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

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Table of Contents

List of	Figures	4
1. T	iming of introduction of allergenic foods and risk of eczema – summary of finding	gs6
1.1.	Studies identified	6
1.2.	Populations	6
1.3.	Exposure assessment	6
1.4.	Outcome assessment methods used	6
1.5.	Risk of bias assessment	7
1.6.	Key findings	7
2. T	iming of cow's milk introduction and risk of eczema	15
2.1.	Timing of cow's milk introduction and risk of eczema at age \leq 4 years	15
2.2.	Timing of cow's milk introduction and risk of eczema at age 5-14 years	18
2.3.	Studies of cow's milk introduction and eczema which could not be included in	
meta-a	nalysis	19
2.4.	Conclusions: cow's milk introduction and eczema	20
3. T	iming of soya introduction and risk of eczema	21
3.1.	Timing of soya introduction and risk of eczema	21
3.2.	Studies of soya introduction and eczema which could not be included in meta-	
analys	is 22	
3.3.	Conclusions: soya introduction and eczema	22
4. T	iming of egg introduction and risk of eczema	23
4.1.	Timing of egg introduction and risk of eczema	23
4.2.	Studies of egg introduction and eczema which could not be included in meta-	
analys	is 24	
4.3.	Conclusions: egg introduction and eczema	25
5. T	iming of nut introduction and risk of eczema	26
5.1.	Timing of nut introduction and risk of eczema	26

5.2.	Conclusions: nut introduction and eczema	27
6. Tin	ning of fish introduction and risk of eczema2	28
6.1.	Timing of fish introduction and risk of eczema	28
6.2.	Studies of fish introduction and eczema which could not be included in meta-	
analysis	30	
6.3.	Conclusions: fish introduction and eczema	30
7. Tin	ning of cereal introduction and risk of eczema	32
7.1.	Timing of cereal introduction and risk of eczema	32
7.2.	Studies of cereal introduction and eczema which could not be included in meta-	
analysis	34	
7.3.	Conclusions: cereal introduction and eczema	34
8. Tin	ning of any allergenic food introduction	35
8.1.	Timing of allergenic food (AF) and risk of eczema	35
Reference	ces	36

List of Figures

Figure 1 Risk of bias in observational studies of timing of allergenic food introduction and
risk of eczema
Figure 2: Cow's milk introduction \leq 0-2 months and eczema at \leq 4, OR 15
Figure 3: Cow's milk introduction \leq 3-4 months and eczema at \leq 4, OR 15
Figure 4: Cow's milk introduction \leq 5-7 months and eczema at \leq 4, OR 16
Figure 5: Cow's milk introduction \leq 8-12 months and eczema at \leq 4, OR 16
Figure 6: Cow's milk introduction ≤0-2 months and eczema at 5-14, OR
Figure 7: Cow's milk introduction ≤5-7 months and eczema at 5-14, OR
Figure 8: Cow's milk introduction ≤0-2 months and atopic eczema at 5-14, OR 18
Figure 9: Soya introduction \leq 0-2 months and eczema at \leq 4, OR 21
Figure 10: Soya introduction \leq 5-7 months and eczema at \leq 4, OR
Figure 11: Soya introduction ≤8-12 months and eczema at ≤4, OR
Figure 12: Soya introduction ≤0-2 months and eczema at 5-14, OR 22
Figure 13: Egg introduction \leq 3-4 months and eczema at \leq 4, OR 23
Figure 14: Egg introduction \leq 5-7 months and eczema at \leq 4, OR 23
Figure 15: Egg introduction \leq 8-12 months and eczema at \leq 4, OR 23
Figure 16: Egg introduction \leq 8-12 months and atopic eczema at \leq 4, OR 24
Figure 17: Egg introduction \leq 5-7 months and eczema at 5-14, OR
Figure 18: Egg introduction ≤8-12 months and eczema at 5-14, OR
Figure 19: Nut introduction \leq 5-7 months and eczema at \leq 4, OR
Figure 20: Nut introduction \leq 8-12 months and eczema at \leq 4, OR
Figure 21: Fish introduction ≤3-4 months and eczema at ≤4, OR
Figure 22: Fish introduction \leq 5-7 months and eczema at \leq 4, OR 28
Figure 23: Fish introduction \leq 8-12 months and eczema at \leq 4, OR
Figure 24: Fish introduction ≤5-7 months and atopic eczema at ≤4, HR
Figure 25: Fish introduction ≤5-7 months and eczema at 5-14, OR
Figure 26: Fish introduction ≤8-12 months and eczema at 5-14, OR
Figure 27: Cereal introduction \leq 3-4 months and eczema at \leq 4, OR
Figure 28: Cereal introduction \leq 5-7 months and eczema at \leq 4, OR
Figure 29: Cereal introduction \leq 8-12 months and eczema at \leq 4, OR
Figure 30: Cereal introduction \leq 5-7 months and atopic eczema at \leq 4, HR
Figure 31: Cereal introduction ≤3-4 months and eczema at 5-14, OR

