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

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1. Timing of introduction of allergenic foods and risk of wheezing – 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 30 observational studies which reported the association between timing of introduction of allergenic food(s) and risk of wheeze. Of these, 23 were prospective cohort studies, 2 case-controls and 5 cross-sectional studies.

1.2. Populations

The majority of studies (n=17) were carried out in European populations. Other studies were from North America (n=1), Asia Pacific region (n=8), the Middle East (n=2), and Latin America (n=2).

1.3. Exposure assessment

We identified 25 studies which assessed cow's milk introduction and wheeze or lung function, 3 studies of soya, 9 studies of egg, 8 studies of fish, 1 studies of nut (peanut or tree nut) introduction, 6 studies of cereal/gluten 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 wheeze. Questionnaire was the most common method used to collect exposure data (n=20), followed by interview (n=13), records (n=4) and food diary (n=4), not mutually exclusive because more than one method was used in several studies. Fourteen studies used only questionnaires. It was unclear if all studies using a dietary questionnaire had validated or piloted the questionnaire: information that the questionnaire was validated was found in only one study (1)(2).

1.4. Outcome assessment

In 5 studies outcome assessment relied on physician assessment by a study doctor, one study assessed lung function and others used information collected from medical records, interviews and questionnaires – in 6 cases the ISAAC questionnaire. Twenty studies

explored the association between dietary intake and outcomes at age 0-4, nineteen at ages 5-14 and three at age 15 and over (not mutually exclusively, as some studies assessed wheeze at more than one age).

1.5. Risk of Bias assessment

Among 30 studies, overall bias was considered to be low in 13 (43%), unclear in 6 (20%), and high in 11 (37%). The risk of bias was most commonly considered high due to lack of adjustment for potential confounders.

1.6. Key Findings

i. The number of studies included in each analysis was small, and opportunities for meta-analysis were limited. No subgroup analysis or assessment of publication bias was possible in this report.

ii. We found evidence from 3 prospective cohort studies with over 11,000 participants that introduction of fish to the infant diet prior to 8-12 months age is associated with reduced risk of recurrent wheeze at age ≤4 years (OR 0.72 95%CI 0.59, 0.87; I^2=0%). However 5 other studies including 3 further prospective cohort studies with over 12,000 participants found no evidence for an association between timing of fish introduction and risk of wheeze or recurrent wheeze. It was not possible to combine all 8 studies in meta-analysis, and overall there was no consistent evidence for an association between timing of fish introduction (before or after age 5-12 months) and risk of wheezing.

iii. We found no evidence that timing of cow's milk, soya, egg, nut, cereal or 'any allergenic food' introduction in the infant diet is associated with risk of wheeze or recurrent wheeze, or (for cow's milk) lung function.

Table 1 Characteristics of included studies evaluating timing of allergenic food introduction in infants and wheeze/ lung function

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Businco, 1993(3)	PC	101	Italy	Infants of atopic parents recruited at birth in a hospital in Rome between 1985 and 1988	Cow's milk and soya, I	0-2	Physician assessment PLUS parent report
Fergusson, 1983 (4); Horwood, 1995 (5)	PC	1110	New Zealand	Christchurch Child Development Study: cohort of children born in the Christchurch urban region during mid-1977	Cow's milk, R/D/Q	0-4, 0-6	DD asthma/medical records and Q
Goksor, 2009 (6); Goksor, 2013 (7)	PC	5654	Sweden	West of Sweden cohort: urban, rural and coastal areas in Western Sweden, ~60% with atopic heredity	Gluten, egg and fish, Q	4.5, 8	ISAAC
Gustafasson, 1992 (8)	PC	736	Sweden	Healthy full term children born in Karlskoga, 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	DD (medical files and questionnaire)
Hesselmar, 2010 (9)	PC	184	Sweden	ALLERGYFLORA: Birth cohort in Sweden enriched with children with family history of allergies	Cow's milk, egg and fish, I/D	1.5	Physician assessment (>=3 episodes of wheeze in the last 1.5 year)
Kemeny, 1991 (10)	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	Parent report of symptoms
Kiefte-de Jong, 2012 (2); Tromp, 2011 (1)	PC	7210	Netherlands	GENERATION R: Population based birth cohort with pregnant women recruited < 25 weeks gestation in Rotterdam	Cow's milk, soya, egg, peanut, fish, gluten, Q	2,3,4	Parent report (ISAAC Q); DD wheeze

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Kull, 2006 (11)	PC	3230	Sweden	BAMSE: Prospective birth cohort of newborns in a predefined area of Stockholm, Sweden between 1994 and 1997	Fish, Q	4	>= 3 episodes of wheeze in the last 12 months OR wheeze PLUS ICS
Kurukulaaratchy, 2004 (12); Tariq, 1998 (13)	PC	1218	UK	Isle of Wight Prevention Study: Population based birth cohort of mainly Caucasian infants born in the Isle of Wight 1989 and 1990	Cow's milk, Q/D	10, 4	Parent report of symptoms
Lucas, 1999 (14)	PC	447	UK	Participants in a RCT of a formula intervention	Cow's milk, I/Q	0.75	DD wheeze
Marini, 1996 (15)	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	3	Physician assessment PLUS parent reported asthma
Midwinter, 1987 (16)	PC	453	UK	Children with family history of atopy	Cow's milk and soya, I/Q	5	Q/DD asthma
Mihrshahi, 2007 (17)	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	0-5	Parent report PLUS DD
Miskelly, 1988 (18)	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	Wheat, rye, egg and cow's milk, D	1	Parent report wheeze

