TIMING OF INTRODUCTION OF ALLERGENIC FOODS IN INFANTS, AND RISK OF FOOD ALLERGY

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1. Timing of introduction of allergenic foods and risk of food allergy – 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 18 observational studies which reported the association between timing of introduction of allergenic food(s) and risk of FA. Of these, 13 were prospective cohort studies, 1 retrospective cohort, 3 case-control and 1 nested case-control study.

1.2. Populations

The majority of studies (n=11) were carried out in European populations. Other studies were from North America (n=4), Asia and Middle East (n=2) and Africa (n=1). Studies included a total of almost 40,000 participants.

1.3. Exposure assessment

We identified 12 studies which assessed cow's milk introduction and FA, 4 studies of soya, 5 studies of egg, 5 studies of fish, 4 studies of nut (peanut or tree nut) introduction, 3 studies of wheat introduction (usually assessed as gluten-containing cereal), and 2 studies of timing of introduction of multiple allergenic foods. We identified one study of the interaction between allergenic food introduction and breastfeeding status, and food allergy. Questionnaire was the most common method used to collect data (n=10), followed by interview (n=9), food diary (n=2) and records (n=1), and unclear method (n=2), not mutually exclusive because more than one method was used in several studies. Five studies used only questionnaire. It was unclear whether any study used a validated or piloted dietary questionnaire.

1.4. Outcome assessment methods used

In 10 studies outcome was defined by parent report of doctor diagnosis and/or symptoms, in 5 studies food challenge was used, in 1 assessment by a study doctor, in 5 diagnosis required support by evidence of allergic sensitisation, and in 1 method of outcome

assessment was unclear. Fourteen studies assessed FA at age 0-4, 3 at age 5-14; none at age 15 and over and one at any age.

1.5. Risk of bias assessment

Among 18 studies, overall bias was considered to be low in 7 (39%), unclear in 1 (6%) and high in 10 (56%). Risk of bias was considered high due to method of outcome assessment in 1 study, to lack of adjustment for potential confounders in 8 studies, and selection bias in 4 studies. In 10 studies risk of conflict of interest was low and in 8 studies it was unclear.

1.6. Key findings

i. We found LOW evidence (-1 imprecision, +1 dose-response relationship) that early egg introduction is associated with *decreased* probability of egg allergy.

ii. We found no evidence that timing of introduction of other foods is associated with food allergy.

