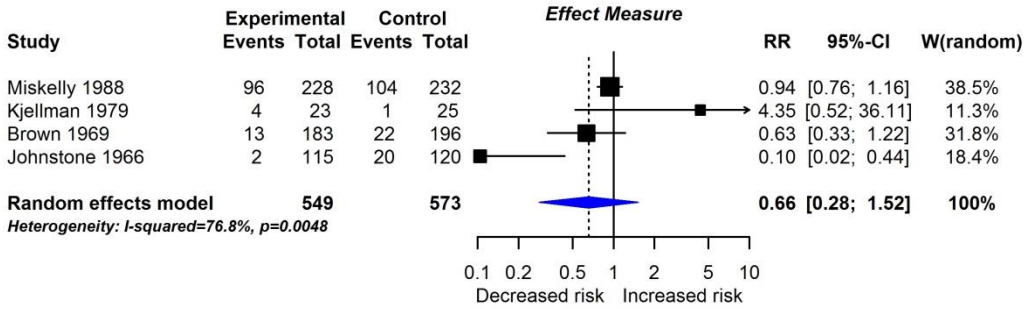


Figure 10 Early soya milk introduction and risk of AR at age ≤ 4 years CCT

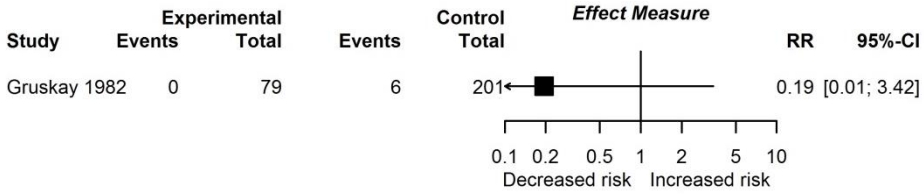


Figure 11 Early soya milk introduction and risk of AR at age 5-14 years

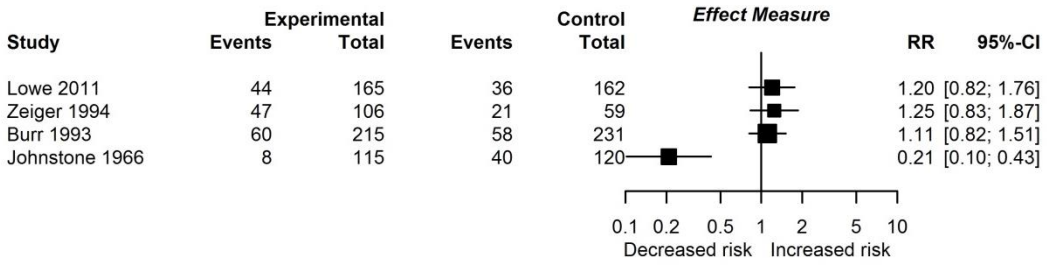
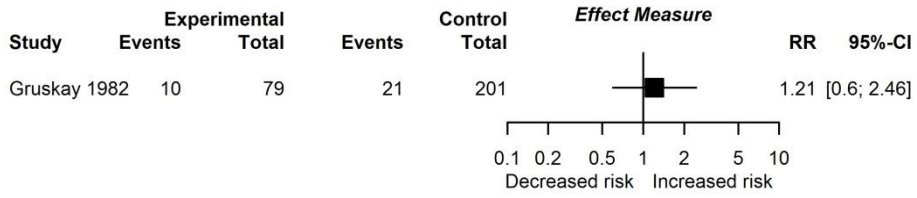


Figure 12 Early soya milk introduction and risk of AR at age 5-14 years CCT



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

The study of **Johnstone 1966** reported perennial rhinitis (shown in Figures 9 and 11), and also reported the outcome 'hayfever'. Johnstone found no significant difference between groups in risk of hayfever at age 3 (RR 0.70 95% CI 0.12, 4.09 for early soya introduction) or at age 10 (RR 0.57 95% CI 0.30, 1.10). The study of **Zeiger 1994** (22) reported AR by age 4 years in graphical form in 225 participants, so could not be included in meta-analysis. The graph suggests that ~30% in each group developed AR by 4 years, with no significant difference. The CCT of **Halpern 1973** did not report outcome data that could be included in meta-analysis, but reported 'the incidence of allergy was remarkably similar in the 3 dietary groups. The kind of milk fed to the infant did not influence the development of allergy.'

3.2. Conclusions: soya introduction and AR

Overall 8 studies reported this association – 6 RCTs and 2 CCTs. We found no evidence of a relationship between timing of soya introduction and risk of AR.

