

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

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## Table of Contents

List of Figures .....	3
1. Timing of introduction of allergenic foods and risk of allergic sensitisation – summary of findings .....	4
1.1. Studies identified .....	4
1.2. Populations.....	4
1.3. Exposure assessment.....	4
1.4. Outcome assessment methods used .....	4
1.5. Risk of bias assessment.....	5
1.6. Key findings.....	5
2. Timing of cow’s milk introduction and risk of AS .....	10
2.1. Studies of cow’s milk introduction and AS which could not be included in meta-analysis	12
2.2. Conclusions: cow’s milk introduction and AS.....	13
3. Timing of soya introduction and risk of AS .....	14
4. Timing of egg introduction and risk of AS.....	15
4.1. Studies of egg introduction and AS which could not be included in meta-analysis	16
4.2. Conclusions: egg introduction and AS.....	17
5. Timing of fish introduction and risk of AS .....	18
5.1. Studies of fish introduction and AS which could not be included in meta-analysis	20
5.2. Conclusions: fish introduction and AS.....	20
6. Timing of cereal introduction and risk of AS .....	21
6.1. Conclusions: cereal introduction and AS .....	22
7. Timing of any allergenic food introduction.....	23
7.1. Timing of allergenic food (AF) and risk of AS.....	23
7.2. Conclusions: timing of any AF introduction and AS .....	23
References.....	24

## List of Figures

Figure 1 Risk of bias in observational studies of timing of allergenic food introduction and risk of allergen sensitisation.....	9
Figure 2: Cow's milk introduction $\leq 0-2$ months and AS-any .....	10
Figure 3: Cow's milk introduction $\leq 3-4$ months and AS-any .....	10
Figure 4: Cow's milk introduction $\leq 0-2$ months and AS-food.....	10
Figure 5: Cow's milk introduction $\leq 3-4$ months and AS-CM.....	11
Figure 6: Cow's milk introduction $\leq 3-4$ months and AS-Egg.....	11
Figure 7: Cow's milk introduction $\leq 3-4$ months and AS-Peanut .....	11
Figure 8: Cow's milk introduction $\leq 0-2$ months and AS-aero .....	12
Figure 9: Cow's milk introduction $\leq 3-4$ months and AS-aero .....	12
Figure 10: Cow's milk introduction $\leq 5-7$ months and AS-aero .....	12
Figure 11: Egg introduction $\leq 8-12$ months and AS-any, HR .....	15
Figure 12: Egg introduction $\leq 8-12$ months and AS-food, OR.....	15
Figure 13: Egg introduction $\leq 8-12$ months and AS-CM, OR.....	15
Figure 14: Egg introduction $\leq 8-12$ months and AS-Egg, OR .....	16
Figure 15: Egg introduction $\leq 8-12$ months and AS-aero, OR.....	16
Figure 16: Fish introduction $\leq 8-12$ months and AS-any, OR.....	18
Figure 17: Fish introduction $\leq 5-7$ months and AS-any, HR.....	18
Figure 18: Fish introduction $\leq 5-7$ months and AS-food, OR .....	18
Figure 19: Fish introduction $\leq 8-12$ months and AS-food, OR .....	19
Figure 20: Fish introduction $\leq 5-7$ months and AS-CM, OR .....	19
Figure 21: Fish introduction $\leq 5-7$ months and AS-Egg, OR .....	19
Figure 22: Fish introduction $\leq 5-7$ months and AS-aero, OR.....	19
Figure 23: Fish introduction $\leq 8-12$ months and AS-aero, OR.....	20
Figure 24: Wheat introduction $\leq 5-7$ months and AS-any, OR .....	21
Figure 25: Wheat introduction $\leq 3-4$ months and AS-aero, OR.....	21
Figure 26: Wheat introduction $\leq 5-7$ months and AS-aero, OR .....	21
Figure 27: AF introduction $\leq 8-12$ months and AS-Any, OR .....	23

## **1. Timing of introduction of allergenic foods and risk of allergic sensitisation – summary of 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 20 observational studies which reported the association between timing of introduction of allergenic food(s) and risk of AS. Of these, 19 were prospective cohort studies, and 1 was a cross-sectional study.

### **1.2. Populations**

The majority of studies (n=13) were carried out in European populations. Other studies were from North America (n=2), Asia Pacific region (n=3), Latin America (n=1) and the Middle East (n=1).

### **1.3. Exposure assessment**

We identified 12 studies which assessed cow's milk introduction and AS, 2 studies of soya, 7 studies of egg, 4 studies of fish, 3 studies of nut (peanut or tree nut) introduction, 3 studies of cereal introduction, and 1 study of timing of 'any allergenic food' introduction, defined as cow's milk, egg, nuts or fish. We did not identify any studies of the interaction between allergenic food introduction and breastfeeding status, and AS. Questionnaire was the most common method to collect data (n=11), followed by interview (n=9), food diary (n=2) and records (n=1), not mutually exclusive because more than one method was used in several studies. Seven studies used only questionnaire. It was unclear whether any study used a validated or piloted dietary questionnaire.