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

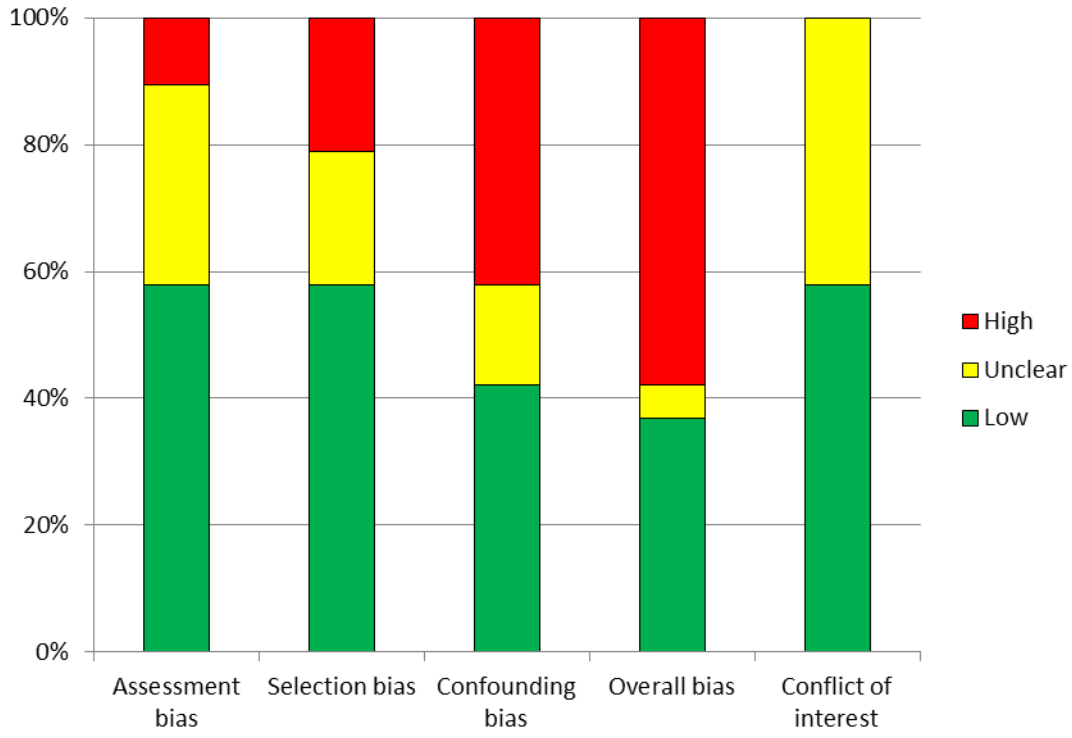
Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Businco, 1993 (1)	PC	101	Italy	Infants of atopic parents recruited at birth in a hospital in Rome, Italy between 1985 and 1988	Cow's milk, soya, I	0-2	History of reaction to food
Hesselmar, 2010 (2)	PC	184	Sweden	ALLERGYFLORA: Birth cohort in Sweden enriched with children with family history of allergies	Cow's milk, fish, egg, I/Q	0.5, 1.5	Physician assessment PLUS open food challenge
Host, 1991 (3)	PC	315	Denmark	Population birth cohort of infants from the municipality of Odense born during 1985	Cow's milk, R/I	0-1	Food challenge (open)
Katz, 2010 (4)	PC	12704	Israel	Population based birth cohort of all newborns born between 2004 and 2006, at the Assaf-Harofeh Hospital in Zerifin	Cow's milk, Q	1	Parent reported PLUS sensitisation followed by OFC
Kemeny, 1991 (5)	PC	180	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London	Cow's milk, unclear how data were collected	0-1	History of reaction to food
Koplin, 2010 (6); Koplin, 2012 (7)	PC	699	Australia	HealthNUTS study. 11-15 months old infants were recruited as they attended 131 council-run immunization sessions across Melbourne between June 2008 and January 2010	Egg, I/Q	1	Sensitisation PLUS open food challenge
Kumar, 2010 (8)	PC	789	USA	Children enrolled as part an ongoing family-based food allergy study in Chicago, IL	Egg, peanut, tree nut, shellfish, fish, sesame, rice/wheat wheat, cow's milk, I/Q	5	History of reaction to food PLUS sensitisation to food

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Lack, 2003 (9)	PC	12324	UK	ALSPAC: Population based birth cohort study, of mother-child pair recruited in 1991-1992	Soya, Q	5.5	Food challenge (double blind)
Luccioli, 2014 (10)	PC	1542	USA	Sample of the study population of The Infant Feeding Practices Study II (IFPS II), a panel survey, representative of pregnant women in USA in 2005, and who were present in the year 6 of follow-up	Wheat, cow's milk, egg, fish, peanut, soy, Q	6	Mother was asked about physician diagnosis of food allergy
Poole, 2006 (11)	PC	1612	UK	DAISY: Prospective birth cohort of children at increased risk for T1DM recruited from 1993 to 2004 in Denver, Colorado US were screened for human leukocyte antigen (HLA) genotype associated with celiac disease and TIDM	Wheat, Q	0-4	DD Plus positive IgE
Saarinen, 1979 (12);	PC	177	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, Diary/I	1	History of allergy - skin reaction or vomiting after ingestion at home
Saarinen, 1980 (13)	PC	375	Finland	Children born in Helsinki 1978-1979 with and without a history of citrus/fish exclusion during infancy	Fish, I	3	Food challenge
Tariq, 1998 (14)	PC	1086	UK	Isle of Wight Study: population based birth cohort of mainly Caucasian infants born in the Isle of Wight between 1989 and 1990	Cow's milk, Q/Diary	4	History of reaction to food
Ivakhnenko, 2013 (15)	RC	1000	Ukraine	One year follow up survey of a survey of full-term infants 1-18 months from families resident in Kyiv	cow' s milk, I/Q	1-2	I/Q