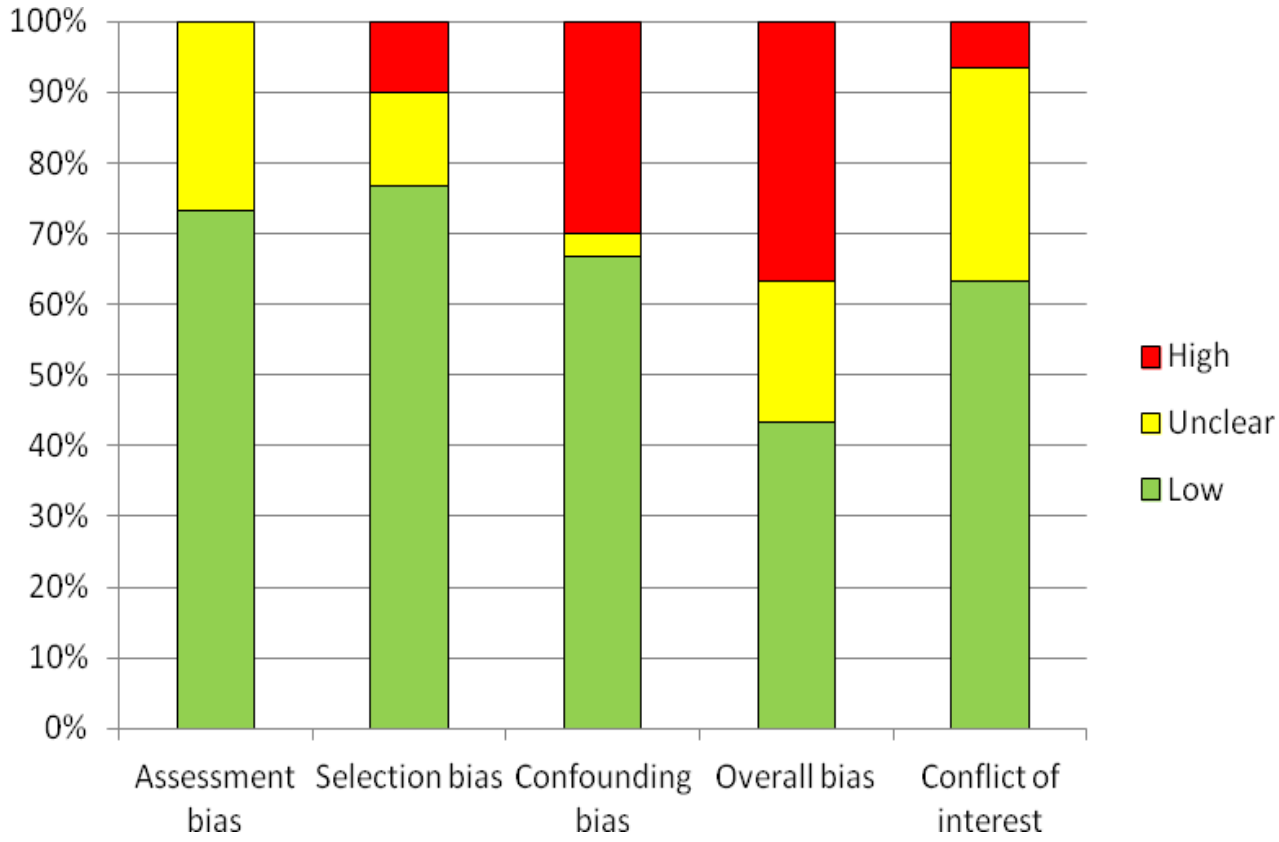
Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Nwaru, 2013a (19)	PC	1924	UK	SEATON study: Recruited healthy pregnant women attending an antenatal clinic	Cereal, egg and fish, Q/Parent reported prospectively	10	ISAAC DD
Nwaru, 2013b (20); Virtanen, 2010 (21)	PC	3109	Finland	DIPP: Prospective birth cohort of children at high risk of TIDM born between 1997 and 2004 in Oulu and Tampere University Hospital	Wheat , rye, oats ,barley, egg, fish, cow's milk, Q	0-5	ISAAC DD
Oddy, 1999 (22); Oddy, 2000 (23); Oddy 2004 (24)	PC	1977	Australia	Western Australian Pregnancy Cohort: Population based cohort of infants from public antenatal clinic in Perth Western between 1989 and 1992	Cow's milk, D/Q	6	Parent reported wheeze
Per Nafstad, 2003(25)	PC	2271	Norway	The Environment and Childhood Asthma study in Oslo: Population based birth cohort, newborn children born in Oslo in 1992	Fish, Q	2	Q/DD asthma
Simon, 2008 (26)	PC	372	USA	CAS: Middle class mothers enrolled in a health maintenance organisation between 1987 and 1989	Cow's milk, I/R	0-6	Parent reported wheeze up to 3 years and physical assessment at 7 years
Snijders, 2008 (27)	PC	1894	Netherlands	KOALA: Population based birth cohort with healthy pregnant women from an ongoing PC study on pregnancy-related pelvic girdle pain, through posters in organic food shops, physician offices and midwives.	Cow's milk, Q	2	Parent report of DD