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

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. In 8 studies outcome was defined by skin prick testing (SPT) and in 7 by specific IgE testing (sIgE). Sixteen studies reported

outcomes at age 0-4, five at age 5-14 and none at age 15 and over (not mutually exclusively, as some studies assessed AS at more than one age).

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

Among 20 studies, overall bias was considered to be low in 11 (55%), unclear in 4 (20%) and high in 5 (25%). Risk of bias was considered high due to lack of adjustment for potential confounders in 1 study and selection bias in 4 studies.

### **1.6. Key findings**

- i. Data from relatively few studies contributed to each analysis, but almost all data were from prospective cohort studies, and in several cases measures were taken to account for possible reverse causation in analyses.
- ii. We found no consistent evidence that timing of introduction of cow's milk, egg, soya or cereal is associated with AS.
- iii. We found VERY LOW evidence (-1 indirect outcome) from 3 studies at low risk of bias, with over 13,000 participants, that earlier introduction of fish is associated with reduced AS to both any allergen and to food allergens.

**Table 1 Characteristics of included studies evaluating timing of allergenic food introduction in infants and allergen sensitisation**

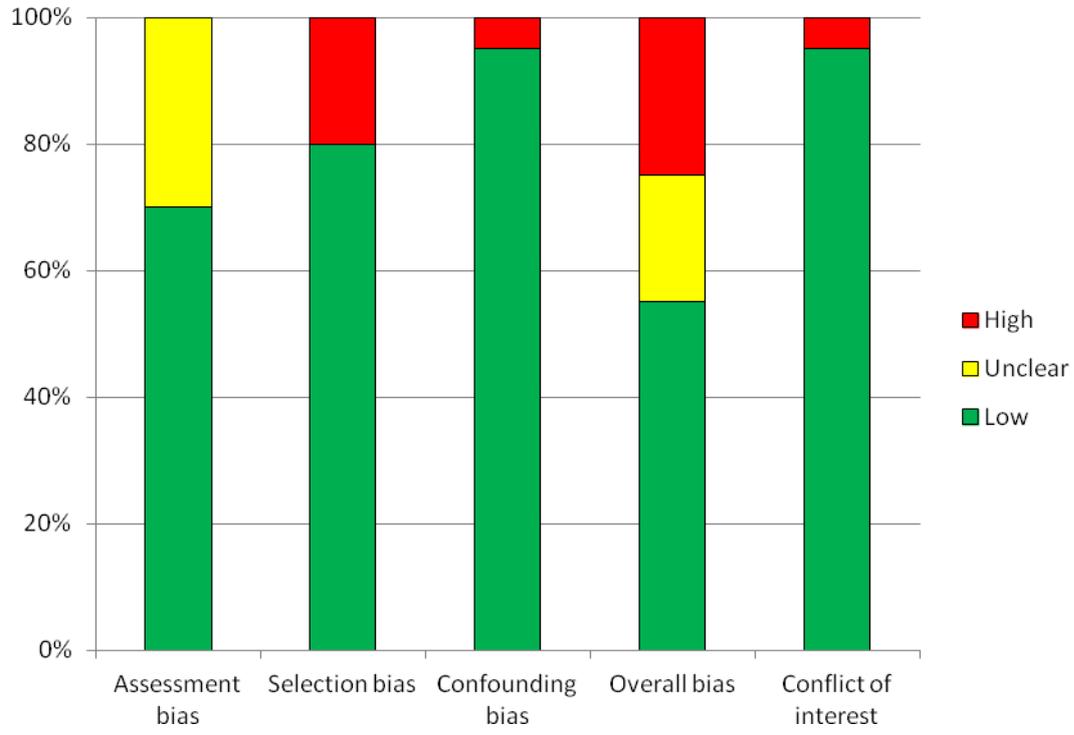
Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Alm, 2011 (1)	PC	4171	Sweden	Infants of Western Sweden: Population based birth cohort of infants born in the region in 2003	Fish, Q	4	SPT/IgEaero
Businco, 1995 (2)	PC	107	Italy	Infants of atopic parents recruited at birth in a hospital in Rome, Italy between 1985 and 1988	Soya, I	0.5	Total-IgE
Cogswell, 1987 (3)	PC	73	UK	Babies of parent with a history of hay fever or asthma born in the maternity department of a district general hospital	Cow's milk, D	5	SPTany
Hesselmar, 2010 (4)	PC	169	Sweden	ALLERGYFLORA: Birth cohort in Sweden enriched with children with family history of allergies	Cow's milk, egg, fish, I/Q	1.5	sIgEfood
Joseph, 2011 (5)	PC	594	USA	WHEALS: Population based birth cohort with pregnant woman recruited from prenatal care in Henry Ford Hospital obstetric clinics between 2003 and 2007 in Detroit area	Cow's milk (part of a 'complementary food' definition), I	2-3 yrs	sIgEegg, sIgEcow's milk, sIgEpeanut
Kemeny, 1991 (6)	PC	180	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London	Cow's milk, unclear	1	SPTcow's milk, SPTegg
Koplin, 2008 (7)	PC	449	Australia	Members of MACS, aRCT of the effect of 3 infant formulas in a cohort of children with a family history of allergy born between 1990 and 1994 whose mothers were recruited during pregnancy	Soya, I/Q	2	SPTpeanut
Kull, 2006 (8)	PC	3230	Sweden	BAMSE: Prospective birth cohort of newborns in a predefined area of Stockholm between 1994 and 1997	Fish, Q	4	sIgEany