Figure 32: Cereal introduction \leq 3-4 months and eczema at 5-14, HR	. 33
Figure 33: AF introduction ≤8-12 months and eczema at 5-14, OR	. 35

1. Timing of introduction of allergenic foods and risk of eczema – 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 37 observational studies which reported the association between timing of introduction of allergenic food(s) and risk of eczema. Of these, 34 were prospective cohort studies, 1 nested case-control, 1 case-control and 1 cross-sectional study.

1.2. Populations

The majority of studies (n=29) were carried out in European populations. Other studies were from North America (n=2), Asia Pacific region (n=4), the Middle East (n=2).

1.3. Exposure assessment

We identified 32 studies which assessed cow's milk introduction and eczema, 6 studies of soya, 17 studies of egg, 12 studies of fish, 4 studies of nut (peanut or tree nut) introduction, 12 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 eczema. Questionnaire was the most common method to collect data (n=22), followed by interview (n=13), food diary (n=9) and healthcare records (n=2), not mutually exclusive because more than one method was used in several studies. Fifteen studies used only questionnaire. It was unclear whether any study used a validated or piloted dietary questionnaire.

1.4. Outcome assessment methods used

In 15 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 questionnaires were used in 5 studies.

Thirty studies reported outcomes at age 0-4, five at age 5-14 and one at age 15 and over (not mutually exclusive, as some studies assessed eczema at more than one age).

1.5. Risk of bias assessment

Among 37 studies, overall bias was considered to be low in 12 (32%), unclear in 9 (24%), and high in 16 (43%). The risk of bias was most commonly considered high due to lack of adjustment for potential confounders.

1.6. Key findings

i. Risk of bias was mixed, with over 40% of studies failing to adjust for potential confounders, and only a small number of studies excluding participants with early-onset eczema in order to account for possible reverse causation.

ii. For all exposures other than cereal, at least one meta-analysis had high or extreme statistical heterogeneity. The reason for this was generally not clear, but in some cases may relate to mixed handling of potential reverse causation.

iii. Overall we found no evidence that timing of introduction of allergenic foods influences risk of eczema.

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

					Exposure and	Age at	
Study	Design	Ν	Country	Population	exposure	outcome	Outcome assessment
					assessment	(years)	
Alm, 2008 (1) ;Alm,	PC	4941	Sweden	Infants of Western Sweden: Population based birth cohort of infants born in the region in 2003	Cow's milk, fish, egg,	1	Parent reported
2009 (2)					cereal, Q		
Businco, 1993(3)	PC	101	Italy	Infants of atopic parents recruited at birth in a hospital in Rome, Italy between 1985 and 1988	Cow's milk, and soya, I	2	Physician assessment PLUS parent reported
Cogswell, 1987 (4)	РС	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	Physician assessment PLUS sensitisation
Dunlop, 2006 (5)	PC	1326	Slovakia	Slovak birth cohort: The 1st 250 pregnant women delivering at maternity hospitals in the selected study sites were recruited between 1997 and 1999	Cow's milk, fish, egg, nuts, Q	1	Physician assessment
Epstein 2011 (6)	PC	636	USA	CCAAPS: Newborns at high risk of allergy were identified in the Cincinnati metropolitan area, US by public birth records from 2001 to 2003	Egg, nuts, Q	4	Parent reported (sensitivity analysis with physician assessment)
Fergusson, 1981 (7); Fergusson, 1982 (8); Fergusson, 1990 (9)	PC	1175	New Zealand	Christchurch Child Development Study: A cohort of children born in the Christchurch urban region New Zealand during mid-1977	Cow's milk, egg, cereal, R/D/Q	1, 2, 10	DD

