

## **TIMING OF INTRODUCTION OF ALLERGENIC FOODS IN INFANTS, AND RISK OF ECZEMA**

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## **1. Timing of introduction of allergenic foods and risk of eczema – 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 eczema. Of these, 12 were randomised control trials, 1 quasi-randomised study, and 4 controlled clinical trials. Six 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=8) were carried out in European populations. Other studies were from North America (n=6) and Asia Pacific region (n=3). For the 16 studies with 2 treatment arms, there were over 3000 participants allocated to intervention and 3000 to control groups. In the trial with 3 arms, there were 359 participants allocated to each one of the 3 arms (1,077 in total).

### **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 16 studies (as early intervention in 5 and standard in 11); soya in 10 studies (as early intervention in 1 and standard in 9); fish in 6 studies (standard); egg in 5 studies (standard); peanut in 2 studies (standard); wheat in 2 studies (standard); other nuts in 3 studies all as standard.

#### **1.4. Outcome assessment methods used**

Outcomes studied was based on examination by a study doctor (n=11), parental report of clinical symptoms (n=2) or parental report of doctor diagnosed eczema (n=2). ISAAC questionnaire was used in one study. In two studies the method of outcome assessment was unclear.

Twelve studies reported eczema at age 0-4, eleven studies at ages 5-14, one at age 15 and over (not mutually exclusive, several studies examined the association at various ages).

#### **1.5. Risk of bias assessment**

Overall risk of bias was considered high in 8 studies (47%), due to high risk for assessment bias (n=2), attrition bias (n=3) or selection bias (n=3). Only 1 study had low overall risk of bias. Two studies were considered to have high risk of conflict of interest.

#### **1.6. Key findings**

- i. Data came largely from studies of multifaceted intervention trials, or from studies comparing cow's milk with soya milk formula in infants. For most comparisons data were relatively sparse, and the data did not allow us to confidently exclude potential beneficial or harmful effects.
- ii. We did not however find any consistent evidence that timing of allergenic food introduction influences risk of AD at age  $\leq 4$  years, 5-14 years or  $\geq 15$  years.

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

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
de Jong, 2002 (1)	RCT	758/ 775	Cow's milk formula $\geq 3$ times in the first 3 days, versus protein-free placebo formula.	<b>BOKAAL Study.</b> Healthy term newborns whose mother intended to breastfeed for $\geq 6$ weeks.	Netherlands	Normal	5	ISAAC
Becker, 2004 (2); Chan- Yeung, 2000/5 (3); (4); Carlsten 2013(5)	RCT	268/ 281	<b>MULTIFACETED.</b> Standard care versus BF $\geq 4$ months, allergenic food exclusion during pregnancy/lactation, delayed solid ( $\geq 6$ months) and allergenic food (milk, seafood, peanut $\geq 12$ months) and environmental control.	<b>Canadian Asthma Primary Prevention study (CAPPS).</b> Children with family history of atopic disease.	Canada	High	7	Physician assessment
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	<b>MONTEFIORE Study.</b> Mothers in a Health Insurance Plan in Greater New York.	USA	Normal	2.3	Physician assessment
Halmerbauer, 2002/3 (7, 8)	RCT	347/ 349	<b>MULTIFACETED.</b> Standard care versus e BF $\geq 3$ months, delayed solid ( $\geq 6$ months) and allergenic food (milk, egg, fish, nuts $\geq 1$ year), and environmental control.	<b>Study on the Prevention of Allergy in Children in Europe (SPACE).</b> $\geq 1$ parent with a positive allergy history plus aeroallergen sensitisation.	UK, Germany, Austria	High	1	DD eczema
Johnstone, 1966 (9)	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	Physician assessment
Kjellman, 1979 (10)	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	Physician assessment

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Lowe, 2011 (11)	RCT	206/ 208	Cow's milk versus soya formula, as needed from birth. Introduced at median 4 months.	<b>Melbourne Atopy Cohort Study (MACS).</b> Infants with a first degree relative with eczema, asthma, AR or food allergy.	Australia	High	7	DD eczema
Matthew, 1977 (12)	RCT	35/ 27	<b>MULTIFACETED.</b> Standard care in cow's milk formula fed infants, versus BF for $\geq 6$ months, soya in place of cow's milk, delayed solid ( $\geq 3$ months) and allergenic (cow's milk, fish and egg $\geq 6$ months), environmental control	Included mothers with a convincing history of asthma, AR, and eczema from Queen Charlotte's Hospital	UK	High	1	DD
Burr, 1993 (13); Merrett, 1988 (14); Miskelly, 1988 (15)	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	Physician assessment
Hide, 1994/6 (17, 18) Arshad, 1992/ 2003/7 (19-21) Scott, 2012 (22)	RCT	68/ 71	<b>MULTIFACETED.</b> 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.	<b>Isle of Wight Study.</b> Infants with a first degree relative affected by an allergic disorder plus cord blood IgE $> 0.5$ kU/L.	UK	High	1, 8, 18	ISAAC