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

4. Timing of egg introduction and risk of AR

Figures 13 to 15 show data from studies of egg introduction and risk of AR. Data are exclusively derived from studies of multiple interventions (either multifaceted interventions, or early introduction of multiple foods) and were sparse. Data shown are comparisons of 'no advice' (intervention) with 'advice to delay egg introduction' (control), and are shown for all multifaceted intervention studies which included advice regarding timing of egg introduction. It is worth noting that advice regarding egg introduction was not the primary intervention in any of the studies identified. Advice was to delay egg introduction beyond 9 months (Arshad 1992, Johnstone 1966) or 12 months (Zeiger 1994). Data could not be pooled for AR at age 5-14 due to extreme statistical heterogeneity (I^2=83%). A single multifaceted intervention study found increased atopic AR at age 5-14 associated with earlier egg introduction.

Figure 13 Early egg introduction and risk of AR at age ≤ 4 years

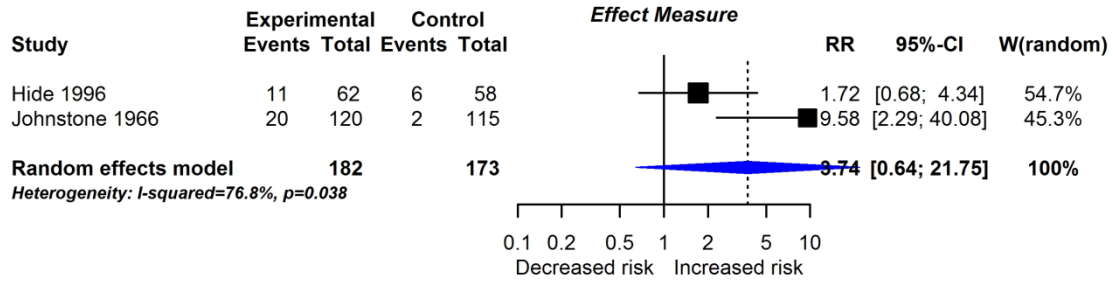


Figure 14 Early egg introduction and risk of AR at age 5-14 years

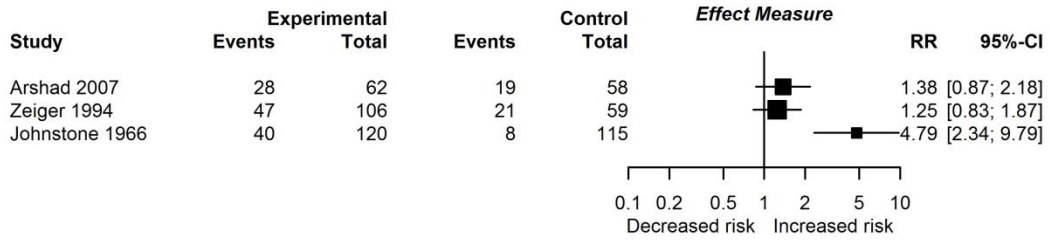
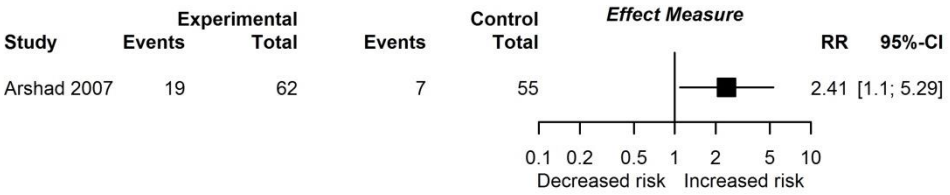


Figure 15 Early egg introduction and risk of atopic AR at age 5-14 years



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

The study of **Johnstone 1966** reported perennial rhinitis (shown in Figures 4 and 6), and also reported the outcome 'hayfever'. Johnstone found no significant difference between groups in risk of hayfever at age 3 (RR 1.44 95% CI 0.24, 8.45 for early egg introduction) or at age 10 (RR 1.76 95% CI 0.91, 3.38). The study of **Zeiger 1994** (22) reported AR by age 4 years in graphical form in 225 participants, so could not be included in meta-analysis. The graph suggests that ~30% in each group developed AR by 4 years, with no significant difference between the delayed and standard egg introduction groups.

4.2. Conclusions: egg introduction and AR

Overall 4 RCTs reported this association. Data were sparse, but overall there was no evidence for an association between timing of egg introduction and risk of AR.

Overall we found no evidence from studies of multiple interventions, that advice to delay egg introduction beyond 9-12 months influences risk of AR.