24th March 2015

Study	Design	Ν	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Gustafasson, 1992 (10)	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
Harris, 2001 (11); Zutavern, 2004 (12)	PC	622	UK	Population based birth cohort of newly pregnant women who presented at one of three general practices in Ashford, Kent UK between 1993 and 1995	Cow's milk, cereal, rice, fish, egg, Q	2, 5.5	DD
Hesselmar, 2010 (13)	PC	184	Sweden	ALLERGYFLORA: Birth cohort in Sweden enriched with children with family history of allergies	Cow's milk, egg, fish, I/Q	1.5	Physician assessment, and full-filling Williams' criteria
Kemeny, 1991 (14)	PC	180	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London	Cow's milk, method unclear	1	unclear
Kull, 2006 (15)	PC	3230	Sweden	BAMSE: Prospective birth cohort of newborns in a predefined area of Stockholm, Sweden between 1994 and 1997	Fish, Q	4	DD eczema and/or dry skin with itchy rash for >= 2 weeks
Kvenshagen, 2011 (16); Per Nafstad, 2003 (17)	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	2, 4	DD
Laubereau, 2003 (18)	PC	1500	Germany	GINI: Term newborn infants born between September 1995 and July 1998 were recruited from 2 regions of Germany to participate into an intervention program according to risk of allergy	Cow's milk, Q	3	DD

Study	Design	Ν	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Lucas, 1999 (19)	PC	447	UK	Participants in a RCT of a formula intervention and screened candidates ineligible for randomisation	Cow's milk, I/Q	0.75	Parent reported
Midwinter, 1987 (20)	PC	455	UK	Children born to parents with a family history of atopy in 1979-1981	Cow's milk, soya, I/Q	5	DD
Mihrshahi, 2007 (21)	PC	516	Australia	CAPS: Pregnant women from antenatal clinics of 6 hospitals of Sydney between 1997 and 1999 with unborn children at high risk of asthma	Cow's milk, eggs, nuts or fish, I	5	Parent reported PLUS DD
Morgan, 2004 (22)	PC	257	UK	Healthy preterm birth (<37 weeks gestational) were recruited from a cross section of socioeconomic groups in southeast England using the Royal Surrey County Hospital (Guildford), St Peter's Hospital (Chertsey), and Frimley Park Hospital (Frimley)	Cereal, cow's milk, fish, egg, I	1	Physician assessment and parent reported
Niinivirta, 2014 (23)	PC	256	Finland	Mother over 18, pregnancy <17 weeks and the child having increased risk for allergy	Cow's milk, egg, fish, cereal, D	4	Physician assessment
Nwaru, 2013a (24)	PC	1924	UK	(SEATON) Study of Eczema and Asthma To Observe the influence of Nutrition: recruited healthy pregnant women attending an antenatal clinic	Cereal, cow's milk, egg, fish, D	10	ISAAC
Nwaru, 2013b (25)	PC	4075	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, cow's milk, egg, fish Q	5	DD-ISAAC

Study	Design	Ν	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Peters, 1987 (26)	PC	1192 0	UK	British Cohort Study (bsc70): sample of all infants born in 1970 in Britain	Cow's milk, Q	5	parent reported
Roduit, 2012 (27)	PC	1041	Austria, Finland, France, Germany, and Switzerland	PASTURE: Population based birth cohort with women recruited in third trimester of pregnancy from rural areas in 5 European countries (Austria, Finland, France, Germany, and Switzerland) and from families living in a farm and from families not living on a farm of the same area	Cereal, cow's milk, egg, fish, nuts, soya, D	4	DD
Ruiz, 1992 (28)	PC	39	UK	Infants with one allergic parent born between 1987 and 1989	Cow's milk, egg, I/Q	1	Physician assessment - Hanifin and Rajka criteria
Saarinen, 1979 (29)	PC	236	Finland	Newborns born at the Helsinki University Central Hospital in the 1st 3 months of 1975, predominantly with upper-middle class parents	Cow's milk, D/I	1, 3	Physician assessment
Shohet, 1985 (30)	PC	368	Israel	Healthy babies at 3-6 months of age without eczema were recruited in 1980	Cow's milk, I	0.5	Physician assessment- Hanifin and Lobitz criteria
Snijders, 2008 (31)	PC	2510	Netherland s	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, anthroposophical, physician offices, and midwives.	Cow's milk, Q	2	UK Working Party criteria