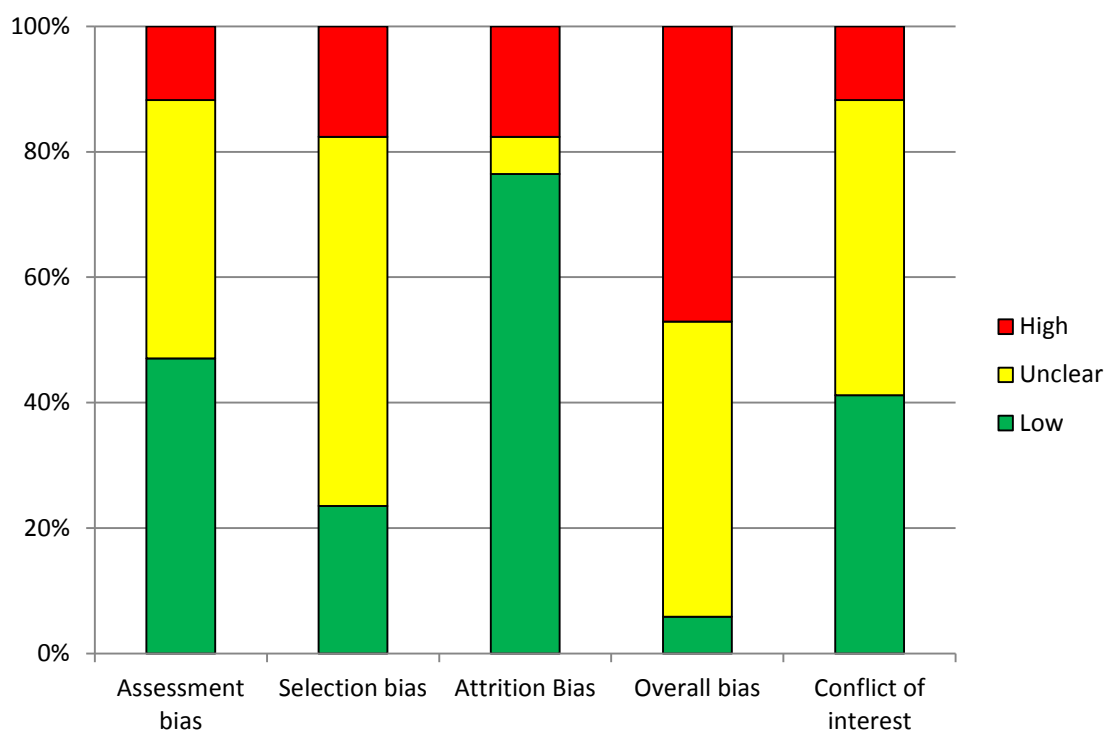


Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Shao, 2006 (23)	RCT	23/ 23	<b>MULTIFACETED.</b> Standard advice versus eBF for 4 months, allergenic food exclusion during lactation, delayed solid (4 months) and allergenic food (fish/prawn $\geq$ 6 months; egg/nuts $\geq$ 12 months), pHF if necessary.	Chinese babies with parental history of allergic disease, with specific food allergies according to + SPT	China	High	1.5	Unclear
Zeiger, 1989/92/94 (24-26)	RCT	~185 / 103	<b>MULTIFACETED.</b> Standard care versus infants cow's milk/ wheat/soy/egg/peanut/fish avoidance to $\geq$ 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	Physician assessment
Zhou, 2014 (27)	RCT	99/ 101	Cow's milk versus goat milk formula from <2 weeks age.	Healthy term infants fully formula fed within 2 weeks of birth.	Australia	Normal	1	Method unclear. Severity assessed using SCORAD.
Juvonen, 1996 (28)	qRCT	~43/ 58	Cow's milk formula versus breast milk for first 3 days of life.	Healthy term infants.	Sweden	Normal	3	Physician assessment
Gruskay, 1982 (29)	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	Physician assessment
Lindfors, 1988 (30) Lindfors, 1992 (31)	CCT	112/ 104	Cow's milk formula given as first meal and increased to $\leq$ 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	Physician assessment

Study	Design	N Int/ Ctrl	Intervention	Population	Country	Disease risk	Age	Outcome assessment
Halpern, 1973 (32)	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<sub>1</sub> 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 AD**

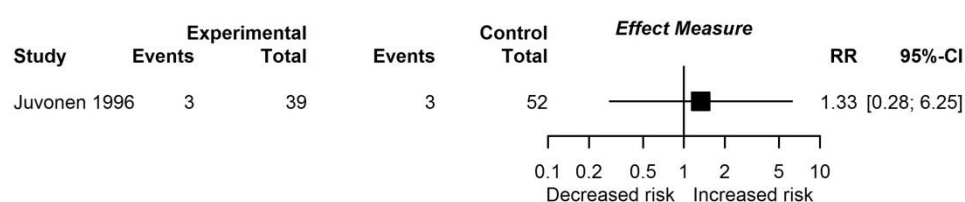


## 2. Timing of cow's milk introduction and risk of eczema

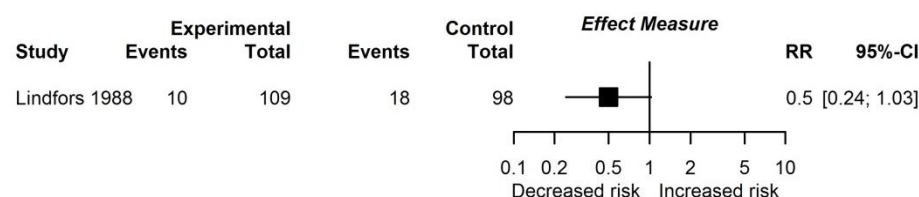
### 2.1. Short term early cow's milk introduction and risk of eczema

Figures 2 to 5 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 AD. Data are sparse, but there are no statistically significant associations seen.

