

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

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1. Timing of introduction of allergenic foods and risk of rhinoconjunctivitis – 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 12 observational studies which reported the association between introduction of allergenic food(s) in infancy and risk of allergic rhinoconjunctivitis (ARC). Of these, 11 were prospective cohort studies and 1 cross-sectional.

1.2. Populations

The majority of studies (n=9) were carried out in European populations, while 1 in USA and 2 in Asia Pacific region..

1.3. Exposure assessment

We identified 10 studies which assessed cow's milk introduction and ARC, 1 study of soya, 1 study of egg, 2 studies of fish, no studies of nut introduction, and 1 study of cereal introduction. We did not identify any studies of the interaction between allergenic food introduction and breastfeeding status, and ARC. Questionnaire was the most common method to collect data (n=8), followed by interview (n=2), food diary (n=1) and healthcare records (n=1), not mutually exclusive because more than one method was used in several studies. Six studies used only questionnaire.

1.4. Outcome assessment methods used

In 5 studies outcome assessment relied on physician assessment by a study doctor, in others outcome assessment was by parent reported symptoms and/or parent-reported doctor diagnosis, and in one study the method of outcome assessment was unclear. ISAAC questionnaire was used in 2 studies.

Nine studies reported outcomes at age 0-4, four at age 5-14 and three at age 15 and over (not mutually exclusively, as some studies assessed ARC at more than one age).

1.5. Risk of bias assessment

Among 12 studies, overall bias was considered to be low in 4 (33%), unclear in 2 (17%), and high in 6 (50%). The risk of bias was most commonly considered high due to lack of adjustment for potential confounders.

1.6. Key findings

- i. Overall risk of bias was low or unclear for the majority of the exposures assessed.
- ii. Small numbers of studies contributed to individual analyses, and data were sparse for soya, egg and cereal and absent for nuts or 'any allergenic food'.
- iii. We found no evidence for an association between timing of cow's milk, soya, egg or cereal introduction and ARC.
- iv. We found LOW grade evidence that early introduction of fish to the infant diet is associated with reduced ARC at age ≤ 4 or age 5-14.

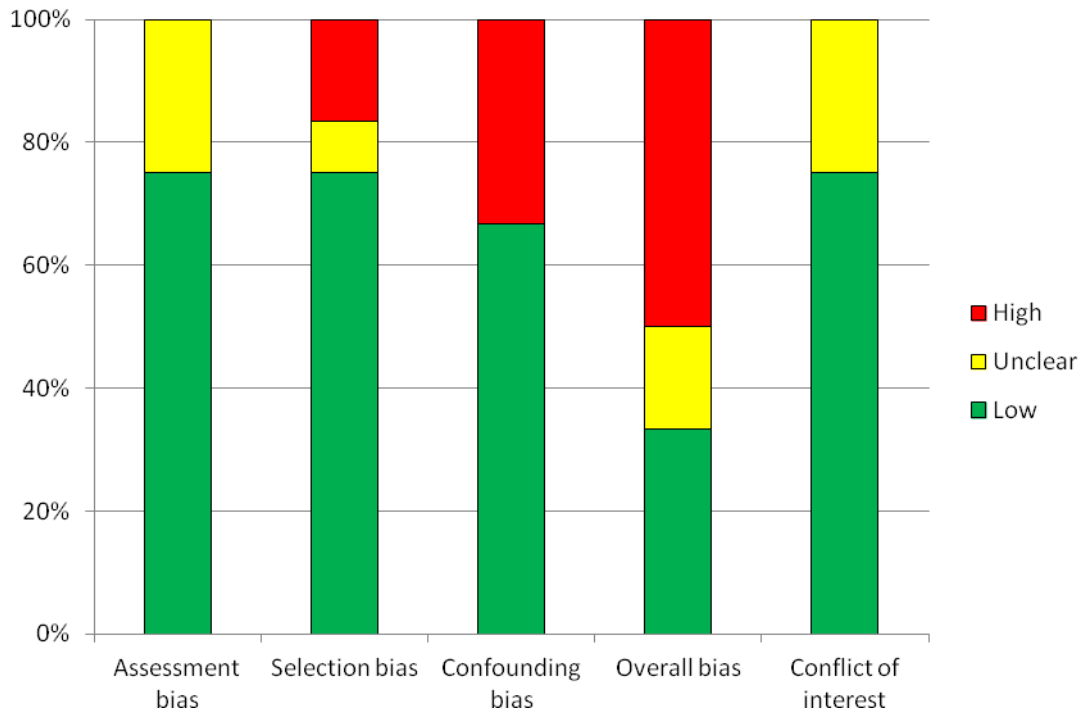
Table 1 Characteristics of included studies evaluating timing of allergenic food introduction in infants and rhinoconjunctivitis