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Mihrshahi, 2007 (9)	PC	516	Australia	CAPS: Pregnant women whose unborn children were at high risk of having asthma had asthma or wheezing, were identified at the antenatal clinics of six hospitals of Sydney between 1997 and 1999	Cow's milk, eggs, nuts or fish; I	0-5	SPTany
Nwaru, 2010 (10); Nwaru, 2013 (11); Nwaru, 2013 (12)	PC	6071	Finland	DIPP: Prospective birth cohort of children at high risk of TIDM (HLA genotype conferred susceptibility) born between 1997 and 2004 in Oulu and Tampere University Hospital	Cow's milk, wheat, oats, rye, egg, fish, wheat, IQ	5	sIgEaero, sIgEcow's milk, sIgEegg, sIgEfood, sIgEany
Oddy, 1999 (13); Oddy, 2000 (14)	PC	1598	Australia	Western Australian Pregnancy Cohort: Population based cohort of infants recruited from public antenatal clinic at King Edward Memorial Hospital and nearby private practice in Perth Western Australia between 1989 and 1992	Cow's milk, D/Q	6	SPTaero
Ostergaard, 1985 (15)	PC	25	Denmark	Full term infants born at the Department of Obstetrics, Aalborg Hospital North, Denmark, from 1979 to 1980 with no family history of atopic disease (eczema, asthma, rhinitis, urticaria)	Cow's milk, I/Q	0.5	Total-IgE
Poysa, 1990 (16)	PC	91	Finland	High risk infant born between 1979 and 1980	Cow's milk, I	0-1	Total-IgE
Sicherer, 2010 (17)	PC	503	USA	The Consortium of Food Allergy Research enrolled infants at 3 to 15 months of age with likely egg or milk allergy but without previously known peanut allergy	Soya, Q	0.8	sIgEpeanut

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Snijders, 2008 (18)	PC	782	Netherlands	KOALA: Population based birth cohort with healthy pregnant women recruited in week 10 -14 of their pregnancy from an ongoing prospective cohort study on pregnancy-related pelvic girdle pain and through posters in organic food shops, physician offices, and midwives.	Cow's milk, Q	2	sIgEaero, sIgEany, sIgEcow's milk, sIgEegg, sIgEpeanut
Strassburger, 2010 (19)	PC	279	Brazil	Birth cohort study nested in a dietary intervention randomized field trial in the city of São Leopoldo, southern Brazil in 2002	Cow's milk, R	3.5	SPTaero
Wickens, 2011 (20)	PC	512	New Zealand	Cohort part of a RCT of daily probiotic supplementation in infants at high risk of allergy	Wheat, nuts, eggs; unclear	2	SPTaero, SPTfood
Zutavern, 2004 (21)	PC	552	UK	Population based birth cohort of infants from all pregnant women presenting in three general practices in Ashford, Kent UK between 1993 and 1995	Cow's milk, egg, fish, wheat, Q	5.5	SPTaero
Zutavern, 2006 (22); Zutavern, 2008 (23)	PC	2549	Germany	LISA: Population based cohort study of newborns recruited between 1997 and 1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef.	Cow's milk, egg, Q	2, 6	sIgEany, sIgEfood
Kucukosmanoglu, 2008 (24)	CS	1015	Turkey	Participants were all born in Okmeydani Teaching Hospital, Turkey, between 2001-2, with and without allergic sensitisation.	Egg, I	1	SPTegg

PC prospective cohort, CS cross-sectional, D food diary, Q questionnaire, I interview, R records

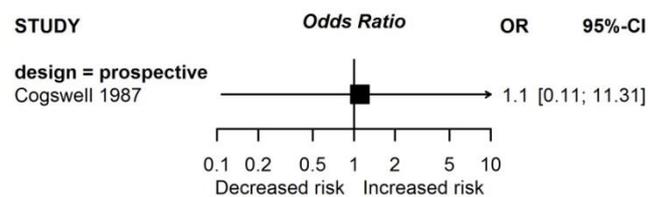
**Figure 1 Risk of bias in observational studies of timing of allergenic food introduction and risk of allergen sensitisation**



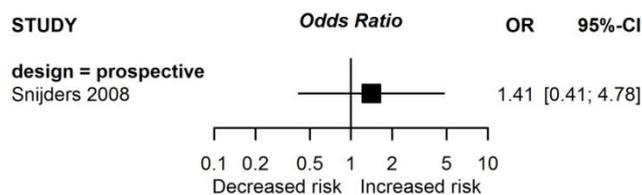
## 2. Timing of cow's milk introduction and risk of AS