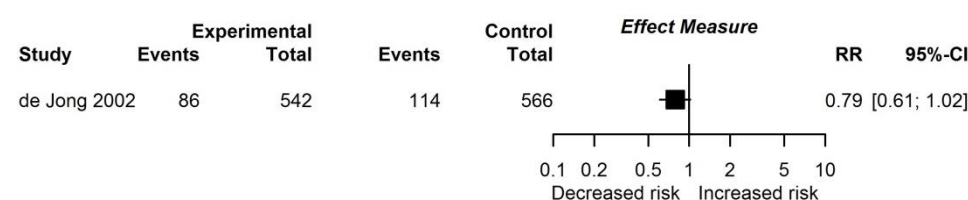
**Figure 2 Short term early cow's milk introduction and risk of AD age  $\leq 4$  years**



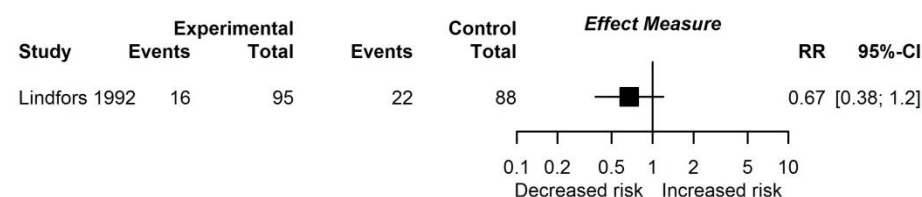
**Figure 3 Short term early cow's milk introduction and risk of AD age  $\leq 4$  CCT**



**Figure 4 Short term early cow's milk introduction and risk of AD age 5-14**



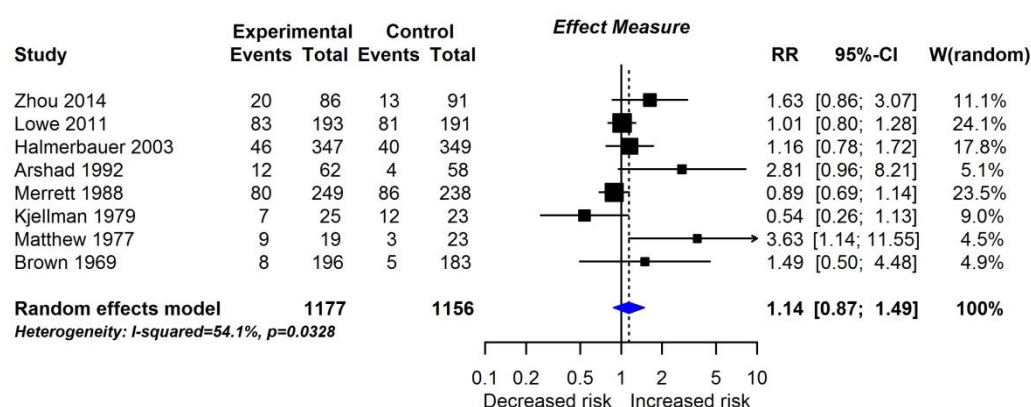
**Figure 5 Short term early cow's milk introduction and risk of AD age 5-14 CCT**



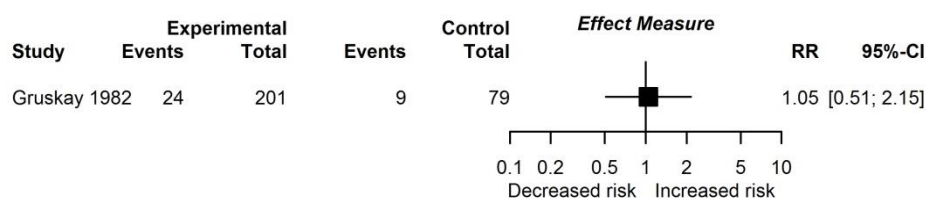
## 2.2. Longer term early cow's milk introduction and risk of eczema

Figures 6 to 11 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 AD. In general data do not show evidence of an association. One multifaceted study found increased atopic AD (but not all AD) at age 5-14 with early cow's milk introduction, however this was not supported by other analyses of AD. 'Atopic' AD is defined as AD associated with a positive skin prick or specific IgE test to a common environmental allergen. Subgroup analysis of early cow's milk introduction and risk of AD at ages  $\leq 4$  and 5-14 years did not show any significant subgroup differences, although opportunities for meaningful subgroup analysis were limited (Tables 2 and 3).

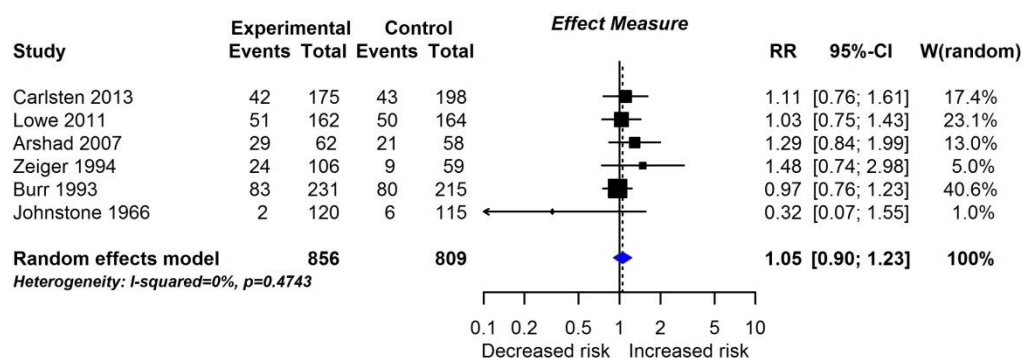
**Figure 6 Early cow's milk introduction and risk of AD at age  $\leq 4$  years**



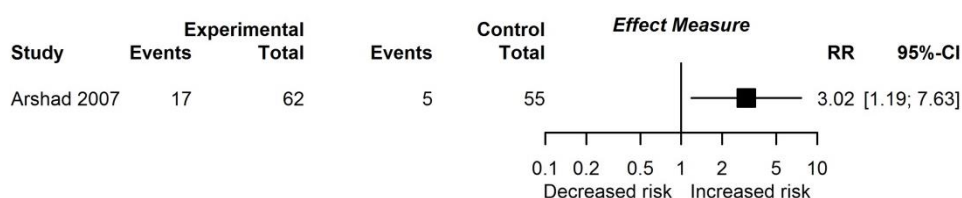
**Figure 7 Early cow's milk introduction and risk of recurrent AD at age  $\leq 4$  CCT**