Study	Design	Ν	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Tariq, 1998 (32)	РС	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
Tromp, 2011 (33)	РС	6905	Netherland s	GENERATION R: Population based birth cohort, with pregnant women recruited < 25 weeks gestation in Rotterdam, The Netherlands	Cereal, cow's milk, egg, peanut, other nuts, soya, Q	2, 3, 4	Parent reported (ISAAC Q) ; DD
Van Asperen, 1983 (34)	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	1.3	Physician assessment
Zutavern, 2006 (35)	РС	2505	Germany	LISA: Population based cohort study of newborns recruited between 1997 and1999 from 4 German cities: Munich, Leipzig, Wesel, and Bad Honnef.	Cereal, egg, fish, Q	2	DD
Miskelly, 1988 (36)	PC (of RCT)	482	UK	Infant recruited through two antenatal clinics in South Wales born to mothers with positive allergy history in at least one member of family, whose mothers were asked to participate in allergy preventive program	Cow's milk, egg, D	1	Physician assessment
Moore, 1985 (37)	PC (of RCT)	475	UK	Infants born in a hospital in 1979-1980 with family history of eczema or asthma (high risk of disease)	Cow's milk, soya, D/I	1	Physician assessment
Porch, 1998 (38)	PC (of RCT)	130	USA	infants recruited from prenatal services in New Orleans US with family history of allergy	Soya, I	1	Physician assessment

24th March 2015

Study	Design	Ν	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Marini, 1996 (39)	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	Physician assessment PLUS parent reported
Sariachvili, 2010 (40)	NCC	557	Belgium	PIPO Cohort: cases and controls with data regarding development of eczema and timing of introduction of solid foods were identified from this prospective cohort: Belgium.	Cow's milk, cereal, egg, fish, Q	4	Parent reported (ISAAC Q)
Ghaderi, 2014 (41)	CC	200	Iran	Sources of cases and controls not specified: Iran.	Cow's milk, Q/I	5	DD
Miyake, 2003 (42)	CS	5614	Japan	Participants were 12-15 years olds from public schools in Suita, Japan.	Cow's milk, Q	15	Parent reported (ISAAC Q)
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PC prospective cohort, NCC nested case-control, CC case-control, 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 eczema

V1.6

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

2.1. Timing of cow's milk introduction and risk of eczema at age ≤4 years

Figures 2 to 5 show the outcomes of 18 eligible observational studies reporting OR for eczema at age \leq 4. The pooled data show no significant association between timing of cow's milk introduction to the infant diet and eczema, but with low, moderate or high statistical heterogeneity in different meta-analyses, for unclear reasons.

Figure 2: Cow's milk introduction ≤0-2 months and eczema at ≤4, OR



Figure 3: Cow's milk introduction ≤3-4 months and eczema at ≤4, OR



Figure 4: Cow's milk introduction ≤5-7 months and eczema at ≤4, OR



Figure 5: Cow's milk introduction ≤8-12 months and eczema at ≤4, OR



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Table 2 Subgroup analyses of association between co	ow's milk introduction at \leq 3-4 months and risk of eczema
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	Number of studies	OR [95% CI]	I ² (%)	P-value for between groups difference
Risk of disease – High	2	0.48 [0.22-1.05]	0	0.17
Risk of disease – Low/Normal	6	0.85 [0.67-1.09]	51.8	0.17
Overall risk of bias – Low	4	0.78 [0.55-1.13]	69.3	0.80
Overall risk of bias – High/Unclear	4	0.84 [0.57-1.24]	13.9	0.80

2.2. Timing of cow's milk introduction and risk of eczema at age 5-14 years

Figures 6 to 8 show the outcomes of 7 eligible observational studies reporting OR for eczema at age 5-14. Pooled data from 5 studies shows no significant association between cow's milk introduction to the infant diet at \leq 0-2 months and eczema, with low statistical heterogeneity (Figure 6). One study reported reduced eczema in infants who had cow's milk introduced prior to 6 months of age (Figure 7), but data were unadjusted. The study of Cogswell 1987 (Figure 8) also reported unadjusted data only.