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Maskell, 2011 (16); Grimshaw, 2013 (17); Grimshaw 2015 (18)	NCC	823	UK	EuroPrevall (UK birth cohort): cases were infants with food allergy, each matched to two controls.	Wheat, cow's milk, egg, fish, tree nuts, peanuts; diary and parent report	1, 2	DD with DBPCFC; double-blind, placebo-controlled food challenge
Ben-Shoshan M 2015 (19)	CC	480/ 4950	Canada	SPAACE random telephone survey: cases were self-reported probable food allergy; controls were age-matched respondents with no self-reported food allergy	Cow's milk, soya, egg, fish, peanut, tree nuts, sesame, shellfish	All ages	Focussed telephone questionnaire – self-reported clinical history consistent with IgE-mediated food allergy and/or physician diagnosis of food allergy
DesRoches, 2010 (20)	CC	403	Canada	Cases and controls were recruited from the Paediatric University Centre between 1998-2004: Canada	Egg, peanut and other nuts, soya, cow's milk, Q	<1.5	History of a clinical reaction within 60 minutes of exposure to peanuts, combined with positive IgE and/or SPT to peanut
Ibsaine, 2014 (21)	CC	450	Algeria	Cases diagnosed over a period of 6 years (2004-2010) and 300 controls matched for sex - prospective case-control study	Cow's milk, no information how data were collected	1	Unclear

PC prospective cohort, RC retrospective cohort, NCC nested case-control, CC case-control, 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 food allergy



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

Figures 2 to 7 show the outcomes of 8 eligible observational studies reporting OR for FA. Due to a lack of studies reporting the same outcome and exposure, and in one case to extreme statistical heterogeneity, it was only possible to conduct one meta-analysis (Figure 2). No single analysis shows a significant association between timing of CM introduction and FA. Assessment of adjusted data from one prospective cohort study Katz 2010 found early regular CM intake before age 14 days is associated with significantly reduced FA-CM; in another prospective study Host 1991, reporting unadjusted data, a significant association was seen with *increased* FA-CM. Meta-analysis was not possible due to extreme statistical heterogeneity (Figure 5; I^2=97%). Neither study was able to adequately adjust for reverse causation. The reason for the extreme heterogeneity may be differing outcome definitions. When Host assessed FA-CM associated with evidence of IgE sensitisation, their findings were more consistent with those of Katz, but not statistically significant – unadjusted OR 0.60 95% CI 0.14, 2.66.