5. Timing of nut (peanut or tree nut), wheat or fish introduction and risk of AR

Figures 16 to 18 show data from studies of nut (peanut, tree nut or both), wheat or fish introduction and risk of AR. Data are mainly derived from multifaceted interventions. Data shown are comparisons of 'no advice' (intervention) with 'advice to delay nut, wheat and fish introduction' (control), and are shown for all multifaceted intervention studies which included advice regarding timing of nut, wheat and fish introduction. We identified just one study of peanut introduction alone (Du Toit 2016). Advice in other studies was to delay introduction of all nuts, wheat and fish beyond 9 months (Arshad 1992) or peanut, fish +/- wheat beyond 12 months (Chan-Yeung 2005, Zeiger 1994). The finding that early allergenic food introduction is associated with increased AR at age ≤4 was downgraded -2 (indirectness – nut/wheat/fish introduction advice was a minor component of the intervention in these trials); -1 inconsistency across different studies/age groups; -1 imprecision.

Figure 16 Early nut, wheat and fish introduction and risk of AR at age ≤ 4 years

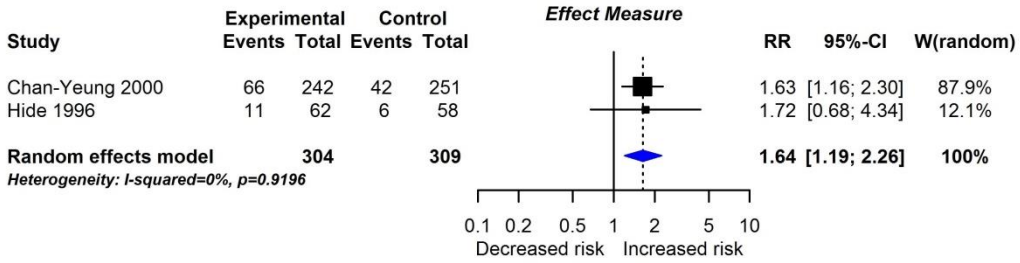
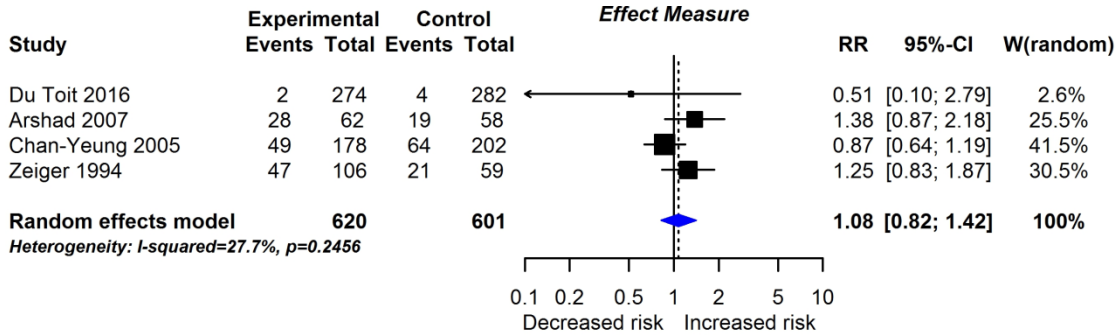
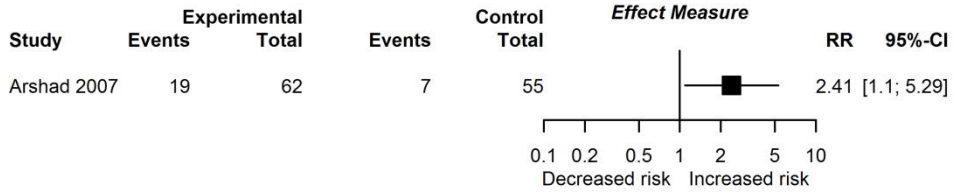


Figure 17 Early nut, wheat and fish introduction and risk of AR at age 5-14 years



The studies of Arshad and Zeiger (but not Chan-Yeung) included advice regarding timing of wheat introduction, and separate meta-analysis of these studies showed no statistically significant effect.

Figure 18 Early nut, wheat and fish introduction and risk of atopic AR at age 5-14 years



5.1. Data for nut, wheat and fish introduction and AR which were not included in meta-analysis

The study of **Zeiger 1994** (22) reported AR by age 4 years in graphical form in 225 participants, so could not be included in meta-analysis. The graph suggests that ~30% in each group developed AR by 4 years, with no significant difference between the delayed and standard nut, wheat and fish introduction groups.

5.2. Conclusions: nut, wheat and fish introduction and AR

Overall 3 RCTs reported this association. Data were sparse, but overall there was no evidence for an association between timing of nut, wheat and fish introduction and risk of AR.

Overall we found no consistent evidence from studies of multiple interventions, that advice to delay nut, wheat and fish introduction beyond 9-12 months influences risk of AR.