Figures 2 to 10 show the outcomes of 7 eligible observational studies reporting OR for AS. The data show no significant association between timing of cow's milk introduction to the infant diet and AS to 'any allergen', food, cow's milk, egg or peanut (Figures 2 to 7). Numbers of studies included in individual analyses were small, but where meta-analysis was possible statistical heterogeneity was low. Three prospective cohort studies contributed to a meta-analysis which found increased allergic sensitisation to aeroallergens with introduction of cow's milk prior to 3-4 months age (Figure 9). This association was not seen in analyses using different cut-offs (Figures 8 and 10). Figure 9 was dominated by the study of Oddy 1999, which reported adjusted data and had low overall risk of bias, and found a significant association using a cut-off of 4 months, but reported non-significant findings using different cut-offs for timing of cow's milk introduction (3 months, 5 months, 6 months). In the same analysis Strassburger 2010 reported unadjusted data from a study at low overall risk of bias; Snijders 2008 reported adjusted data from a study at low overall risk of bias.

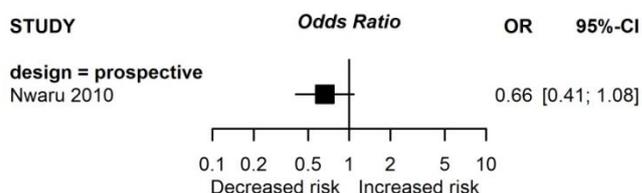
**Figure 2: Cow's milk introduction  $\leq$ 0-2 months and AS-any**



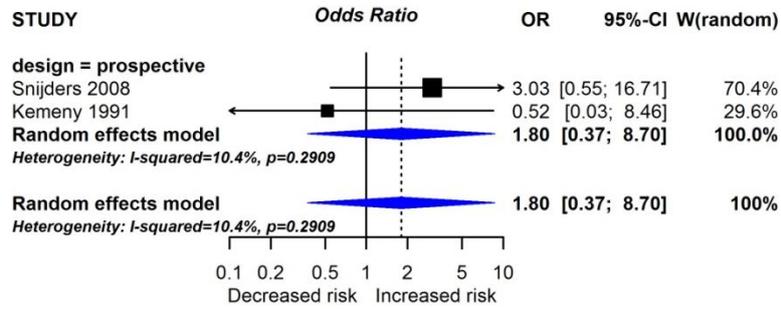
**Figure 3: Cow's milk introduction  $\leq$ 3-4 months and AS-any**



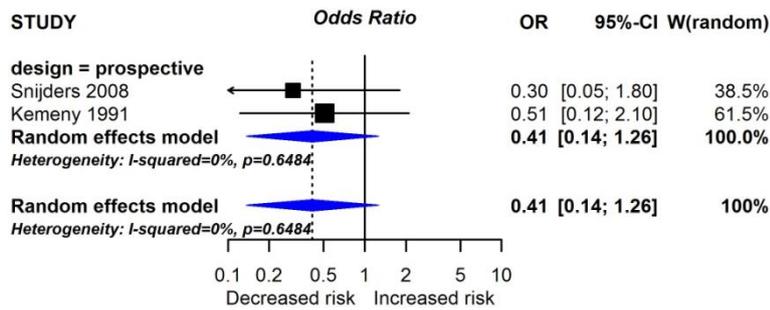
**Figure 4: Cow's milk introduction  $\leq$ 0-2 months and AS-food**



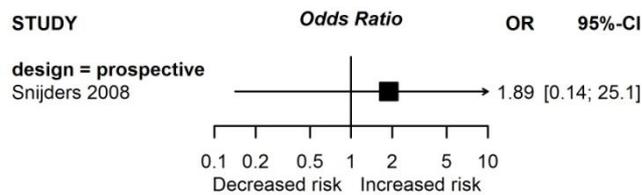
**Figure 5: Cow's milk introduction  $\leq 3$ -4 months and AS-CM**



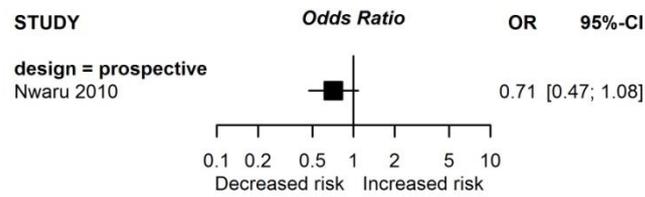
**Figure 6: Cow's milk introduction  $\leq 3$ -4 months and AS-Egg**