Figure 2: Cow's milk introduction ≤0-2 months and FA-Any at age 0-4

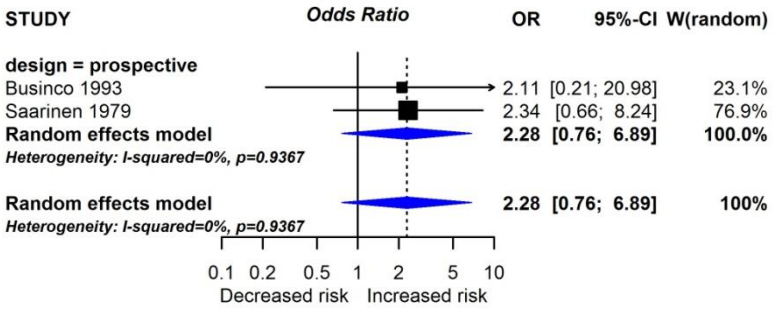


Figure 3: Cow's milk introduction ≤3-4 months and FA-Any at age 0-4

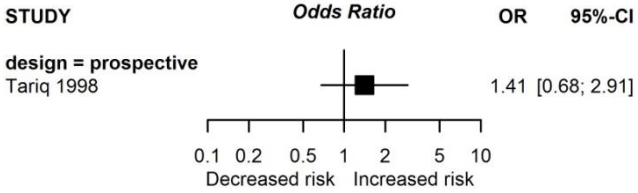


Figure 4: Cow's milk introduction ≤5-7 months and FA-Any at age 5-14

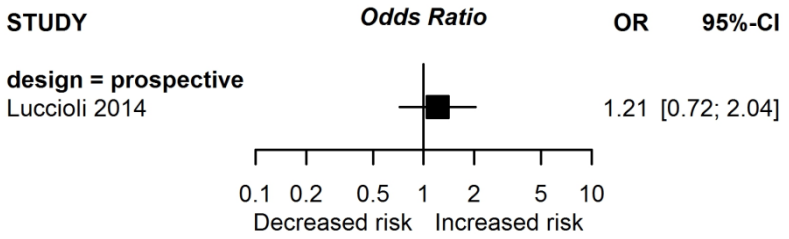


Figure 5: Cow's milk introduction ≤0-2 months and FA-CM at age 0-4

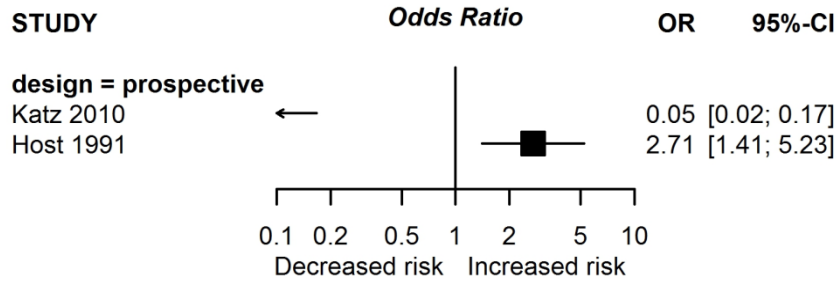


Figure 6: Cow's milk introduction ≤8-12 months and FA-CM at age 0-4

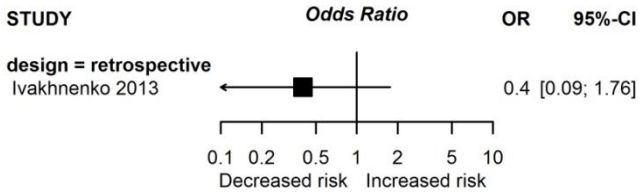
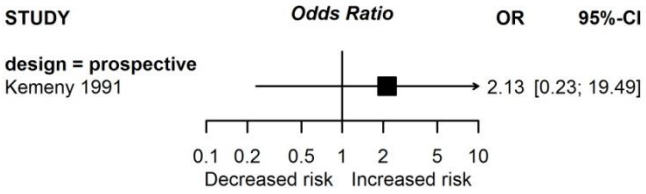


Figure 7: Cow's milk introduction ≤3-4 months and FA-Egg at age 0-4



2.1. Cow's milk studies which could not be included in meta-analysis

Five further studies reported timing of cow's milk introduction and risk of FA. In 1 study there was an association between increased FA-CM and early cow's milk introduction, and in another study there was a significant association in the opposite direction, with

reduced FA-CM seen where cow's milk was introduced early. In the other 2 studies no association was seen between timing of cow's milk introduction and FA-Any or FA-PN. **Hesselmar 2010** reported median age of cow's milk introduction 5 months (IQR 4, 6) in infants without FA-Any in the first 18 months, compared with 13 months (IQR 6.5, 13) in infants with FA-Any (P<0.01). Similarly, unadjusted analysis showed later cow's milk introduction in infants with FA-CM compared to non-milk allergic infants (P<0.001). **Grimshaw 2013** reported median cow's milk introduction at 3 weeks (IQR 1, 11.5) in infants with food allergy, and 5 weeks (IQR 1, 14.3) in infants without food allergy (P=0.28). Multivariate analysis did not identify any association between timing of introduction of cow's milk and food allergy, data not shown**.** The authors also explored the cases and controls exposed to both cow's milk and breast milk where they found an association between continued breastfeeding during first cow's milk exposure, and reduced food allergy aOR 0.27 95% CI 0.09, 0.83. In a case control study **Des Roches 2010** reported no association between timing of cow's milk introduction and FA-PN. Mean time of introduction was 3.8 months (sd 2.7) in cases with peanut allergy, compared with 3.9 months (sd 3.2) in controls with no peanut allergy. **Ibsaine 2014**, in an abstract publication, reported a significant association between introduction of cow's milk in the first week of life and a 4-fold increase in FA-CM (P<0.001). Data were reportedly adjusted, but details are limited in this abstract publication. **Ben-Shoshan 2015** reported introduction of cow's milk formula after 12 months age was more common in cases with milk allergy (n=31) than in controls – OR 9.4 (95% CI 1.4, 68.7). This could not be included in meta-analyses because the age range of cases ranged from 0-4 through to >18.

2.2. Conclusions: cow's milk introduction and FA

Overall 13 studies reported this association. Statistical heterogeneity was extreme for associations with FA-CM. For allergy to foods other than cow's milk there was no evidence of association. Overall there was no consistent evidence to suggest a specific relationship between timing of introduction of cow's milk to the infant diet, and FA risk.

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

3. Timing of soya introduction and risk of FA

Figures 8 to 10 show the outcomes of 3 eligible observational studies reporting OR for FA. Due to a lack of studies reporting the same outcome and exposure, it was not possible to conduct meta-analysis. Two studies found no significant association between timing of soya introduction and FA-Any (Figures 8 and 9). One study found a significant association between early soya introduction and increased FA-Peanut. This association remained in adjusted analysis, and after attempts to control for the possibility of reverse causation by adjusting for early eczema.