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Strassburger, 2010 (28)	PC	293	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	Parent report (ISAAC Q) wheeze
Van Asperen, 1983 (29)	PC	79	Australia	Infants with family history of atopy born at two major obstetric units from 1980 to 1981	Cow's milk, I	1.3	Physician assessment wheeze
Zutavern, 2004 (30)	PC	606	UK	Population based birth cohort of infants from all pregnant women presenting in three general practices in Ashford, Kent, between 1993 and 1995	Cereal, egg, cow's milk, fish, Q	2; 5.5	Parent reported wheeze
Lopez Campos, 2001 (31)	CC	75	Mexico	Asthmatic patients recruited from allergy clinics and control patients from familial medicine clinics of Hospital de Especialidades, Mexico.	Egg, Q	6-10	DD asthma
Wickens, 2001 (32)	CC	474	New Zealand	Cases and potential controls selected from the ISAAC Wellington survey participants aged 7-9 years	Cow's milk, I	6.5	Parent reported and DD asthma (ISAAC)
Alper, 2006 (33)	CS	857	Turkey	7-year-old children randomly selected from seven primary schools	Cow's milk, Q	7	Parent reported wheeze
Miyake, 2003 (34)	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) wheeze
Salem, 2002 (35)	CS	424	Iraq	All children 0.16-2 years old, living in three areas of Basra, Iraq, were included in the study.	Cow's milk, Q	0.16-5	Parent report wheeze

Study	Design	N	Country	Population	Exposure and exposure assessment	Age at outcome (years)	Outcome assessment
Suwanpromma, 2012 (36)	CS	215	Thailand	Participants randomly recruited school children aged 6-18 years from Bangkok	Cow's milk, Q	6-18	Spirometry: FEV1/FCV ratio <0.8 considered to demonstrate airflow obstruction
Takemura, 2001 (37)	CS	23828	Japan	Students from public elementary schools in Tokorozawa	Cow's milk, Q	6-15	Parent report and DD asthma

PC prospective cohort, 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 wheeze



2. Timing of cow's milk introduction and risk of wheeze/ recurrent wheeze

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

Figures 2 to 4 show the outcomes of 5 eligible observational studies reporting OR for wheeze at age ≤4. The pooled data show no significant association between timing of cow's milk introduction to the infant diet and wheeze with no statistical heterogeneity.

Figure 2: Cow's milk introduction ≤3-4 months and wheeze at ≤4, OR

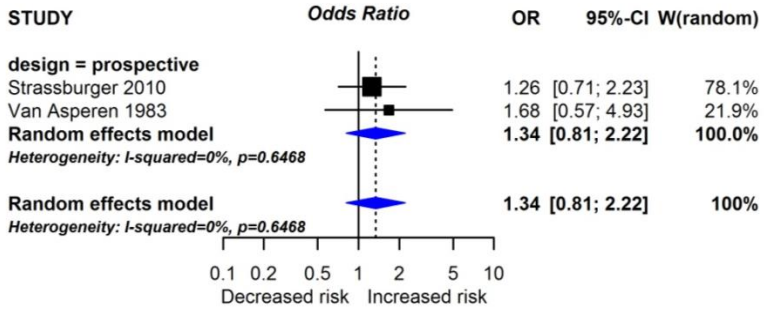


Figure 3 : Cow's milk introduction ≤5-7 months and wheeze at ≤4, OR

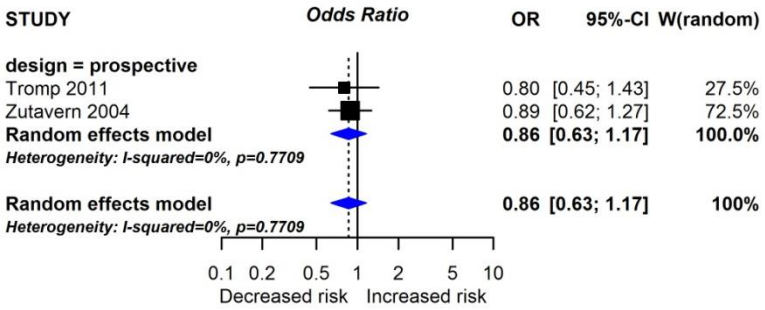
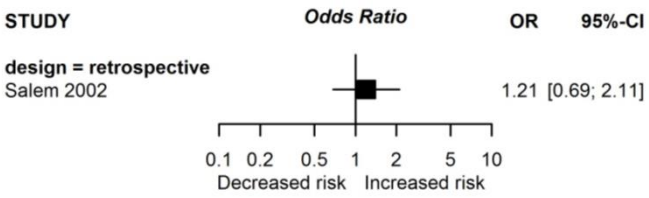


Figure 4 : Cow's milk introduction ≤8+ months and wheeze at ≤4, OR



2.2. Timing of cow's milk introduction and risk of recurrent wheeze at ≤4 years

Figures 5 to 7 show the outcomes of 7 eligible observational studies reporting OR for recurrent wheeze at age ≤4. The data show no significant association between timing of cow's milk introduction to the infant diet and recurrent wheeze, but with high statistical heterogeneity.