6. Timing of any allergenic food introduction and risk of AR

It is possible that the 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 in relation to risk of AR. These analyses were stratified by the intervention, and studies which compared timing of introduction of one allergenic food with another e.g. cow's milk versus soya milk) were not included in these analyses (Brown 1969, Johnstone 1966, Kjellman 1979, Lowe 2011, Merrett 1988, Zhou 2014, Gruskay 1982). Figures 25 to 27 show data from studies of AF introduction and risk of AR. Data are sparse, and mainly derived from studies of multifaceted interventions. Evidence from the multifaceted studies suggests early AF introduction may increase risk of AR at age ≤4 years (Figure 25). The association between multifaceted interventions and reduced AR has been discussed in section 5. No association was found at age 5-14 years. One of the multifaceted studies which included environmental control in the study intervention, found increased risk of atopic AR at age 5-14 in participants who had early introduction of allergenic food and no environmental control intervention (Figure 27).

Figure 19 Early AF introduction and risk of AR at age ≤ 4 years

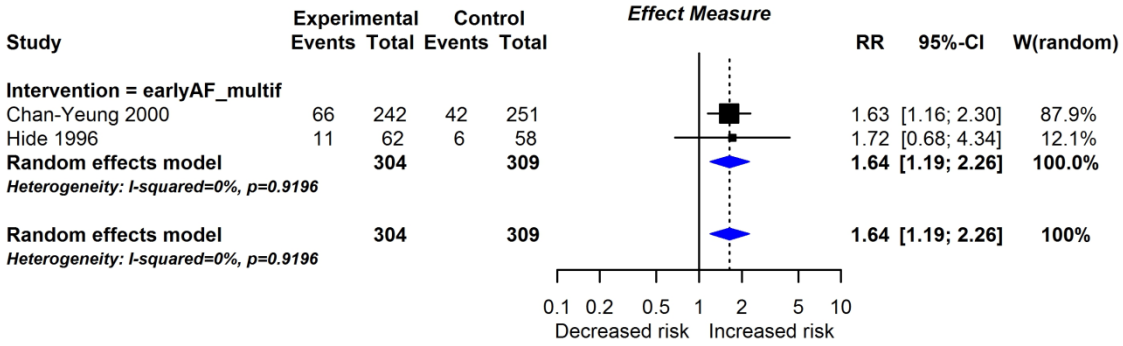


Figure 20 Early AF introduction and risk of recurrent AR at age 5-14 years

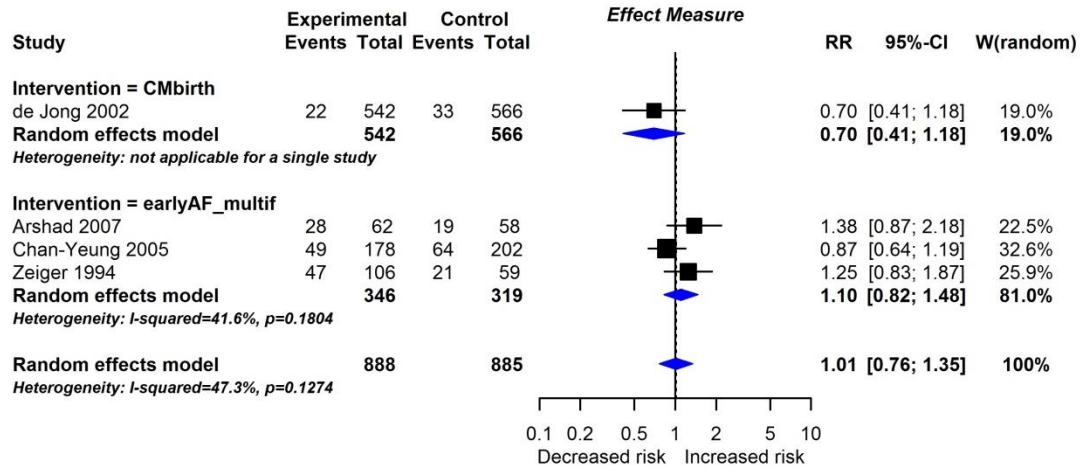
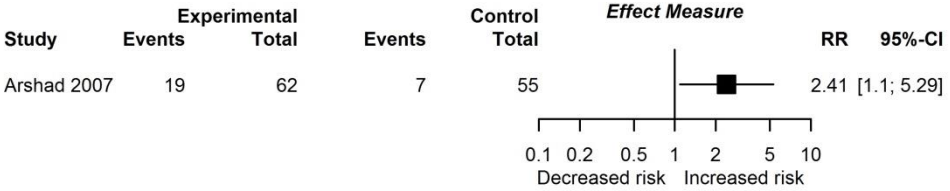


Figure 21 Early AF introduction and risk of atopic AR at age 5-14 years



6.1. Conclusions: any allergenic food introduction and AR

Overall 4 RCTs reported this association. There was no evidence for an association between timing of allergenic food introduction and risk of AR.

Overall we found no evidence that timing of allergenic food introduction influences risk of AR.

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