Figure 6: Cow's milk introduction ≤0-2 months and eczema at 5-14, OR



Figure 7: Cow's milk introduction ≤5-7 months and eczema at 5-14, OR







2.3. Studies of cow's milk introduction and eczema which could not be included in meta-analysis

Nine further studies reported the relationship between timing of cow's milk introduction to the infant diet, and risk of eczema. In 7 there was no association reported, in 1 cross-sectional study at high risk of bias an association was reported in a subgroup at low risk of allergic outcomes. The findings from each study are summarised below:

Hesselmar 2010 reported median age of cow's milk introduction 5 months (IQR 4, 6) in infants without eczema in the first 18 months, compared with 5 months (IQR 4, 7) in infants who wheezed (P=1.00). Buscino 1993 reported no cases of eczema in 26 infants fed cow's milk formula after 1 week age, compared with 5 of 75 infants fed cow's milk formula prior to 1 week age. Data were not adjusted and OR could not be calculated due to zero events in the late introduction group. Relative risk for eczema with early cow's milk exposure was 3.91 (95% CI 0.22, 68.35; P=0.35). Miskelly 1988 reported no significant difference in timing of cow's milk introduction between infants with and without eczema in the first year, but did not present numerical data. Lucas 1999 reported no significant difference in risk of eczema in the first 9 months, between infants with and without cow's milk introduction in the first week of life. Niinivirta 2014 found no significant difference in atopic eczema risk in the first 4 years, between infants introduced to cow's milk at before or after 4 months, or with introduction before or after 7 months. Morgan 2004 found no significant difference in timing of cow's milk introduction for infants with and without eczema in the first year of life. In a crosssectional survey judged to be at high risk of selection bias, Miyake 2003 found increase eczema with cow's milk introduction from birth compared with after 3 months age, but only in infants at low hereditary risk of allergic outcomes (OR 1.56, 95% CI 1.13, 2.22). Alm 2009 reported no significant relationship between timing of cow's milk introduction and eczema, but did not report outcome data. In the DIPP study Nwaru 2013 reported no association between introduction of cow's milk at or before 4 months and eczema in adjusted analyses.

2.4. Conclusions: cow's milk introduction and eczema

Overall 32 studies reported this association – 29 prospective cohort studies, some of which were initiated as intervention trials; 1 nested case control study, 1 case control study and 1 cross-sectional study. Statistical heterogeneity was high in some analyses, for unclear reasons. However overall there was no evidence to suggest a relationship between timing of introduction of cow's milk to the infant diet, and eczema risk.

Overall we found no evidence that timing of cow's milk introduction influences risk of eczema.

3. Timing of soya introduction and risk of eczema

3.1. Timing of soya introduction and risk of eczema

Figures 9 to 12 show the outcomes of 5 eligible observational studies reporting OR for eczema at age \leq 4 or age 5-14. Pooled data from 2 studies shows no significant association between soya introduction at age \leq 0-2 months and eczema, but with high statistical heterogeneity. The small prospective study of Porch 1998, considered at high risk of bias due to reporting unadjusted data, found an association between early soya introduction and reduced eczema; the other 4 studies did not find an association.

Figure 9: Soya introduction ≤0-2 months and eczema at ≤4, OR



Figure 10: Soya introduction ≤5-7 months and eczema at ≤4, OR



Figure 11: Soya introduction ≤8-12 months and eczema at ≤4, OR





Figure 12: Soya introduction ≤0-2 months and eczema at 5-14, OR



3.2. Studies of soya introduction and eczema which could not be included in metaanalysis

One further study reported the relationship between timing of soya introduction to the infant diet, and risk of eczema. **Buscino 1993** reported no cases of eczema in 26 infants fed soya formula prior to 1 week age, compared with 5 of 75 infants not fed soya formula prior to 1 week age. Data were not adjusted and OR could not be calculated due to zero events in the soya group. Relative risk for eczema with early soya exposure was 0.26 (95%CI 0.01, 4.48; P=0.35). **Tromp 2011** reported the same comparison at age 2 (in Figure 10) and also at ages 3 and 4, where there was no significant association between soya introduction before 6 months and odds of eczema.