Figure 5: Cow's milk introduction ≤0-2 months and recurrent wheeze at ≤4, OR

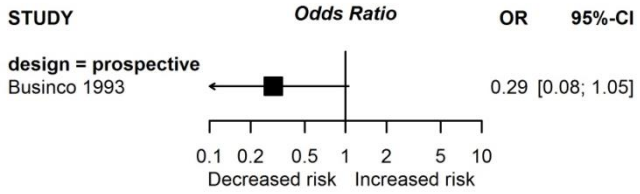


Figure 6: Cow's milk ≤3-4 months and recurrent wheeze at ≤4, OR

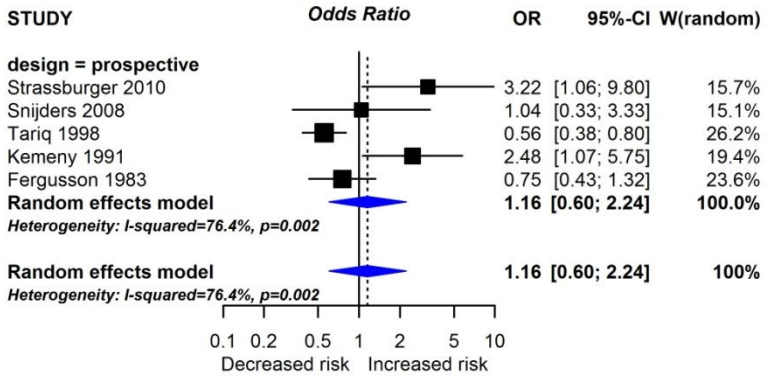
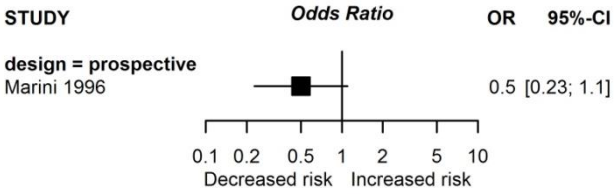


Figure 7: Cow's milk ≤5-7 months and recurrent wheeze at ≤4, OR



2.3. Timing of cow's milk introduction and risk of wheeze at 5-14 years

Figures 8 to 11 show the outcomes of 6 eligible observational studies reporting OR or HR for wheeze at age 5-14. The data show no significant association between cow's milk introduction to the infant diet at ≤0-2 months and wheeze from 4 studies with no statistical heterogeneity (Figure 8). However the prospective cohort study of Oddy 1999 found increased risk of wheeze with cow's milk introduction before 3-4 months (Figures 9 and 10), and 5-7 months – a retrospective study Alper 2006 also found increased wheeze with introduction before 5-7 months, but could not be pooled with the study of Oddy due to extreme statistical heterogeneity (I^2=81%). Oddy, Alper, Miyake, Simon and Nwaru all reported adjusted data – other studies reported unadjusted data. The reason for the difference in outcome between Oddy, Alper and other studies is not clear.

Figure 8: Cow's milk introduction ≤0-2 months and wheeze at 5-14, OR

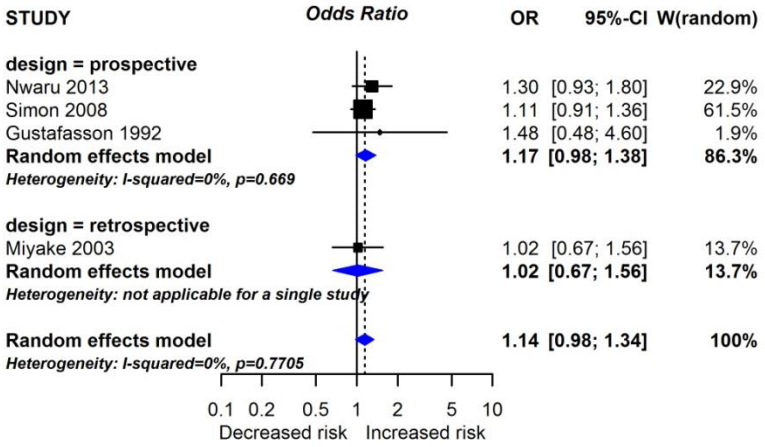


Figure 9: Cow's milk introduction ≤3-4 months and wheeze at 5-14, OR

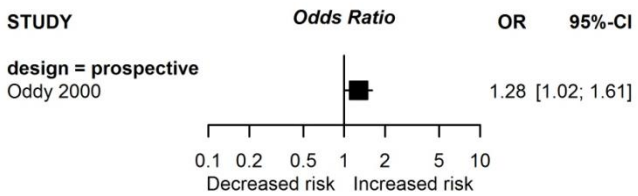


Figure 10: Cow's milk introduction ≤3-4 months and wheeze at 5-14, HR

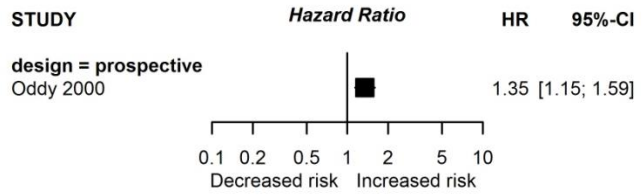
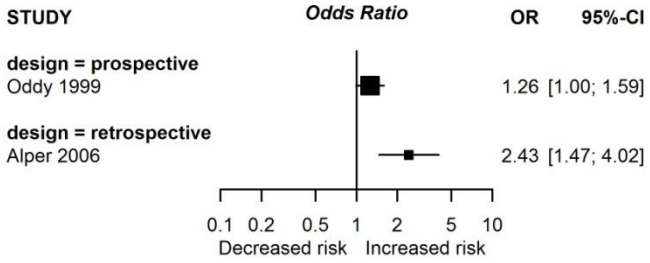


Figure 11: Cow's milk introduction ≤5-7 months and wheeze at 5-14, OR



2.4. Timing of cow's milk introduction and risk of recurrent wheeze at 5-14

Figures 12 to 16 show the outcomes of 7 eligible observational studies reporting OR or HR for recurrent wheeze at age 5-14. The data show no significant association between cow's milk introduction to the infant diet at ≤0-2 months and recurrent wheeze from 2 studies with no statistical heterogeneity (Figure 12). However the prospective cohort study of Oddy 1999 and the retrospective study of Alper 2006 reported increased risk of recurrent wheeze with cow's milk introduction before 3-4 months and 5-7 months respectively. These could not be pooled with data from other studies due to extreme statistical heterogeneity (I^2=88% Figure 13; 83% Figure 15). Oddy, Alper and Nwaru all reported adjusted data – other studies reported unadjusted data. The reason for the difference in outcome between Oddy, Alper and other studies is not clear.