Figure 8: Soya introduction ≤0-2 months and FA-Any at age 0-4

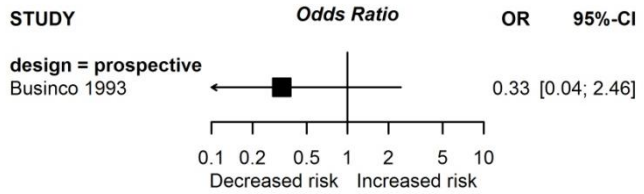


Figure 9: Soya introduction ≤5-7 months and FA-Any at age 5-14

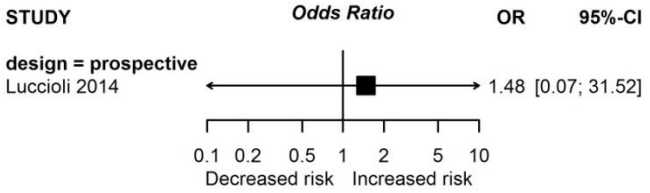
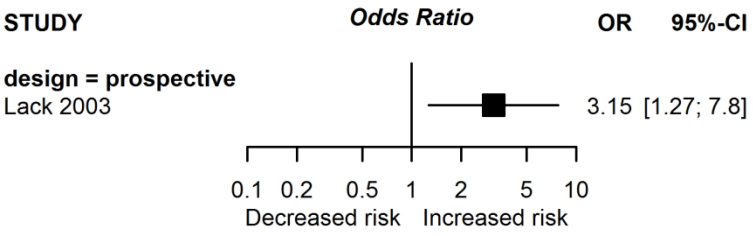


Figure 10: Soya introduction ≤8-12 months and FA-PN at age 5-14



3.1. Soya milk studies which could not be included in meta-analysis

One further study reported the relationship between timing of soya introduction to the infant diet, and risk of FA. In a case control study **Des Roches 2010** reported no association between timing of soya introduction and FA-PN. Mean time of introduction was 7.6 months (sd 3.6) in cases with peanut allergy, compared with 7.3 months (sd 3.4) in controls with no peanut allergy which was not statistically significant.

3.2. Conclusions: soya introduction and FA

Overall 4 studies reported this association. Meta-analysis was not possible. Overall there was no evidence to suggest a specific relationship between timing of introduction of soya to the infant diet, and FA risk. One study found a specific association between early soya introduction and increased peanut allergy, but this association was not found in a single case control study.

Overall we found no consistent evidence that early soya introduction is associated with risk of FA.

4. Timing of egg introduction and risk of FA

Figures 11 and 12 showthe outcomes of 2 eligible observational studies reporting OR for FA. Luccioli 2014 reported unadjusted data and was considered at high risk of selection and confounding bias. Koplin 2010 reported adjusted data for egg introduction at 4-6 months compared with >12 months, and was considered at low overall risk of bias. The data were adjusted for early eczema and family history of allergic disease, to account for possible reverse causation. Moreover, a dose-response relationship was seen with later introduction associated with increased risk of egg allergy (P<0.001 for trend).

Figure 11: Egg introduction ≤5-7 months and FA-Any at age 5-14

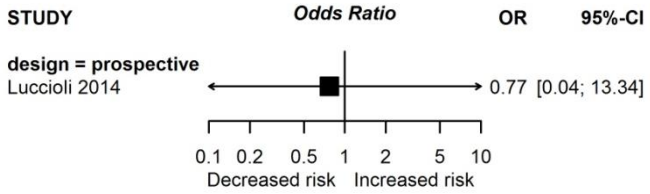
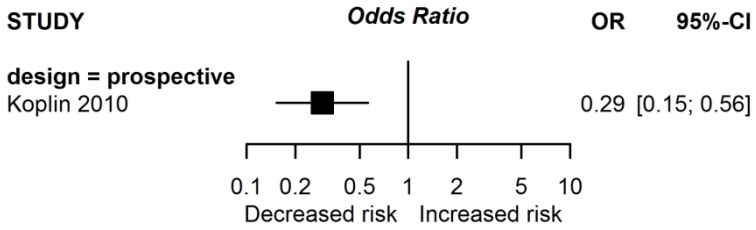


Figure 12: Egg introduction ≤5-7 months and FA-Egg at age 0-4



4.1. Egg studies 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 FA. In 1 study there was weak evidence for an association between increased FA-CM and later egg introduction in unadjusted analysis; in the other