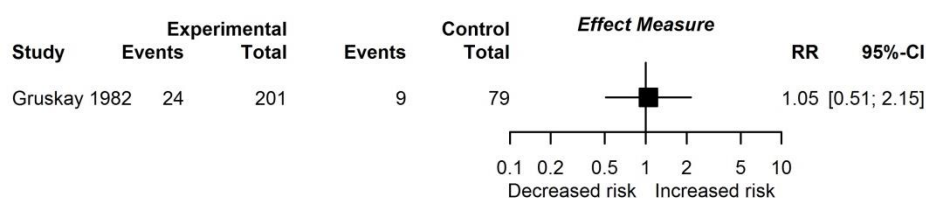
**Figure 8 Early cow's milk introduction and the risk of AD at age 5-14 years**



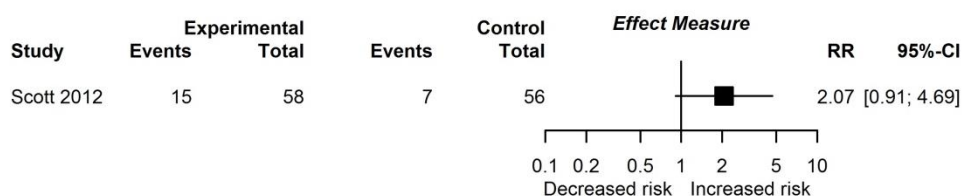
**Figure 9 Early cow's milk introduction and risk of atopic AD at age 5-14 years**



**Figure 10 Early cow's milk introduction and risk of recurrent AD at age 5-14 CCT**



**Figure 11 Early cow's milk introduction and risk of AD at age >15**



**Table 2 Subgroup analyses of early cow's milk introduction and risk of AD at age  $\leq 4$  years**

	Number of studies	RR [95% CI]	I <sup>2</sup> (%)	P-value for between groups difference
Study design – RCT	8	1.14 [0.87-1.49]	54.1	-
Study design – qRCT	-	-	-	
Intervention – early introduction	1	1.63 [0.86-3.07]	-	0.25
Intervention – ‘standard’ introduction	7	1.09 [0.82-1.43]	54.2	
Risk of disease – High	6	1.07 [0.80-1.44]	60.2	0.21
Risk of disease – Low/Normal	2	1.59 [0.92-2.76]	0	
Intervention – multifaceted	3	1.96 [0.89-4.30]	60.9	0.1210
Intervention – not multifaceted	5	0.98 [0.77-1.24]	36.1	
Overall risk of bias – High/Unclear	7	1.13 [0.85-1.50]	59.4	0.63
Overall risk of bias – Low	1	1.49 [0.50-4.48]	-	
Risk of conflict of interest – High/Unclear	6	1.32 [0.80-2.19]	66.6	0.40
Risk of conflict of interest – Low	2	1.05 [0.86-1.28]	0	

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

	Number of studies	RR [95% CI]	I <sup>2</sup> (%)	P-value for between groups difference
Study design – RCT	6	1.05 [0.90-1.23]	0	-
Study design – qRCT	-	-	-	
Intervention – early introduction	-	-	-	-
Intervention – ‘standard’ introduction	6	1.05 [0.90-1.23]	0	
Risk of disease – High	6	1.05 [0.90-1.23]	0	-
Risk of disease – Low/Normal	-	-	-	
Intervention – multifaceted	3	1.22 [0.94-1.59]	0	0.18
Intervention – not multifaceted	3	0.97 [0.80-1.19]	2.8	
Overall risk of bias – High/Unclear	6	1.05 [0.90-1.23]	0	-
Overall risk of bias – Low	-	-	-	
Risk of conflict of interest – High/Unclear	2	0.81 [0.19-3.58]	67.6	0.74
Risk of conflict of interest – Low	4	1.05 [0.89-1.23]	0	



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

The CCT of **Halpern 1973** (32) 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.' In the Isle of Wight Study (**Arshad 1992**) 2-year outcomes were also reported, which could not be included in meta-analysis. Here there were increased odds for AD with early cow's milk introduction – OR 9.5 95%CI 1.8, 50.1 (17). The study by **Zeiger 1994** (24) reported AD by age 4 years in graphical form in 225 participants, so could not be included in meta-analysis. The graph suggests that ~20% in the standard versus ~14% in the delayed cow's milk intervention group developed AD by 4 years, which the authors describe as not statistically significant.

### **2.4. Conclusions: cow's milk introduction and eczema**

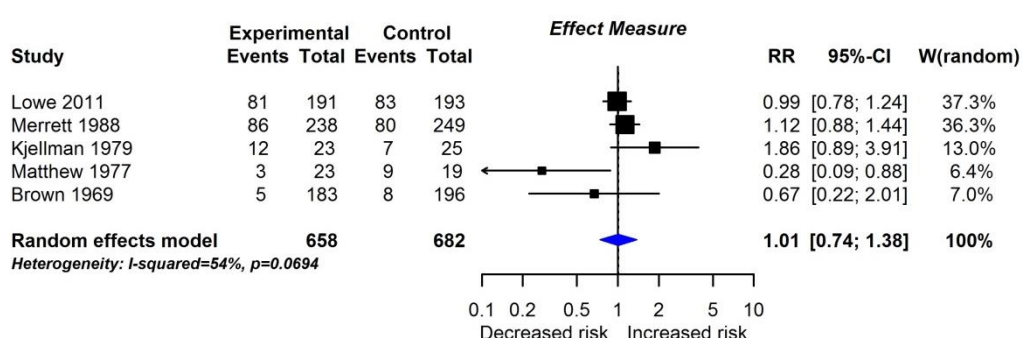
Overall 16 studies reported this association – 12 RCT, 1 qRCT and 3 CCT. We found no evidence that timing of cow's milk introduction influences risk of AD.