3.3. Conclusions: soya introduction and eczema

Overall 6 prospective cohort studies reported this association. Statistical heterogeneity was high in the only meta-analysis, due to reduced eczema with early soya introduction reported in one small study (Porch 1998). The other studies did not find evidence to suggest a relationship between timing of introduction of soya to the infant diet, and eczema risk.

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

4. Timing of egg introduction and risk of eczema

4.1. Timing of egg introduction and risk of eczema

Figures 13 to 18 show the outcomes of 8 eligible observational studies reporting OR for eczema at age \leq 4 or age 5-14. Pooled data from 2 studies shows no significant association between egg introduction at age \leq 5-7 months and eczema, with no statistical heterogeneity (Figure 14). It was not otherwise possible to pool data, due either to lack of eligible studies, or to extreme statistical heterogeneity (I²=81% Figure 15). The study of Dunlop 2006 reported increased eczema at age 1, with egg introduction prior to 12 months, and reported unadjusted data only. The studies of Epstein 2011, Zutavern 2004 and Roduit 2012 reported adjusted data for eczema at age 2-5 years. The former two studies found reduced eczema with earlier egg introduction in at least some analyses.

Figure 13: Egg introduction ≤3-4 months and eczema at ≤4, OR



Figure 14: Egg introduction ≤5-7 months and eczema at ≤4, OR



Figure 15: Egg introduction ≤8-12 months and eczema at ≤4, OR



Figure 16: Egg introduction ≤8-12 months and atopic eczema at ≤4, OR



Figure 17: Egg introduction ≤5-7 months and eczema at 5-14, OR



Figure 18: Egg introduction ≤8-12 months and eczema at 5-14, OR



4.2. Studies of egg introduction and eczema which could not be included in metaanalysis

Eight further studies reported the relationship between timing of egg introduction to the infant diet, and risk of eczema. In 7 there was no association reported, in 1 cross-sectional study at high risk of bias an association was reported in a subgroup at low risk of allergic outcomes. The findings from each study are summarised below:

Hesselmar 2010 reported median age of egg introduction 11 months (IQR 9, 13) in infants without eczema in the first 18 months, compared with 13 months (IQR 10, 13) in infants who wheezed (P=0.07). **Miskelly 1988** reported no significant difference in timing of egg introduction between infants with and without eczema in the first year, but did not present numerical data. **Niinivirta 2014** found no significant difference in atopic

eczema risk in the first 4 years, between infants introduced to egg at before or after 7 months. **Morgan 2004** found no significant difference in timing of egg introduction for infants with and without eczema in the first year of life. **Alm 2009** reported no significant relationship between timing of egg introduction and eczema, but did not report outcome data. In the **DIPP study Nwaru 2013** reported no association between introduction of egg at or before 8 months and eczema at age 5. **Fergusson 1990** and **Sariachvili 2010** found no association between introduction of egg before or after 4 months age and risk of eczema at 10 and 4 years respectively, but did not present data that could be included in meta-analysis.

4.3. Conclusions: egg introduction and eczema

Overall 16 prospective cohort studies reported this association. Statistical heterogeneity was extreme in one of two meta-analyses, due to increased eczema during the period of egg introduction with introduction of egg in the first year of life in one study (Dunlop 2006). In other studies eczema was either less common (1 study), not different (13 studies) or there was a mixed picture (1 study – Epstein 2011) with earlier introduction of egg to the infant diet. While it is possible that early egg introduction increases eczema during the period of introduction, but reduces eczema in the longer term, the majority of studies in this area have null findings – while opportunities for meta-analysis were limited, the majority of evidence suggests no relationship between timing of egg introduction and eczema risk. Delayed introduction of allergenic food due to the presence of early eczema and concerns about possible food allergy, may plausibly lead to an association between early allergenic food introduction and reduced eczema, through reverse causality. The study of Roduit 2011 excluded children with onset of eczema in the first year of life in order to account for this potential bias.

Overall we found no consistent evidence that timing of egg introduction influences risk of eczema.