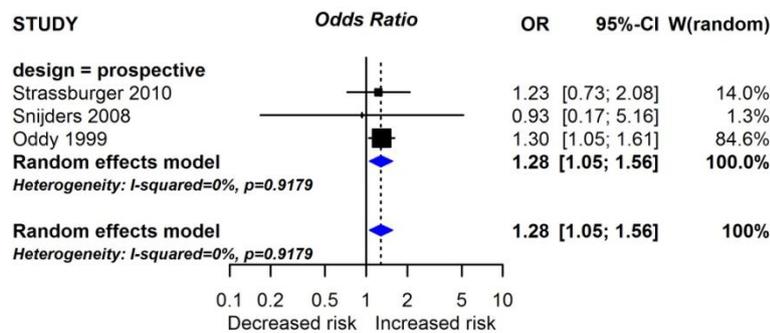
**Figure 7: Cow's milk introduction  $\leq 3$ -4 months and AS-Peanut**



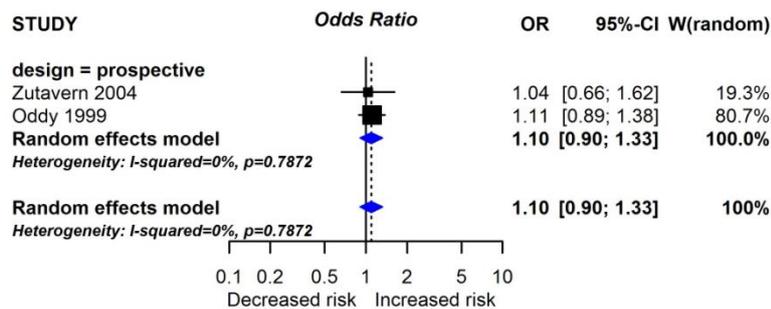
**Figure 8: Cow’s milk introduction ≤0-2 months and AS-aero**



**Figure 9: Cow’s milk introduction ≤3-4 months and AS-aero**



**Figure 10: Cow’s milk introduction ≤5-7 months and AS-aero**



**2.1. Studies of cow’s milk introduction and AS which could not be included in meta-analysis**

Five further studies reported the relationship between timing of cow’s milk introduction to the infant diet, and risk of AS. In one small study there was an association between increased total IgE and early cow’s milk introduction, and in 3 other studies there was no

association between allergic sensitisation and timing of cow's milk introduction. The findings from each study are summarised below:

**Hesselmar 2010** reported median age of cow's milk introduction 5 months (IQR 4, 6.5) in infants without AS-food in the first 18 months, compared with 5 months (IQR 4, 6) in infants with AS-food (P=0.49). **Zutavern 2006** reported no association between timing of introduction of cow's milk or egg and AS-any or AS-food, but did not present numerical data. **Joseph 2011** reported no significant relationship between early 'complementary food' introduction and AS-CM, AS-Egg or AS-Peanut, and the definition of 'complementary food' included cow's milk formula. However, the study did not separately report analysis of cow's milk introduction and these outcomes.

**Ostergaard 1985**, in a small study, reported a significant increase in total IgE' in infants with early infant formula introduction before 4 months, but did not present numerical data. **Poysa 1990** found no significant difference in total IgE between infants with cow's milk formula introduction prior to 3 months, and no formula for the first 3 months, but did not present numerical data.

## **2.2. Conclusions: cow's milk introduction and AS**

Overall 12 studies reported this association. Statistical heterogeneity was generally low. One study found a significant association between early cow's milk introduction and increased aeroallergen sensitisation, but only in one analysis. One small study found an association with increased total IgE, but this was not supported by a larger study evaluating the same outcome. 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 timing of cow's milk introduction influences risk of AS.**

### **3. Timing of soya introduction and risk of AS**

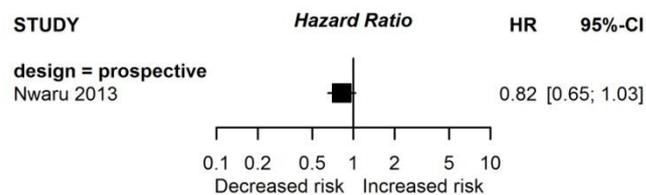
Three studies reported the association between timing of soya introduction and risk of AS. Buscino 1995 reported geometric mean total IgE level of 14 in infants with early soya introduction, compared with 8.5 in infants without early soya introduction, at age 6 months, which was not a statistically significant difference. Koplin 2008 undertook cohort analysis of an RCT and found no significant difference between infants with and without early soya introduction in AS-peanut at age 2 years. Sicherer 2010 reported no significant association between use of soya formula and allergic sensitisation to peanut, in a cohort of food allergic infants, in adjusted analysis. Numerical data were not shown.

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

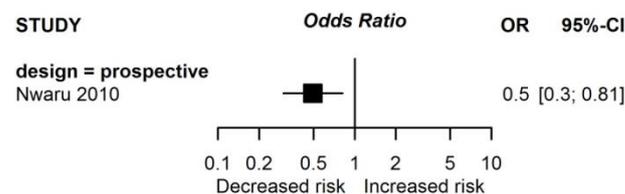
#### 4. Timing of egg introduction and risk of AS

Figures 11 to 15 show the outcomes of 2 eligible observational studies reporting OR or HR for AS. Data from the DIPP cohort study (Nwaru 2010/13) showed a significant association between earlier egg introduction and reduced AS-food (Figure 12). The same study did not find a similar association with AS-CM and AS-Egg, but when all dietary exposures were assessed in a backward logistic regression model, the final model showed a significant association between earlier egg introduction and reduced AS-food (P=0.008) and reduced AS-CM and AS-Egg (both P=0.017). Of note, the authors did explore interactions with early onset eczema and a family history of allergic disease, to try to account for the possibility of reverse causality. There was evidence from this study and the study of Zutavern 2004, which also reported adjusted data that earlier egg introduction is associated with reduced AS-aero, but this did not quite reach statistical significance (Figure 15).