**Overall we found no evidence that earlier cow's milk introduction during infancy influences risk of AD, compared with later introduction.**

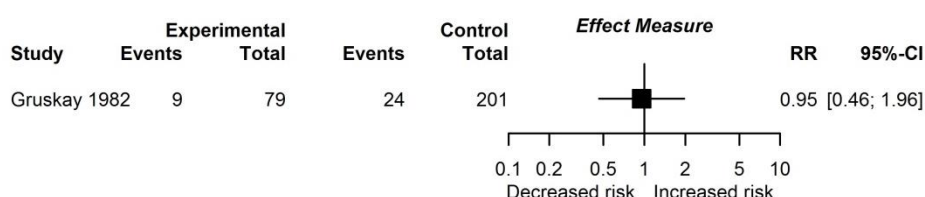
### 3. Timing of soya introduction and risk of eczema

Figures 12 to 15 show data from studies of soya introduction and risk of AD. 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.

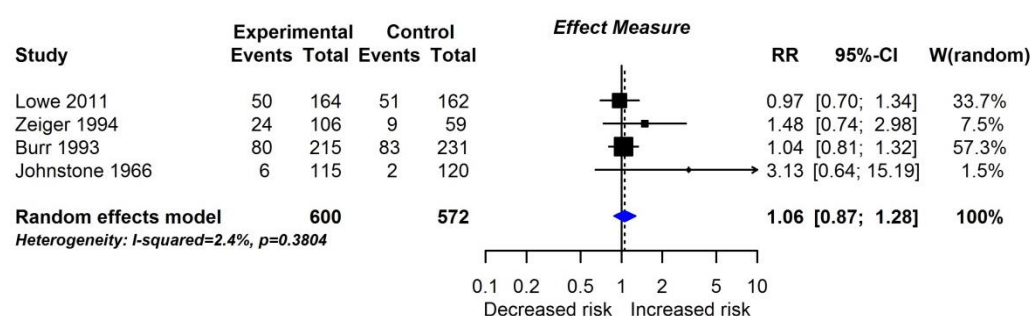
**Figure 12 Early soya milk introduction and risk of AD at age  $\leq 4$  years**



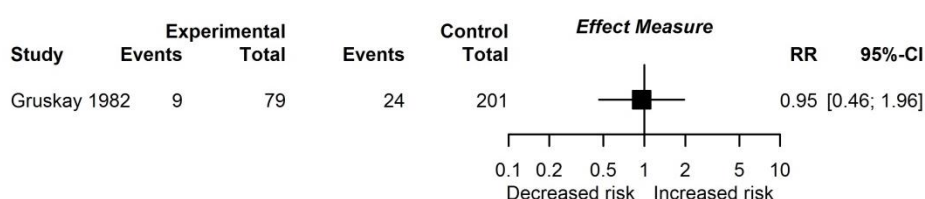
**Figure 13 Early soya milk introduction and risk of AD at age  $\leq 4$  years CCT**



**Figure 14 Early soya milk introduction and risk of AD at age 5-14 years**



**Figure 15 Early soya milk introduction and risk of AD at age 5-14 years CCT**



### **3.1. Data for soya introduction and eczema which were not included in meta-analysis**

The CCT of **Halpern 1973** (32) 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.’ The study by **Zeiger 1994** (24) reported AD by age 4 years in graphical form in 225 participants, so could not be included in meta-analysis. The graph suggests that ~20% in the standard versus ~14% in the delayed soya introduction group developed AD by 4 years, which the authors describe as not statistically significant.

### **3.2. Conclusions: soya introduction and eczema**

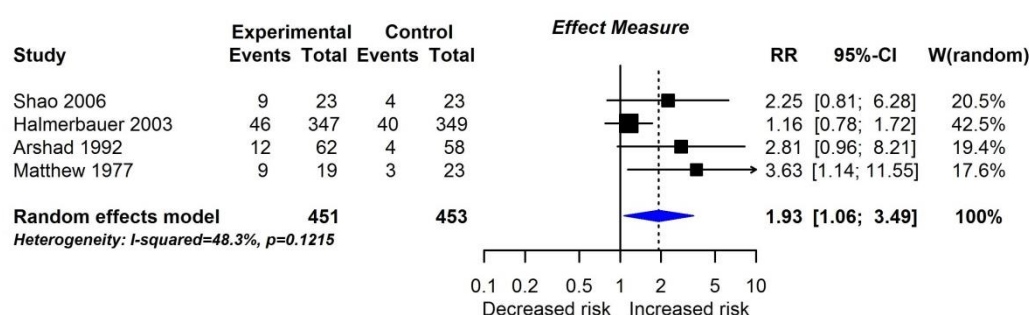
Overall 9 studies reported this association – 8 RCT and 1 CCT. We found no evidence that timing of soya introduction influences risk of eczema.

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

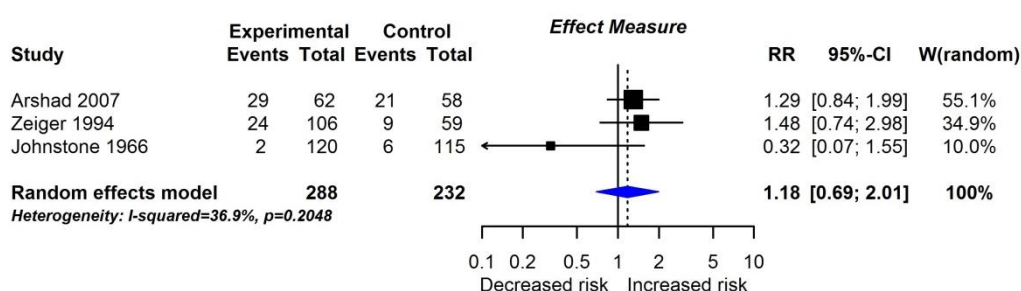
#### 4. Timing of egg introduction and risk of eczema

Figures 16 to 19 show data from studies of egg introduction and risk of AD. 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. Advice was to delay egg introduction beyond 6 months (Matthew 1977), 9 months (Arshad 1992/Scott 2012, Johnstone 1966) or 12 months (Shao 2006, Halmerbauer 2003, Zeiger 1994). It is worth noting that timing of egg introduction was not the main focus of any of the interventions included in these meta-analyses. Data show some evidence that earlier introduction of egg may increase risk of AD, however this evidence was downgraded to no evidence due to indirectness (-2, egg introduction advice was a minor component of the intervention in these trials), inconsistency (-1) and imprecision (-1).