5. Timing of nut (peanut or tree nut) introduction and risk of eczema

5.1. Timing of nut introduction and risk of eczema

Figures 19 and 20 show the outcomes of 4 eligible observational studies reporting OR for eczema at age \leq 4. Pooled data show no significant association between age of nut introduction and eczema, with high statistical heterogeneity in one analysis (Figure 19) and no statistical heterogeneity in one analysis (Figure 20). The study of Epstein 2011 reported 'any nut' whereas the data included in this analysis from Tromp reported 'peanut'. Tromp reported the same comparison at age 2 (in Figure 19) and also at ages 3 and 4, where there was no significant association between peanut introduction before 6 months and odds of eczema. Tromp also reported this outcome for timing of tree nut introduction, and found no significant association at ages 2, 3 or 4.

Figure 19: Nut introduction ≤5-7 months and eczema at ≤4, OR



Figure 20: Nut introduction ≤8-12 months and eczema at ≤4, OR



5.2. Conclusions: nut introduction and eczema

Overall 4 prospective cohort studies reported this association. Statistical heterogeneity was high in one of two meta-analyses, for unclear reasons – with one study reporting reduced eczema associated with early nut introduction, and another study reporting no association. Delayed introduction of allergenic food due to the presence of early eczema and concerns about possible food allergy, may plausibly lead to an association between early allergenic food introduction and reduced eczema, through reverse causality. Two further studies, reported in a separate meta-analysis, found no association.

Overall we found no evidence that timing of nut introduction influences risk of eczema.

6. Timing of fish introduction and risk of eczema

6.1. Timing of fish introduction and risk of eczema

Figures 21 to 26 show the outcomes of 11 eligible observational studies reporting OR or HR for eczema or atopic eczema at age \leq 4 or age 5-14. Pooled data from 2 studies shows no significant association between fish introduction at age \leq 3-4 months and eczema, with no statistical heterogeneity (Figure 21). It was not otherwise possible to pool data, due either to lack of eligible studies, or to extreme statistical heterogeneity (I²=81% Figure 23). The study of Dunlop 2006 reported increased eczema at age 1, with fish introduction prior to 12 months, and reported adjusted data. Four other studies reported adjusted data for eczema at age 1-4, and all reported significantly reduced eczema associated with early fish introduction. The reason for the discrepancy in findings was not clear – however the studies of Kull 2006 and Roduit 2012 were the only studies that excluded infants with eczema onset during the first year from analysis, in order to reduce the risk of reverse causation. Overall 1 study reported increased eczema with early fish introduction, 4 studies reported reduced eczema with early fish introduction, and 6 studies reported no association.



Figure 21: Fish introduction ≤3-4 months and eczema at ≤4, OR

Figure 22: Fish introduction ≤5-7 months and eczema at ≤4, OR



Figure 23: Fish introduction ≤8-12 months and eczema at ≤4, OR



Figure 24: Fish introduction ≤5-7 months and atopic eczema at ≤4, HR



Figure 25: Fish introduction ≤5-7 months and eczema at 5-14, OR



Figure 26: Fish introduction ≤8-12 months and eczema at 5-14, OR



6.2. Studies of fish introduction and eczema which could not be included in metaanalysis

Three further studies reported the relationship between timing of fish introduction to the infant diet, and risk of eczema. In 1 there was no association reported, in 2 an association was reported in unadjusted analyses, and in 1 of these adjusted analysis showed no association. The findings from each study are summarised below:

Hesselmar 2010 reported median age of fish introduction 8 months (IQR 6, 11) in infants without eczema in the first 18 months, compared with 11 months (IQR 8, 13) in infants with eczema, with a significant trend for earlier fish intake to be associated with reduced eczema risk (P=0.004). **Morgan 2004** found no significant difference in timing of fish introduction for infants with and without eczema in the first year of life. In the **DIPP study Nwaru 2013** reported median age of fish introduction 7 months (IQR 6, 9) in infants without eczema at age 5, compared with 8 months (IQR 6, 10) in infants with eczema, and this difference was statistically significant. In the same study adjusted analyses of timing of fish introduction categorised as <6, 6-9 and >9 months showed no significant association with eczema.