2 studies there was no evidence for association with FA-Any or FA-PN. Findings from the individual studies are summarised below:

Hesselmar 2010 reported median age of egg introduction 13 months (IQR 13, 13) in infants with FA-Any in the first 18 months, compared with 11 months (IQR 9, 13) in infants without FA-Any (P=0.08). Similarly, unadjusted analysis showed weak evidence of later egg introduction in infants with FA-CM compared to non-milk allergic infants (P=0.04). **Grimshaw 2013** reported median egg introduction at 39 weeks (IQR 30, 39) in infants with food allergy, and 35 weeks (IQR 39, 39) in infants without food allergy (P=0.087). Multivariate analysis did not identify any association between timing of introduction of egg and food allergy, data not shown**.** In a separate report from the same study (Grimshaw 2015) the authors reported significantly increased age of egg introduction (P=0.026) in infants with IgE-mediated food allergy in univariate analysis, but did not include this in multivariate analysis due to likely reverse causality. In a case control study **Des Roches 2010** reported no association between timing of egg introduction and FA-PN. Mean time of introduction was 9.1 months (sd 2.4) in cases with peanut allergy, compared with 8.9 months (sd 2.4) in controls with no peanut allergy, which was not significantly different. **Ben-Shoshan 2015** reported no significant association between timing of egg introduction and self-reported egg allergy in a case-control study undertaken by telephone survey in participants aged between 0-4 and >18. No data were shown for this comparison.

4.2. Conclusions: egg introduction and FA

Overall 6 studies reported this association. Meta-analysis was not possible due to different outcomes and data presented. There was evidence from one well-conducted study that early egg introduction is associated with decreased FA-egg. Grade of evidence was decreased -1 due to sparse data/imprecision, and increased +1 due to the dose-response relationship. There was no consistent evidence for association with other outcomes.

Overall we found LOW evidence that egg introduction at 4-6 months age is associated with reduced FA-Egg compared with later introduction of egg to the infant diet.

5. Timing of Peanut, Fish and Cereal introduction and risk of FA

Figures 13 to 16 show outcomes from 2 eligible observational studies reporting OR for FA. Due to a lack of studies reporting the same outcome and exposure, meta-analysis was not possible. No significant associations were seen.

Figure 13: Peanut introduction ≤8-12 months and FA-Any at age 0-4

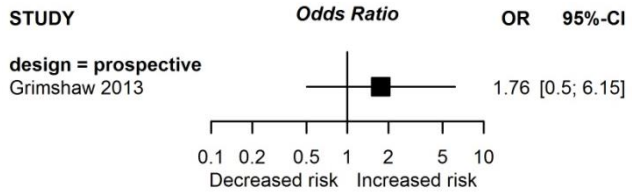


Figure 14: Peanut introduction ≤5-7 months and FA-Any at age 5-14

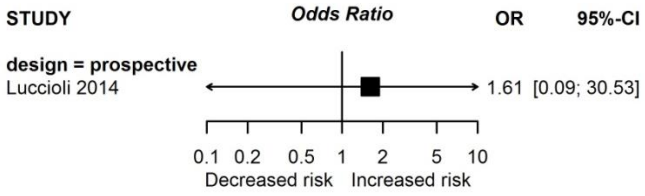


Figure 15: Fish introduction ≤5-7 months and FA-Any at age 5-14

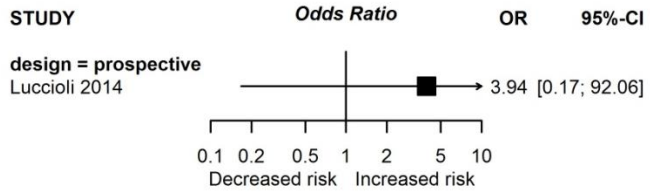
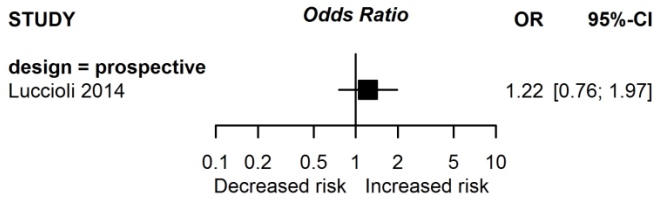


Figure 16: Cereal introduction ≤5-7 months and FA-Any at age 5-14



5.1. Other allergenic food studies which could not be included in meta-analysis

Six further studies reported the relationship between timing of other allergenic food introduction to the infant diet, and risk of FA. In 1 study there was an association in unadjusted analysis between later introduction of fish and increased FA-Any and FA-CM. In one study there was an association in adjusted analysis between increased wheat allergy and later introduction of cereals (wheat, barley, rye, oats). In the other 3 studies no association was seen between allergenic food introduction and FA.