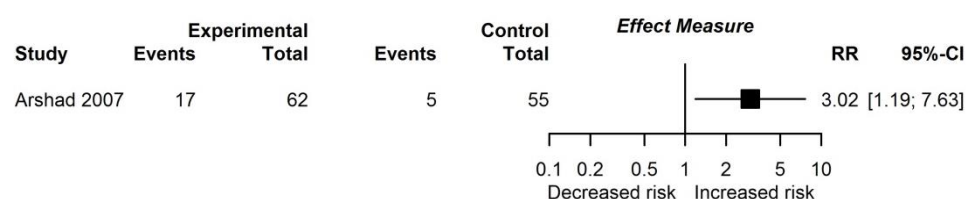
**Figure 16 Early egg introduction and risk of AD at age  $\leq 4$  years**



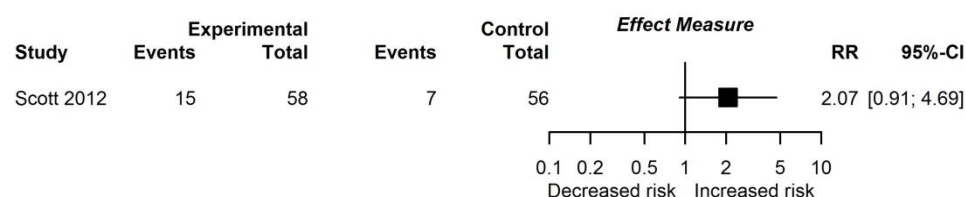
**Figure 17 Early egg introduction and risk of AD at age 5-14 years**



**Figure 18 Early egg introduction and risk of atopic AD at age 5-14 years**



**Figure 19 Early egg introduction and risk of AD at age >15**



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

The study by **Zeiger 1994** (24) also reported AD by age 4 years in 225 participants, but in graphical form so that the data could not be included in meta-analysis. The graph suggests that ~20% in the standard versus ~14% in the delayed egg introduction group developed AD by 4 years, which the authors describe as not statistically significant.

#### 4.2. Conclusions: egg introduction and eczema

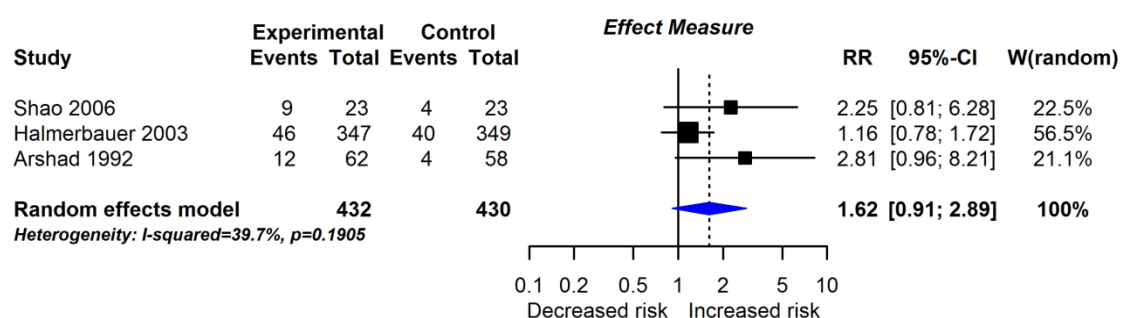
Overall 6 RCTs reported this association. There was evidence for an association between early egg introduction and increased AD at age  $\leq 4$  years but not at age 5-14. Evidence for increased AD at age  $\leq 4$  years was downgraded to no evidence due to indirectness (-2) since all studies in the meta-analysis were of multiple interventions; for imprecision (-1) since the association was of borderline statistical significance; and for inconsistency (-1) due to high statistical heterogeneity.

**Overall we found no consistent evidence that early egg introduction influences risk of AD.**

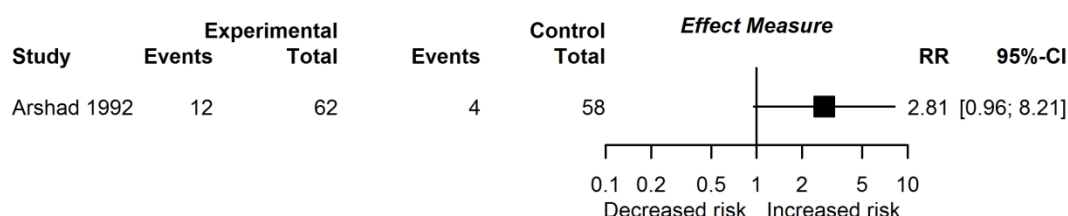
## 5. Timing of nut, wheat or fish introduction and risk of eczema

Figures 20 to 23 show data from studies of nut (peanut, tree nut or both), wheat or fish introduction and risk of AD. Data are all 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 did not identify studies of nut or fish introduction alone. Advice was to delay introduction of all nuts, wheat and/or fish beyond beyond 6 months (Matthew 1977), 9 months (Arshad 1992/Scott 2012, Johnstone 1966) or 12 months (Carlsten 2013, Shao 2006, Halmerbauer 2003, Zeiger 1994). Findings were suggestive of a possible increase in AD risk with early fish introduction at age  $\leq 4$  years, however this evidence was downgraded -2 (indirectness – egg introduction advice was a minor component of the intervention in these trials); -1 inconsistency; -1 imprecision. We also found a possible increase in atopic AD at age 5-14 with early nut, wheat and fish introduction.