Figure 12: Cow's milk introduction ≤0-2 months and recurrent wheeze at 5-14, OR

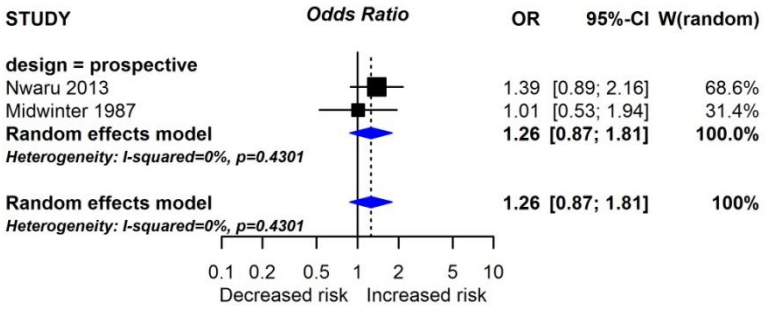


Figure 13: Cow's milk introduction ≤3-4 months and recurrent wheeze at 5-14, OR

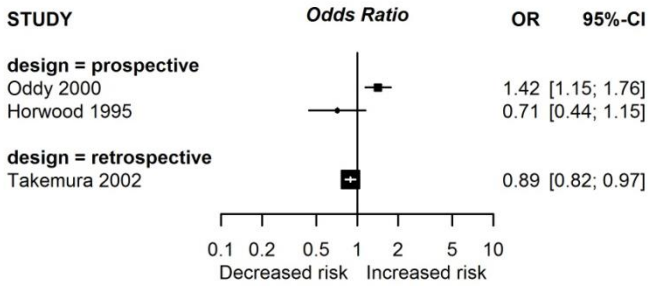


Figure 14: Cow's milk introduction ≤3-4 months and recurrent wheeze at 5-14, HR

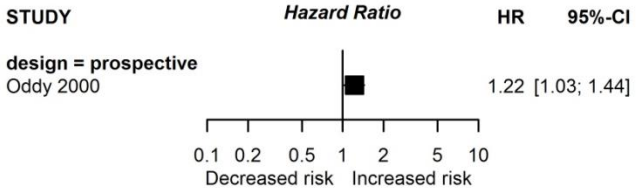


Figure 15: Cow's milk introduction ≤5-7 months and recurrent wheeze at 5-14, OR

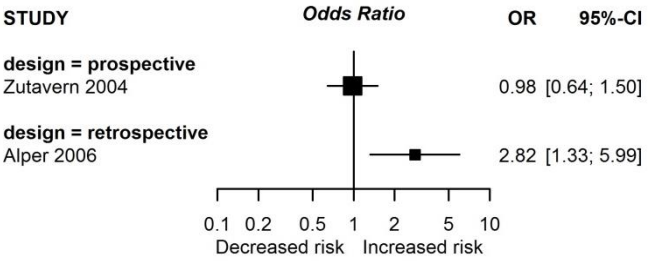
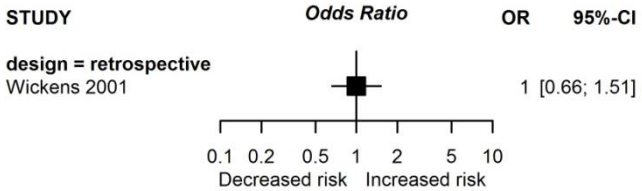


Figure 16: Cow's milk introduction ≤8-12 months and recurrent wheeze at 5-14, OR



2.5. Timing of cow's milk introduction and risk of reduced lung function at age 5-14

Figures 17 and 18 show the outcome of 1 eligible observational study reporting a measure of lung function at age 5-14. This cross-sectional study reported adjusted data for cow's milk introduction to the infant diet at ≤0-2 months and airflow obstruction (FEV1/FCV ratio <0.8), with a significant increase in risk for early cow's milk introduction (Figure 17). In the same study there was no significant increase in airflow obstruction with cow's milk introduction ≤3-4 months with unadjusted (Figure 18) or adjusted (numerical data not presented) analysis.

Figure 17: Cow's milk introduction ≤0-2 months and airflow obstruction at 5-14, OR

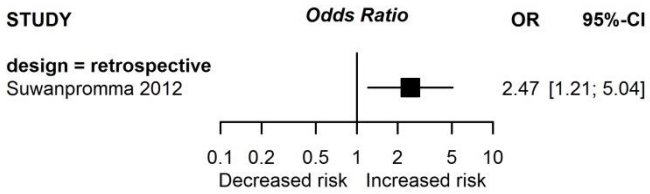
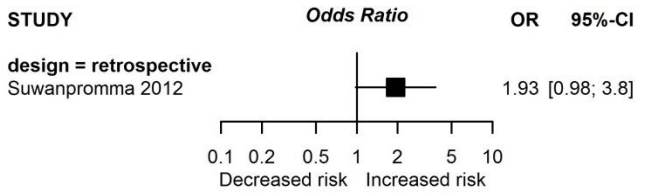


Figure 18: Cow's milk introduction ≤3-4 months and lung function at 5-14, OR



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

Three further studies reported the relationship between timing of cow's milk introduction to the infant diet, and risk of wheeze. **Hesselmar 2010** reported median age of cow's milk introduction 5 months (IQR 4, 6) in infants without recurrent wheezing in the first 18 months, compared with 7 months (IQR 5, 10) in infants who wheezed (P=0.092). **Miskelly 1988** reported no significant difference in timing of cow's milk introduction between infants with and without parent-reported wheeze in the first year, but did not present numerical data. **Lucas 1999** reported no significant difference in risk of wheeze or parent reported asthma in the first 9 months, between infants with and without cow's milk introduction in the first week of life.