Study	Design	N	Country	Population	Exposure and 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	Cow's milk, fish, Q	4	Parent report and/or DD
Businco, 1993 (2)	PC	101	Italy	Infants of atopic parents recruited at birth in a hospital in Rome, Italy between 1985 and 1988	Cow's milk, soya, I	0-2	Physician assessment PLUS parent report
Gustafasson, 1992 (3)	PC	736	Sweden	Healthy full term children born in Karlskoga, Sweden, nursed on the local maternity ward during 1970, 1973 and 1976, and attended 1st, 4th and 7th grades at the compulsory school in 1984.	Cow's milk, R	7, 14	Physician assessment
Kull, 2006 (4)	PC	3230	Sweden	BAMSE: Prospective birth cohort of newborns in a predefined area of Stockholm, between 1994 and 1997	Fish, Q	4	DD and/or parent report
Marini, 1996 (5)	PC (of RCT-CCT)	68	Italy	Infants with family history of allergy born in maternity wards of 3 hospitals from 1989 whose mothers were refused to participate in an allergy prevention intervention program	Cow's milk, Q	1-3	Physician assessment PLUS parent report
Nwaru, 2013 (6); Virtanen, 2010 (7)	PC	3109	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 Finland	Cereal, egg, cow' milk, fish, Q	0-5	Parent report (ISAAC Q)
Per Nafstad, 2003 (8)	PC	2271	Norway	The Environment and Childhood Asthma study in Oslo: Population based birth cohort of newborn children included born in Oslo, Norway in 1992	Fish, Q	4	Questionnaire with parent report

Study	Design	N	Country	Population	Exposure and assessment	Age at outcome (years)	Outcome assessment
Strachan, 1996 (9)	PC	3935	UK	Sheffield child development study: Each baby born in Sheffield since August 1975 has been included in a screening programme to predict the risk of sudden infant death and other perinatal outcomes	Cow's milk, I	16	DD
Tariq, 1998 (10)	PC	1086	UK	Isle of Wight Prevention Study: population based birth cohort of mainly Caucasian infants born in the Isle of Wight between 1989 and 1990	Cow's milk, Q/D	4	Physician assessment
Van Asperen, 1983 (11)	PC	79	Australia	Infants with family history of atopy born at two major obstetric units over an 8-month period from 1980 to 1981	Cow's milk, I	1-1.5	Physician assessment
Wright, 1994 (12)	PC	747	USA	Tuscon Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984	Cow's milk, Q	0-6	Parent report
Miyake, 2003 (13)	CS	5614	Japan	Participants were 12-15 years olds from public schools in Suita, Japan.	Cow's milk, Q	12-15	Parent report (ISAAC Q)

PC prospective cohort, CS cross-sectional, D food diary, Q questionnaire, Physician assessment refers to assessment by a study physician, DD doctor diagnosis, I interview, R records

Figure 1 Risk of bias in observational studies of timing of allergenic food introduction and risk of rhinoconjunctivitis



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

2.1. Evidence from meta-analyses

Figures 2 to 6 show the outcomes of 8 eligible observational studies reporting OR for ARC at age ≤ 4 , 5-14 or 15+. The pooled data show increased risk of ARC with cow's milk introduction in the first 2 months (Figure 2), but data from these 2 studies were unadjusted. The other 6 studies, including 2 other meta-analyses, found no significant association between timing of cow's milk introduction to the infant diet and ARC. All meta-analyses had no statistical heterogeneity.