Hesselmar 2010 reported median age of fish introduction 9 months (IQR 6, 12) in infants without FA-Any in the first 18 months, compared with 13 months (IQR 9.8, 13) in infants with FA-Any (P=0.01). Similarly, unadjusted analysis showed later fish introduction in infants with FA-CM compared with non-milk allergic infants (P=0.006). **Grimshaw 2013** reported median fish introduction at 29 weeks (IQR 26, 35) in infants with food allergy, and 29 weeks (IQR 26, 34) in infants without food allergy (P=0.86). For wheat median introduction was at 27 weeks (IQR 24, 30) in infants with food allergy, and 26 weeks (IQR 25, 29) in infants without food allergy. Multivariate analysis did not identify any association between timing of introduction of fish or wheat and food allergy, data not shown**.** Introduction of tree nuts in the first year was also not associated with food allergy. In a case control study **Des Roches 2010** reported no association between timing of peanut introduction and FA-PN. Mean time of introduction was 11.6 months (sd 2.5) in cases with peanut allergy, compared with 11 months (sd 2.6) in controls with no peanut allergy, which was not significantly different. Similarly time of tree nut introduction was not associated with FA-PN. **Saarinen 1980** reported unadjusted analysis showing no significant association between fish introduction in the first year and history of fish allergy OR 0.73 (95% CI 0.31, 1.74), or challenge-proven fish allergy OR 1.47 (0.39, 5.58). **Poole 2006** reported adjusted data showing a significant association

between wheat introduction at over 6 months and increased wheat allergy, compared with wheat introduction at 0-6 months OR 3.8 (95%CI 1.18, 12.28). **Ben-Shoshan 2015** reported no significant association between timing of peanut, tree nut, fish or shellfish introduction and self-reported allergy to the same food, in a case-control study undertaken by telephone survey in participants aged between 0-4 and >18. No data were shown for this comparison.

5.2. Conclusions: other allergenic food introduction and FA

Overall 8 studies reported this association. Meta-analysis was not possible due to different exposure and outcome and types of data reported. In one study reporting unadjusted data, and in one study reporting adjusted data, there was evidence that early introduction of allergenic food may be associated with reduced FA. In 5 studies no association was found. Overall there was no consistent evidence to suggest a specific relationship between timing of introduction of other allergenic food to the infant diet, and FA risk.

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

6. Timing of any allergenic food introduction

Figures 17 and 18 show the outcomes of 1 eligible observational study reporting OR for FA at age 5-14 in relation to timing of introduction of 'any allergenic food' – defined as egg, nuts, fish or sesame. The data show a mixed picture. Introduction of AF prior to 6 months was not associated with different FA risk at age 5 years compared with later introduction of AF (Figure 17); but introduction of AF prior to 12 months was associated with increased FA at age 5 years (Figure 18).

Figure 17: AF introduction ≤5-7 months and FA-Any at age 5-14

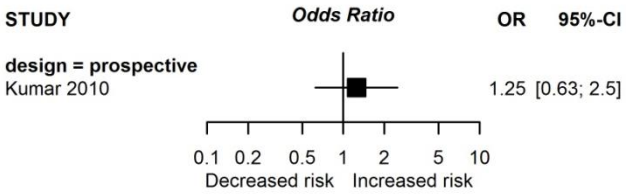
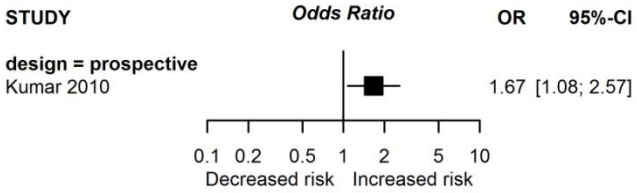


Figure 18: AF introduction ≤8-12 months and FA-Any at age 5-14



6.1. Conclusions: any AF introduction and FA

One study reported this association. No association was found.

Overall we found no evidence that timing of 'any allergenic food' introduction influences risk of FA.

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