2.7. Conclusions: cow's milk introduction and wheeze/ lung function

Overall 19 prospective cohort studies, 1 case control study and 5 cross-sectional studies assessed the relationship between timing of introduction of cow's milk, and wheeze, recurrent wheeze or (1 cross-sectional study) lung function. Data were generally sparse, with high or extreme statistical heterogeneity in some analyses. While 3 prospective studies and 1 retrospective study reported associations between early cow's milk introduction and increased risk of different measures of wheeze, one prospective study reported a significant association in the reverse direction, and there was no consistent direction of effect between studies and meta-analyses.

Overall we found no evidence that timing of cow's milk introduction influences risk of wheeze, recurrent wheeze or lung function.

3. Timing of soya introduction

3.1. Timing of soya introduction and risk of wheeze/ recurrent wheeze

Figures 19 to 21 show the outcomes of 3 eligible observational studies reporting OR for wheeze. The data show no evidence of a relationship between timing of soya introduction and risk of wheeze. 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 soya introduction before 6 months and odds of wheeze.

Figure 19: Soya introduction ≤5-7 months and wheeze at ≤4, OR

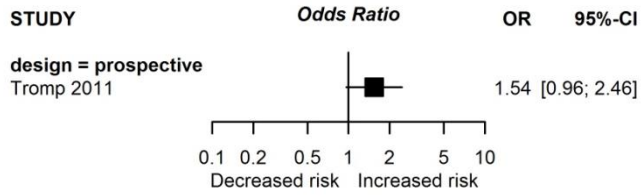


Figure 20: Soya introduction ≤0-2 months and recurrent wheeze at ≤4, OR

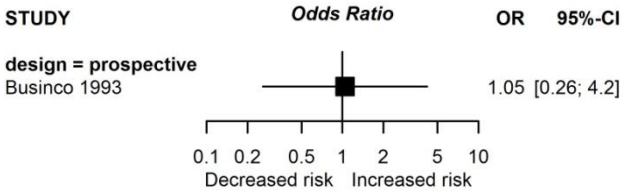
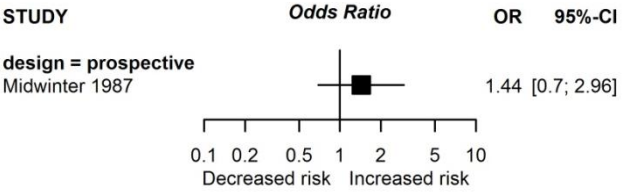


Figure 21: Soya introduction ≤0-2 months and recurrent wheeze at 5-14, OR



3.2. Conclusions: soya introduction and wheeze

Overall 3 prospective cohort studies assessed the relationship between timing of introduction of soya, and wheeze or recurrent wheeze. Data were generally sparse, with no meta-analysis possible and no evidence for association.

Overall we found no evidence that timing of soya introduction influences risk of wheeze or recurrent wheeze.

4. Timing of egg introduction

4.1. Timing of egg introduction and risk of wheeze at age ≤4

Figures 22 to 23 show the outcomes of 2 eligible observational studies reporting OR for wheeze at age ≤4. The data show no evidence of a relationship between timing of egg introduction and risk of wheeze.

Figure 22: Egg introduction ≤5-7 months and wheeze at ≤4, OR

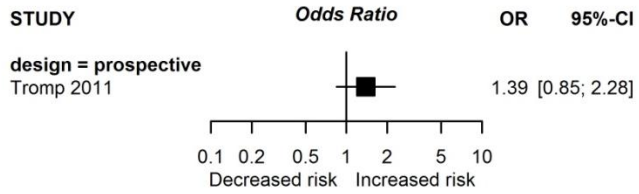
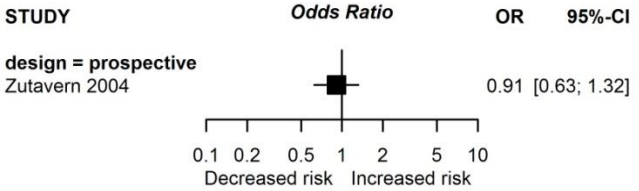


Figure 23: Egg introduction ≤8-12 months and wheeze at ≤4, OR



4.2. Timing of egg introduction and risk of wheeze/ recurrent wheeze/ atopic wheeze at age 5-14

Figures 24 to 28 show the outcomes of 3 eligible observational studies reporting OR or HR for wheezing outcomes at age 5-14. The data show no evidence of a relationship between egg introduction <5 months and risk of wheeze/recurrent wheeze from the SEATON cohort (Figures 24 and 25), but evidence for reduced recurrent wheeze and atopic wheeze with egg introduction <8 months in the DIPP cohort (Figures 27 and 28). Both studies were judged to be at low overall risk of bias and reported adjusted data.