Figure 2: Cow's milk introduction $\leq 0-2$ months and ARC at ≤ 4 , OR

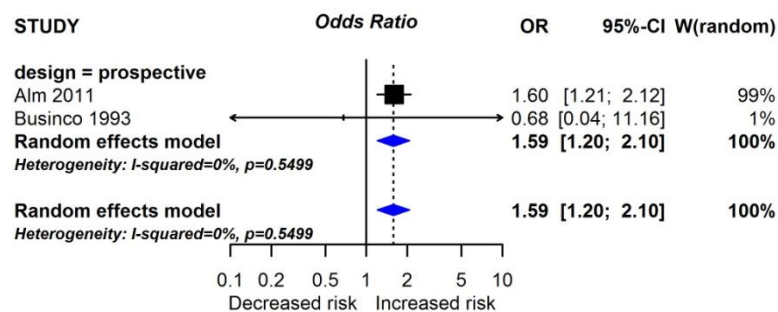


Figure 3: Cow's milk introduction $\leq 3-4$ months and ARC at ≤ 4 , OR

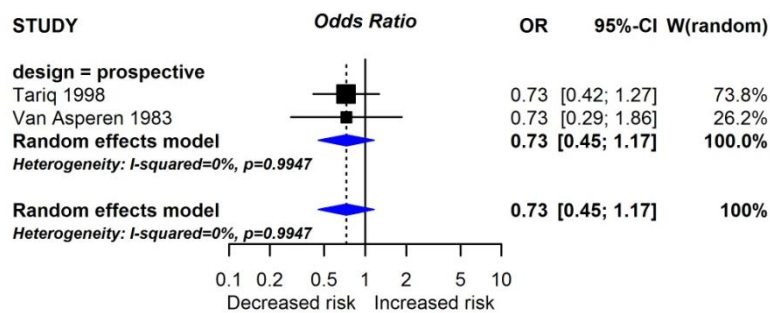


Figure 4: Cow's milk introduction $\leq 5-7$ months and ARC at ≤ 4 , OR

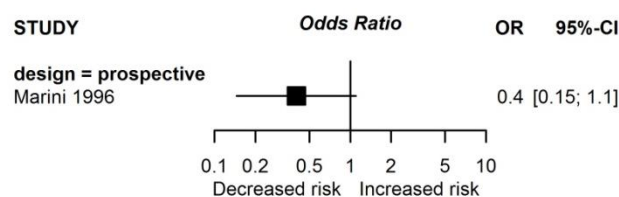


Figure 5: Cow’s milk introduction ≤ 0 -2 months and ARC at 5-14, OR

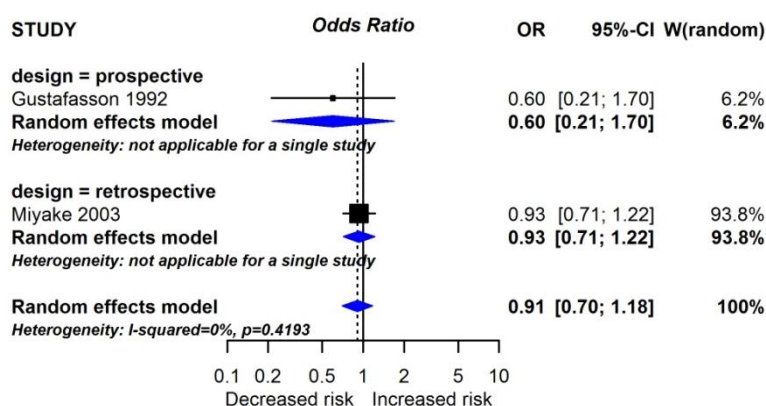
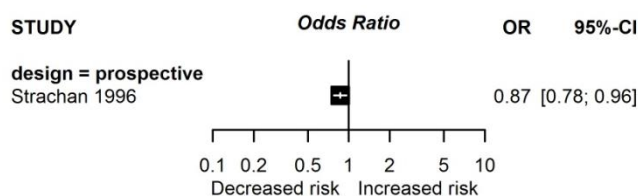


Figure 6: Cow’s milk introduction ≤ 0 -2 months and ARC at ≥ 15 , OR



2.2. Studies of cow’s milk introduction and ARC which could not be included in meta-analysis

Two further studies reported the relationship between timing of cow’s milk introduction to the infant diet, and risk of ARC. In the **DIPP study Nwaru 2013** reported no association between timing of introduction of cow’s milk and ARC. **Wright 1994** reported no significant association between timing of introduction of cow’s milk formula and risk of ARC.

2.3. Conclusions: cow’s milk introduction and ARC

Overall 10 studies reported this association – 9 prospective cohort studies and 1 cross-sectional study. Overall there was no evidence to suggest a relationship between timing of introduction of cow’s milk to the infant diet, and ARC risk.

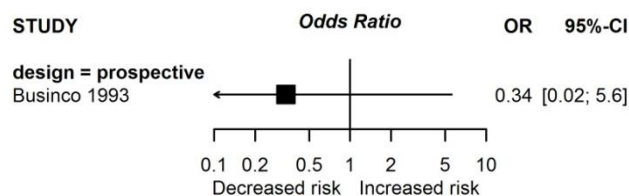
Overall we found no evidence that timing of cow’s milk introduction influences risk of ARC.