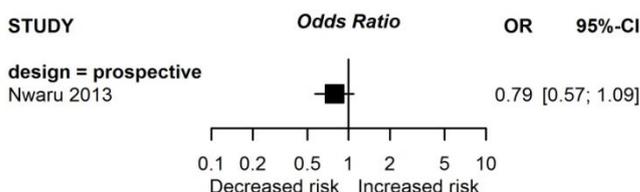
**Figure 11: Egg introduction  $\leq$ 8-12 months and AS-any, HR**



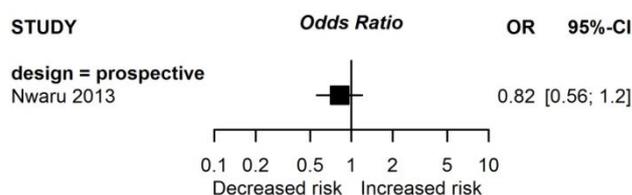
**Figure 12: Egg introduction  $\leq$ 8-12 months and AS-food, OR**



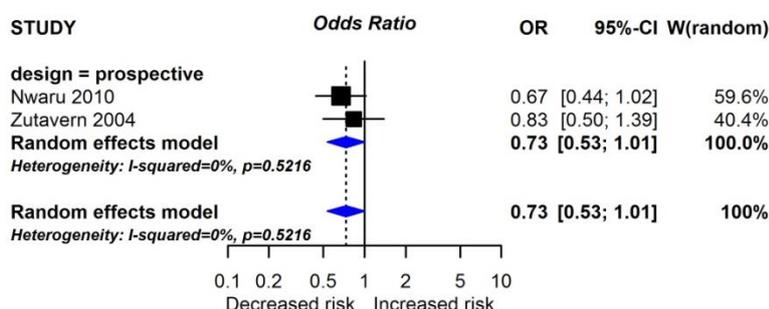
**Figure 13: Egg introduction  $\leq$ 8-12 months and AS-CM, OR**



**Figure 14: Egg introduction  $\leq$ 8-12 months and AS-Egg, OR**



**Figure 15: Egg introduction  $\leq$ 8-12 months and AS-aero, OR**



#### 4.1. Studies of egg introduction and AS which could not be included in meta-analysis

Four further studies reported the relationship between timing of egg introduction to the infant diet, and risk of AS. In 3 studies no association was found, and in 1 study a strong association was found between early egg introduction and reduced allergic sensitisation. The findings from each study are summarised below:

**Hesselmar 2010** reported median age of egg introduction 11 months (IQR 9, 13) in infants without AS-food in the first 18 months, compared with 13 months (IQR 10, 13) in infants with AS-food (P=0.30). **Zutavern 2006** reported no association between timing of introduction of milk or egg and AS-any or AS-food, but did not present numerical data. **Kucokosmanoglu 2008** found no association between timing of introduction of egg in the infant diet, and AS-egg at 1 year – mean (sd) time of introduction of egg was 7.0 (2.3) months in sensitised infants, and 6.8 (2.45) months in non-sensitised infants. **Wickens 2011** reported in an abstract publication, a finding in adjusted analyses that

early egg introduction was associated with reduced AS-food (P=0.0001) and reduced AS-aero (P=0.007).

#### **4.2. Conclusions: egg introduction and AS**

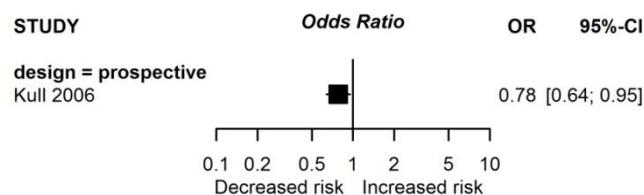
Overall 6 studies reported this association. Statistical heterogeneity was low in the single meta-analysis. Overall 2 studies (~6500 participants) reported an association between early egg introduction and reduced AS-food, and 1 study reported the same association for AS-aero. Four studies(~4000 participants) found no significant association between timing of egg introduction and AS-food (3 studies) or AS-aero (1 study). No studies reported total IgE.