Figure 24: Egg introduction ≤5-7 months and wheeze at 5-14, OR

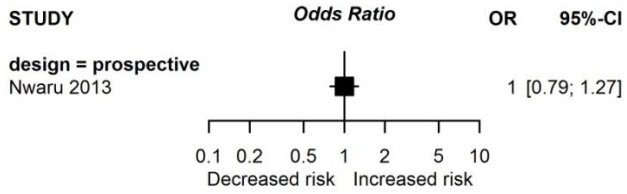


Figure 25: Egg introduction ≤5-7 months and recurrent wheeze at 5-14, OR

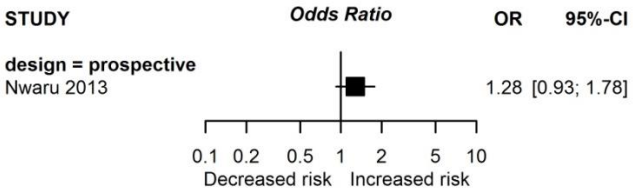


Figure 26: Egg introduction ≤8-12 months and recurrent wheeze at 5-14, OR

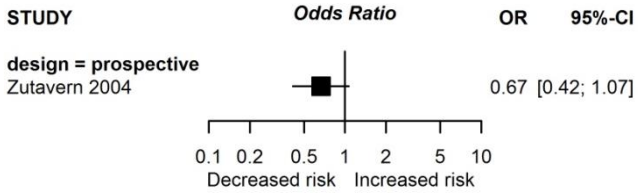


Figure 27: Egg introduction ≤8-12 months and recurrent wheeze at 5-14, HR

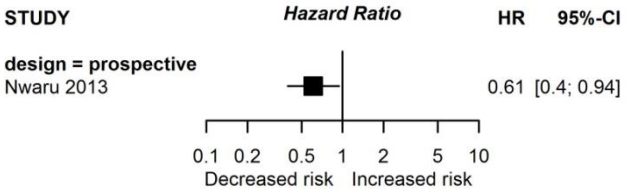
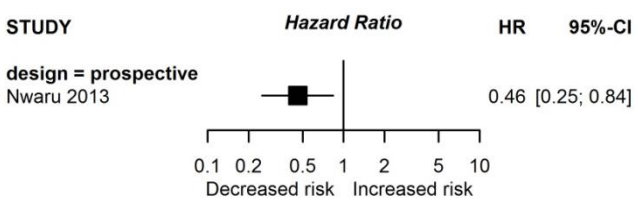


Figure 28: Egg introduction ≤8-12 months and atopic wheeze at 5-14, HR



4.3. Studies of egg introduction and wheeze 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 wheeze. **Hesselmar 2010** reported median age of egg introduction 11 months (IQR 9, 13) in infants without recurrent wheezing in the first 18 months, compared with 13 months (IQR 12, 13) in infants who wheezed (P=0.079). **Lopez Campos 2001** reported no relationship between timing of egg introduction and risk of doctor diagnosed asthma but did not present numerical data. **Miskelly 1988** reported no significant difference in timing of egg introduction between infants with and without parent-reported wheeze in the first year, but did not present numerical data. **Goksor 2013** reported no significant difference in risk of current wheeze at age 8 years, in relation to timing of egg introduction but did not present numerical data.

4.4. Conclusions: egg introduction and wheeze

Overall 8 prospective cohort studies and one case control study assessed the relationship between timing of introduction of egg, and wheeze or recurrent wheeze. Data from one prospective cohort study (DIPP) showed evidence of an association between egg introduction <8 months and reduced recurrent wheeze or atopic wheeze, however this association was not seen in the other 8 studies evaluated.

Overall we found no evidence that timing of egg introduction influences risk of wheeze or recurrent wheeze.

5. Timing of fish introduction

5.1. Timing of fish introduction and risk of wheeze/ recurrent wheeze at ≤4

Figures 29 to 31 show the outcomes of 5 eligible observational studies reporting OR for wheeze/ recurrent wheeze at age ≤4. The data show no evidence of a relationship between timing of fish introduction and risk of wheeze in 2 studies (Figure 29, 30) but pooled analysis of the other 3 studies shows evidence for reduced recurrent wheeze in infants fed fish before the age of 8-12 months, with no statistical heterogeneity.

Figure 29: Fish introduction ≤5-7 months and wheeze at ≤4, OR

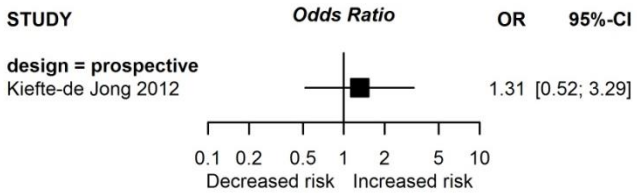


Figure 30: Fish introduction ≤8-12 months and wheeze at ≤4, OR

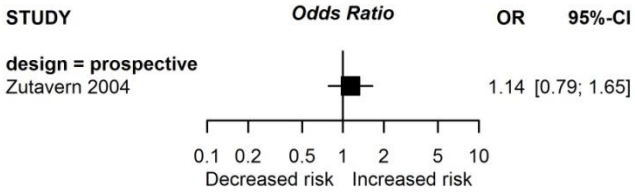
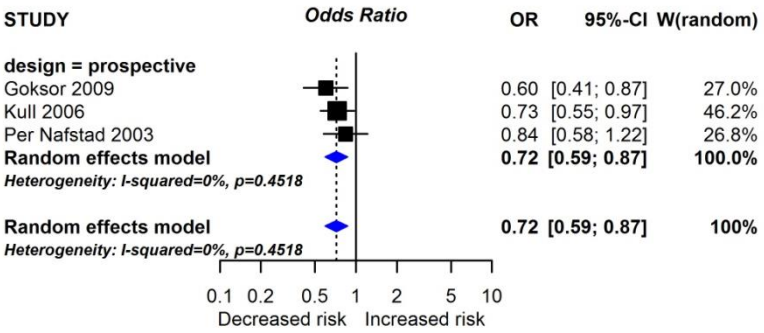


Figure 31: Fish introduction ≤8-12 months and recurrent wheeze at ≤4, OR



5.2. Timing of fish introduction and risk of wheeze/ recurrent wheeze at 5-14

Figures 32 to 35 show the outcomes of 4 eligible observational studies reporting OR or HR for wheeze/ recurrent wheeze at age 5-14. The data show no evidence of a relationship between timing of fish introduction and risk of wheeze in 3 studies, but reduced recurrent wheeze in infants fed fish before the age of 8-12 months in the study of Goksor 2013, leading to high statistical heterogeneity in the only meta-analysis (Figure 36).