3. Timing of other allergenic food introduction and risk of ARC

Figures 7 to 11 show the outcomes of 5 eligible observational studies reporting the relationship between timing of introduction of other allergenic foods (soya, egg, fish and cereal) and OR for ARC at age ≤ 4 or 5-14. The data show no significant association between timing of introduction of soya, egg or cereal and risk of ARC, but data from 4 studies show reduced ARC at ages 4 to 5 years with early introduction of fish. Meta-analysis of 3 of these studies shows high statistical heterogeneity, for unclear reasons. All data reporting fish introduction and ARC are adjusted. The data of Nwaru 2013 and Kull 2006 also excluded infants with early onset eczema to account for reverse causation. Data of Per Nafsted 2003 did not exclude early eczema cases – the authors did present an analysis excluding early eczema cases which showed OR 0.56 (0.30, 1.04) for this outcome, but that was not included in our analysis as it was unclear whether this OR was adjusted for other potential confounders. Sensitivity analysis substituting this figure for the adjusted OR in the study of Per Nafsted 2003 showed reduced statistical heterogeneity (OR 0.67 95% CI 0.52, 0.88; $I^2=20\%$).

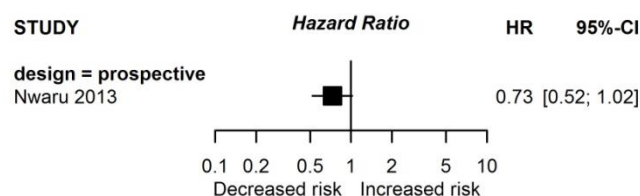
3.1. Timing of soya introduction and risk of ARC

Figure 7: Soya introduction $\leq 0-2$ months and ARC at ≤ 4 , OR



3.2. Timing of egg introduction and risk of ARC

Figure 8: Egg introduction $\leq 8-12$ months and ARC at 5-14, HR



3.3. Timing of fish introduction and risk of ARC

Figure 9: Fish introduction $\leq 8-12$ months and ARC at ≤ 4 , OR

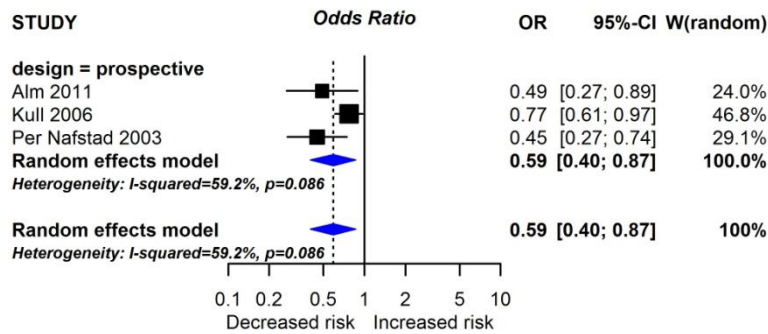
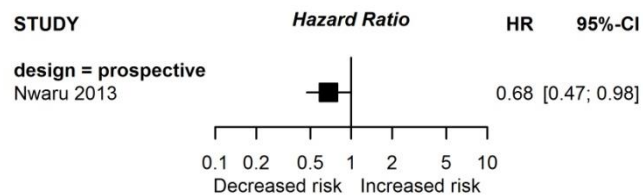
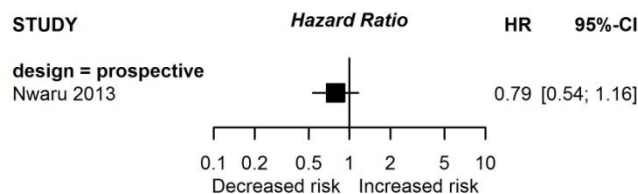


Figure 10: Fish introduction $\leq 5-7$ months and ARC at 5-14, HR



3.4. Timing of cereal introduction and risk of ARC

Figure 11: Cereal introduction $\leq 5-7$ months and ARC at 5-14, HR



3.5. Conclusions: other allergenic food introduction and ARC

Data for introduction of soya, egg and cereal were sparse, and showed no evidence of association with ARC. Four prospective cohort studies each found statistically significant associations between earlier fish introduction and reduced risk of ARC, and meta-analysis of 3 of these studies showed a statistically significant association, albeit with high statistical heterogeneity, for unclear reasons. Earlier fish introduction in these studies was classified as before 6 months age (Nwaru 2013), before 8 months age (Kull 2006), before 9 months (Alm 2011) or before 12 months (Per Nafstad 2003).

Overall we found LOW evidence that earlier introduction of fish to the infant diet is associated with reduced risk of ARC.

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