**Overall we found no consistent evidence that timing of egg introduction is associated with risk of allergic sensitisation.**

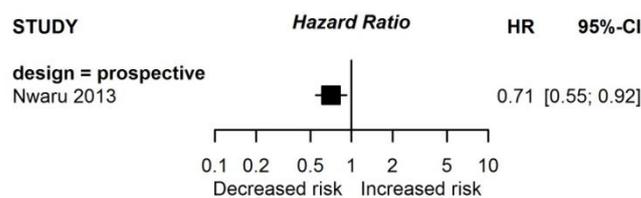
### 5. Timing of fish introduction and risk of AS

Figures 16 to 23 show the outcomes of 4 prospective cohort studies reporting OR for AS. The study of Kull 2006 reported adjusted data, and they also excluded infants with early onset eczema in other analyses, with similar findings, which reduces the possibility that the association seen is due to reverse causation. The study of Nwaru 2010/13 reported adjusted data, showing an association between earlier fish introduction and reduced AS-food, AS-CM, AS-Egg and AS-Aero (Figures 18, 20, 21 and 22). They also adjusted for possible reverse causation by excluding infants with early onset symptoms. Alm 2011 reported adjusted data showing reduced AS-food and AS-aero with early fish introduction, and also attempted to account for possible reverse causation (Figures 19 and 23). Figure 23 shows extreme statistical heterogeneity ( $I^2=86%$ ) - Alm 2011 reported adjusted data, and Zutavern 2004 unadjusted data, which may have contributed to this heterogeneity.

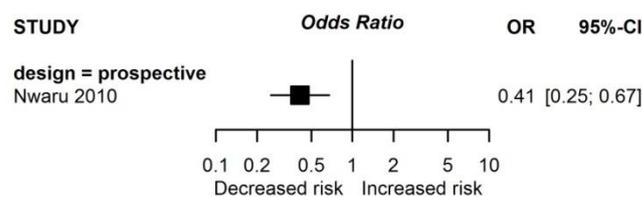
**Figure 16: Fish introduction  $\leq$ 8-12 months and AS-any, OR**



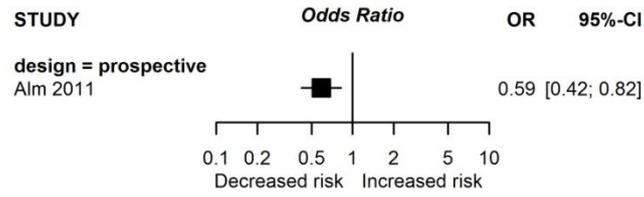
**Figure 17: Fish introduction  $\leq$ 5-7 months and AS-any, HR**



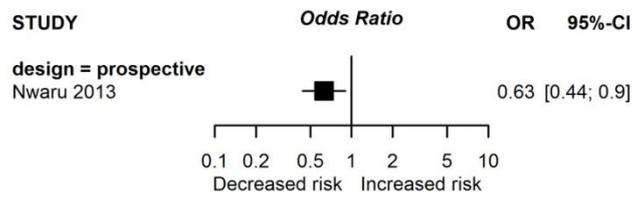
**Figure 18: Fish introduction  $\leq$ 5-7 months and AS-food, OR**



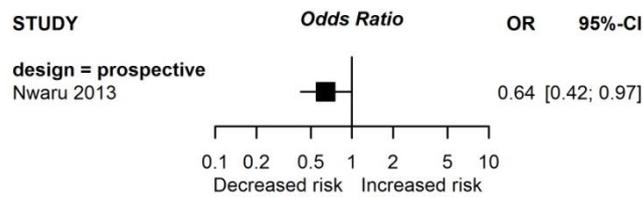
**Figure 19: Fish introduction  $\leq$ 8-12 months and AS-food, OR**



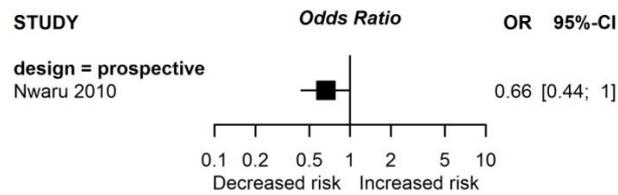
**Figure 20: Fish introduction  $\leq$ 5-7 months and AS-CM, OR**



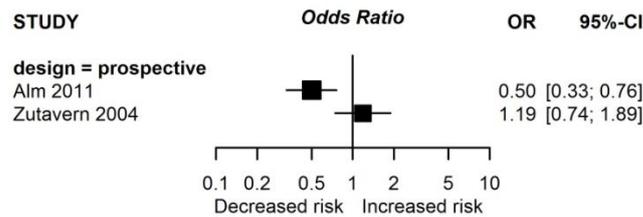
**Figure 21: Fish introduction  $\leq$ 5-7 months and AS-Egg, OR**



**Figure 22: Fish introduction  $\leq$ 5-7 months and AS-aero, OR**



**Figure 23: Fish introduction ≤8-12 months and AS-aero, OR**



### 5.1. Studies of fish introduction and AS which could not be included in meta-analysis

One further study reported the relationship between timing of fish introduction to the infant diet, and risk of AS. **Hesselmar 2010** reported median age of fish introduction 9 months (IQR 6, 12) in infants without AS-food in the first 18 months, compared with 9.5 months (IQR 6, 13) in infants with AS-food (P=0.28).