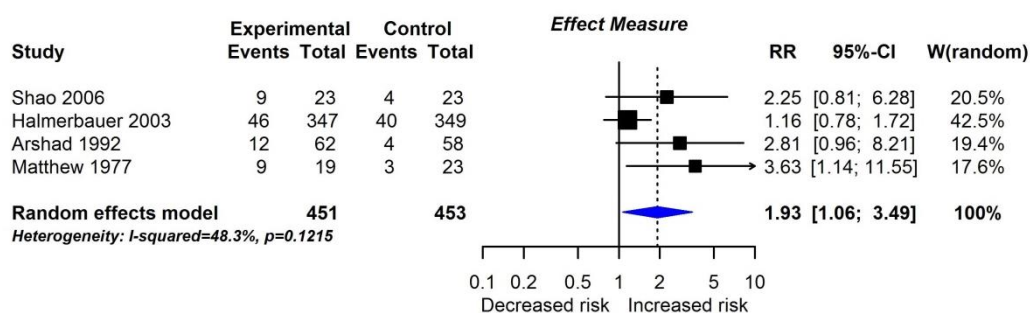
**Figure 20 Early nut introduction and risk of AD at age  $\leq 4$  years**



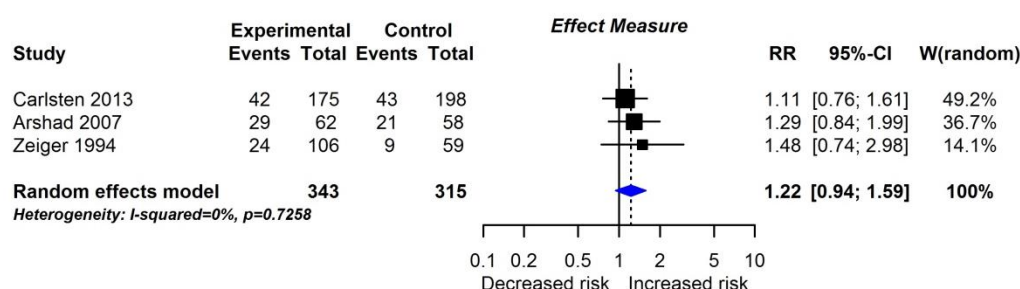
**Figure 21 Early wheat introduction and risk of AD at age  $\leq 4$  years**



**Figure 22 Early fish introduction and risk of AD at age  $\leq 4$  years**

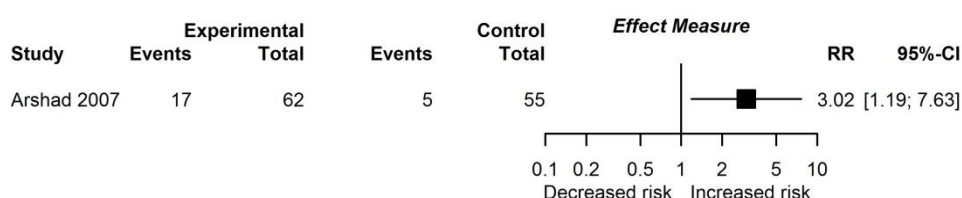


**Figure 23 Early nut and fish introduction and risk of AD at age 5-14 years**

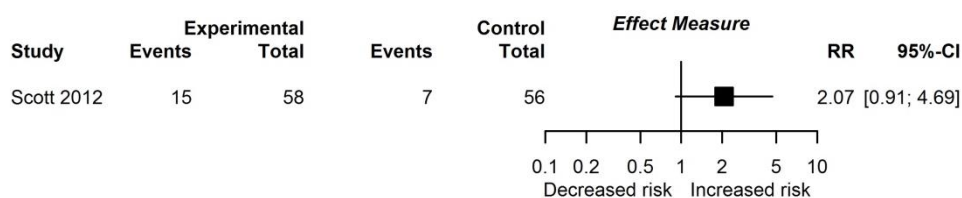


The studies of Arshad 1992 and Zeiger 1994 (but not Carlsten 2013) included advice regarding timing of wheat introduction as part of the study intervention. Meta-analysis of these two studies alone showed no statistically significant effect on risk of AD at age 5-14 years.

**Figure 24 Early nut, wheat and fish introduction and risk of atopic AD at age 5-14 years**



**Figure 25 Early nut, wheat and fish introduction and risk of AD at age >15**



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

The study by **Zeiger 1994** (24) also reported AD by age 4 years in 225 participants, but in graphical form so that the data could not be included in meta-analysis. The graph suggests that ~20% in the standard versus ~14% in the delayed nut, wheat and fish introduction group developed AD by 4 years, which the authors describe as not statistically significant.

### **5.2. Conclusions: nut, wheat and fish introduction and eczema**

Overall 5 studies reported this association. There was no consistent evidence for a relationship between timing of nut, wheat or fish introduction into the infant diet, and risk of AD. Evidence that early fish introduction is associated with reduced AD at age  $\leq 4$  years was downgraded to no evidence, due to indirectness (-2) since all studies in the meta-analysis were of multiple interventions; imprecision (-1) since the association was of borderline statistical significance; and inconsistency (-1) due to high statistical heterogeneity.