6.3. Conclusions: fish introduction and eczema

Overall 14 prospective cohort studies reported this association. Statistical heterogeneity was extreme in one of two meta-analyses, due to increased eczema during the period of fish introduction with introduction of fish in the first year of life in one study (Dunlop 2006). In other studies eczema was either less common (5 studies), or not different (8 studies) with earlier introduction of fish to the infant diet. While it is possible that early fish introduction increases eczema during the period of introduction, but reduces eczema in the longer term, the majority of studies in this area have null findings – while opportunities for meta-analysis were limited, the majority of evidence suggests no relationship between timing of fish introduction and eczema risk. Delayed introduction of allergenic food due to the presence of early eczema and concerns about possible food allergy, may plausibly lead to an association between early allergenic food introduction and reduced eczema, through reverse causality. The studies of Roduit 2011 and Kull 2006 excluded children with onset of eczema in the first year of life in order to account for this potential bias, and still found reduced eczema with early fish introduction. Sensitivity analysis of these two studies alone showed extreme statistical heterogeneity

 $(I^2=80\%)$ for unexplained reasons. Further investigation of a possible association between early fish introduction and reduced eczema is therefore worthwhile.

Overall we found no consistent evidence that timing of fish introduction influences risk of eczema.

7. Timing of cereal introduction and risk of eczema

7.1. Timing of cereal introduction and risk of eczema

Figures 27 to 32 show the outcomes of 8 eligible observational studies reporting OR or HR for eczema or atopic eczema at age \leq 4 or age 5-14. Pooled data from 2 studies shows a significant association between cereal introduction at age \leq 3-4 months and reduced eczema, with no statistical heterogeneity (Figure 27). The data shown in Figure 27 do not exclude early onset eczema, to account for the possibility of reverse causality. Zutavern 2006 did a separate analysis excluding eczema with onset in the first 6 months of life, and here found no evidence of association (OR 0.83 95% CI 0.43, 1.59). Six other studies reported data for eczema at age 2-10 – in 5 cases adjusted, but in the case of Zutavern 2004 unadjusted. In 5 of these studies and 2 meta-analyses there was no relationship seen between timing of cereal introduction and eczema risk. In the DIPP study (Nwaru 2013) introduction of cereals other than wheat/rye/oats/barley at age \leq 3-4 months was associated with increased eczema risk (Figure 32), but timing of introduction of wheat/rye/oats/barley was not associated with eczema risk (numerical data not reported).

Figure 27: Cereal introduction ≤3-4 months and eczema at ≤4, OR



Figure 28: Cereal introduction ≤5-7 months and eczema at ≤4, OR



Figure 29: Cereal introduction ≤8-12 months and eczema at ≤4, OR



Figure 30: Cereal introduction \leq 5-7 months and atopic eczema at \leq 4, HR



Figure 31: Cereal introduction ≤3-4 months and eczema at 5-14, OR



Figure 32: Cereal introduction ≤3-4 months and eczema at 5-14, HR



7.2. Studies of cereal introduction and eczema which could not be included in metaanalysis

Four studies reported the relationship between timing of cereal introduction to the infant diet, and risk of eczema. In general there was no evidence for an association. The findings from each study are summarised below:

Morgan 2004 found no significant difference in timing of rusk introduction for infants with and without eczema in the first year of life. **Alm 2009** reported no significant relationship between timing of gluten introduction and eczema, but did not report numerical data. In the **DIPP study Nwaru 2013** reported associations between timing of introduction of various cereals and eczema, which were not significant in adjusted analyses, other than the outcome presented in Figure 32. **Fergusson 1990** found no association between introduction of cereal before or after 4 months age and risk of eczema at 10 years, but did not present numerical data that could be included in meta-analysis.

7.3. Conclusions: cereal introduction and eczema

Overall 11 prospective cohort studies reported this association. Just one study showed a statistically significant association, in one of a large number of analyses of different cereals undertaken. All other studies found no significant association. One of three meta-analyses found a significant association, but this relied on study data that were generated without excluding early onset eczema, in order to account for the possibility of reverse causation. Delayed introduction of allergenic food due to the presence of early eczema and concerns about possible food allergy, may plausibly lead to an association between early allergenic food introduction and reduced eczema, through reverse causality.

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

8. Timing of any allergenic food introduction

8.1. Timing of allergenic food (AF) and risk of eczema

Figure 33 shows the outcomes of 1 eligible observational study reporting OR for eczema at age 5-14 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 different eczema risk at age 5 years compared with later introduction of AF.

Figure 33: AF introduction ≤8-12 months and eczema at 5-14, OR



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36

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