### 5.2. Conclusions: fish introduction and AS

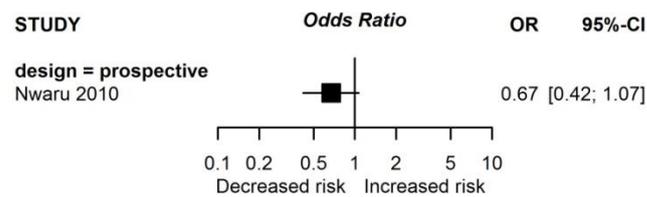
Overall 5 studies reported this association. Statistical heterogeneity was extreme in the only potential meta-analysis, so meta-analysis was not possible. Overall 3 studies including over 13,000 participants reported associations between early fish introduction and reductions in all forms of allergic sensitisation, which remained significant when making adjustments for possible reverse causation. Two smaller studies with over 700 participants found no such association in unadjusted analysis, one for AS-aero and one for AS-food. Overall we found evidence that early fish introduction is associated with reduced AS. The grade of evidence was reduced -1 for indirectness of the outcome measure.

**Overall we found VERY LOW evidence that earlier fish introduction (before 6-9 months) is associated with reduced risk of allergic sensitisation to both any allergen, and to food allergens.**

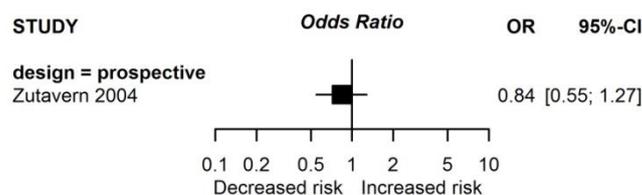
## 6. Timing of cereal introduction and risk of AS

Figures 24 to 26 show the outcomes of 2 eligible observational studies reporting OR for AS. The data show no significant association between timing of cereal introduction to the infant diet and AS to ‘any allergen’ or ‘any inhalant allergen’. No meta-analysis was possible due to a paucity of studies reporting this exposure and outcome. Nwaru 2010 reported multiple analyses of wheat, oat and rye introduction and several measures of allergic sensitisation. In a final adjusted model they found evidence that early oat introduction is associated with reduced AS-food ( $P < 0.01$ ) and that early wheat introduction is associated with reduced AS-wheat ( $P < 0.01$ ), but no evidence for associations with AS-aero.

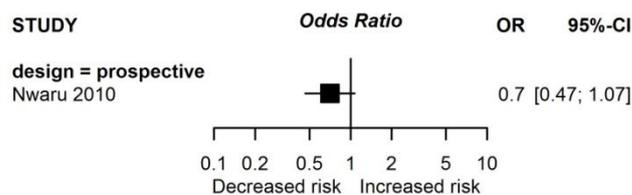
**Figure 24: Wheat introduction  $\leq 5-7$  months and AS-any, OR**



**Figure 25: Wheat introduction  $\leq 3-4$  months and AS-aero, OR**



**Figure 26: Wheat introduction  $\leq 5-7$  months and AS-aero, OR**



### **6.1. Conclusions: cereal introduction and AS**

Only 2 studies reported this association. Neither study found any association with AS-aero, but the study which assessed AS-food found some evidence that early wheat introduction is associated with reduced AS-food. This association was seen for oats, but not for rye and for wheat an association was only seen with AS-wheat, which is an outcome we did not systematically assess in this project. The association with oats was mixed, with reduced AS-food at 5-5.5 month introduction compared with <5 month introduction, but the highest rate of AS-food seen in those with oat introduction >5.5 months. Overall there was no convincing evidence to suggest a relationship between timing of introduction of cereal to the infant diet, and AS risk.

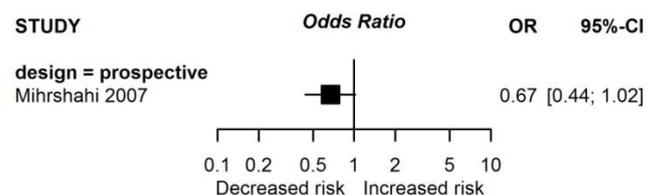
**Overall we found no evidence that timing of cereal introduction influences risk of AS.**

## 7. Timing of any allergenic food introduction

### 7.1. Timing of allergenic food (AF) and risk of AS

Figure 27 shows the outcomes of 1 eligible observational study reporting OR for AS-any in relation to timing of introduction of ‘any allergenic food’ – defined as cow’s milk, egg, nuts or fish. Introduction of AF prior to 9 months was not associated with significantly different AS risk at age 5 years compared with later introduction of AF. The study did not exclude infants with early onset allergic symptoms, or adjust for these, to account for potential reverse causation.

**Figure 27: AF introduction  $\leq$ 8-12 months and AS-Any, OR**



### 7.2. Conclusions: timing of any AF introduction and AS

Only 1 study reported this association. No significant association was seen.

**Overall we found no evidence that timing of ‘any allergenic food’ introduction influences risk of AS.**

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