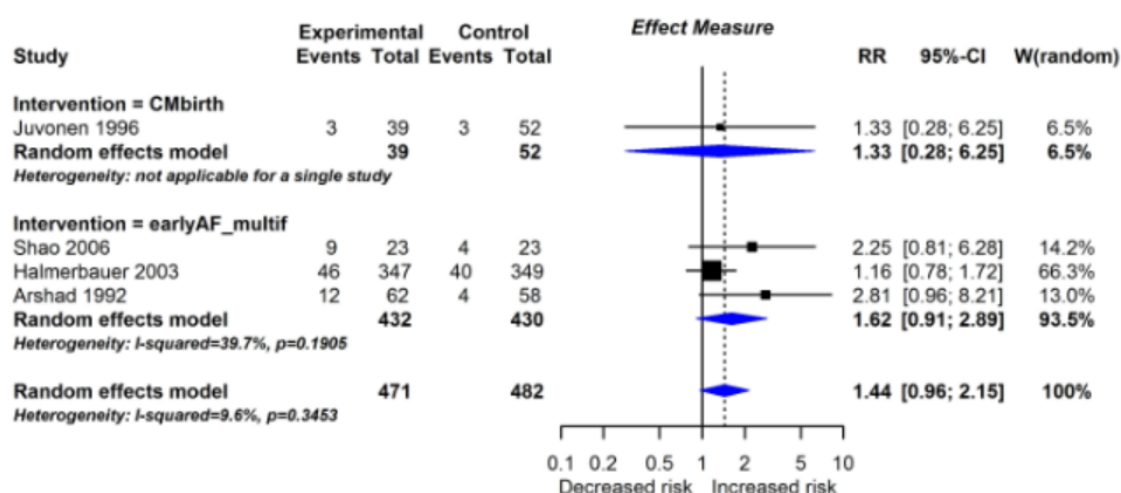
**Overall we found no consistent evidence that early nut, wheat or fish introduction influences risk of AD.**



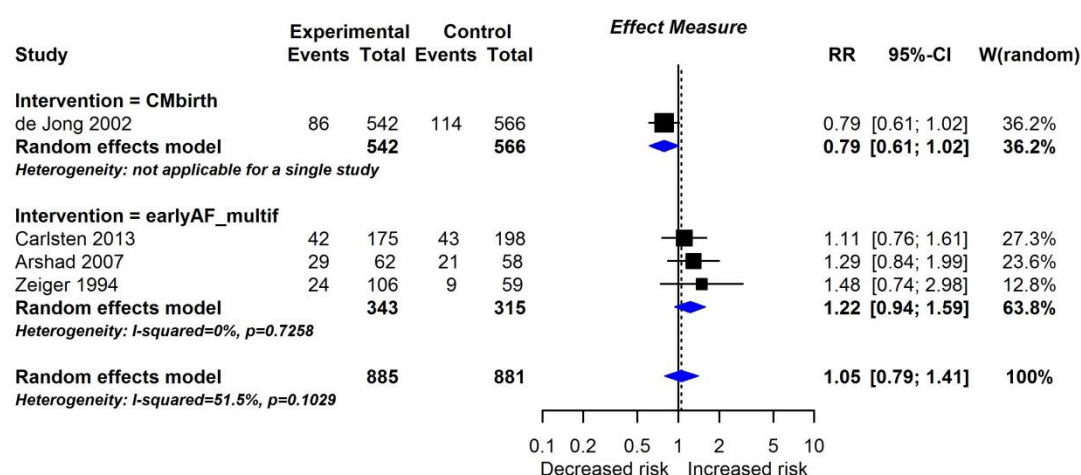
## 6. Timing of ‘any allergenic food’ introduction and risk of eczema

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 AD. These analyses were stratified by the intervention, and studies which compared early 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 32 to 35 show data from studies of AF introduction and risk of AD. Data are sparse, and mainly derived from studies of multifaceted interventions. Evidence shows no general effect of early allergenic food introduction on risk of AD (Figures 33 and 34).

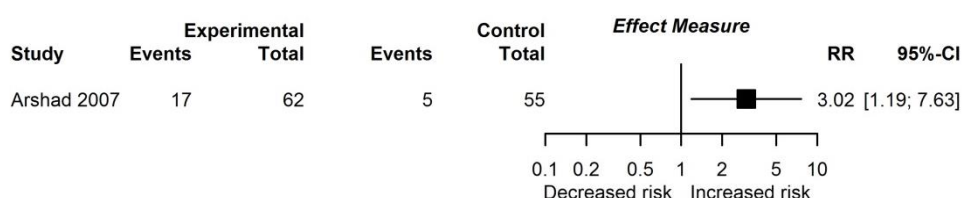
**Figure 26 Early AF introduction and risk of AD at age ≤ 4 years**



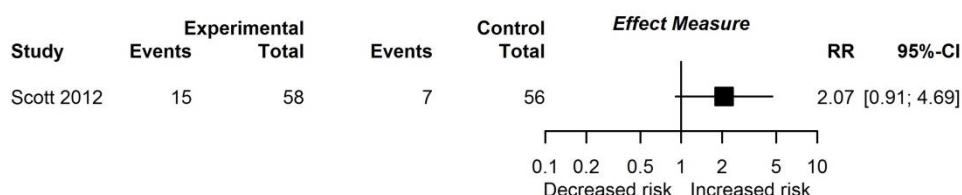
**Figure 27 Early AF introduction and risk of recurrent AD at age 5-14 years**



**Figure 28 Early AF introduction and risk of atopic AD at age 5-14 years**



**Figure 29 Early AF introduction and risk of AD at age >15**



## 6.1. Conclusions: any allergenic food introduction and eczema

Overall 7 studies reported this association. We found no consistent evidence for an association between early AF introduction and AD risk at any age.

**Overall we found no evidence that early AF introduction influences risk of AD.**

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