Figure 32: Fish introduction ≤5-7 months and wheeze at 5-14, OR

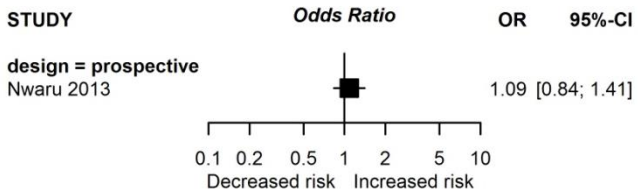


Figure 33: Fish introduction ≤5-7 months and recurrent wheeze at 5-14, OR

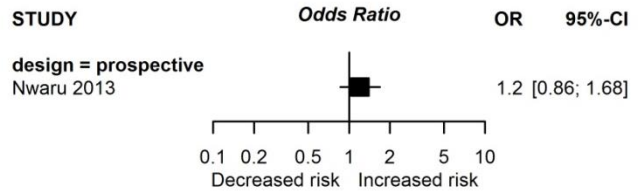


Figure 34: Fish introduction ≤5-7 months and recurrent wheeze at 5-14, HR

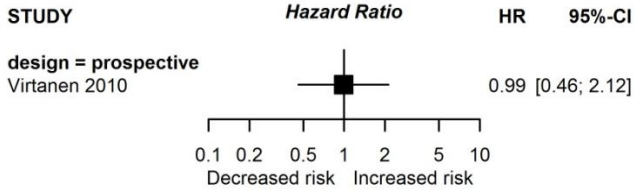
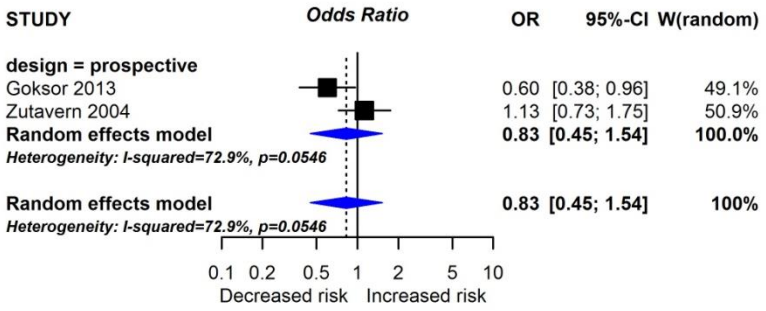


Figure 35: Fish introduction ≤8-12 months and recurrent wheeze at 5-14, OR



5.3. Studies of fish introduction and wheeze 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 wheeze. **Hesselmar 2010** reported median age of fish introduction 9 months (IQR 6, 12) in infants without recurrent wheezing in the first 18 months, compared with 13 months (IQR 8, 13) in infants who wheezed (P=0.13). **Per Nafstad 2003** undertook a subgroup analysis and found a significant association between fish introduction <12 months and reduced recurrent wheeze at age ≤4 in participants without a family history of allergic disease (aOR 0.5 95% CI 0.3, 0.83); but no such association in participants with a family history of allergic disease (aOR 1.0 95% CI 0.61, 1.63). **Kiefte de Jong 2012** reported significantly reduced wheeze at ≤4 associated with introduction of fish at 6-12 months age, compared with other ages.

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5.4. Conclusions: fish introduction and wheeze

Overall 8 prospective cohort studies assessed the relationship between timing of introduction of fish, and wheeze or recurrent wheeze. Meta-analysis of 3 studies with 11,000 participants, 2 of which were assessed as at low risk of bias, showed evidence of an association between fish introduction <8-12 months and reduced recurrent wheeze at age ≤4. This association was not seen in the other 5 studies evaluated, which included 3 studies with 12,000 participants which were assessed as at low risk of bias.

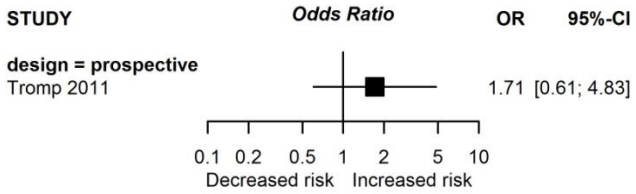
Overall we found no consistent evidence that earlier fish introduction before 5-12 months is associated with reduced risk of wheezing.

6. Timing of nut (peanut or tree nut) introduction

6.1. Timing of nut introduction and risk of wheeze at ≤4

Figure 36 shows the outcomes of 1 eligible observational study reporting OR for wheeze at age ≤4. The data show no evidence of a relationship between timing of peanut introduction and risk of wheeze. Tromp reported the same comparison at age 2 (in Figure 36) and also at ages 3 and 4, where there was no significant association between peanut introduction before 6 months and odds of wheeze. Tromp reported the same comparisons for timing of tree nut introduction, and found no significant association at ages 2, 3 or 4.

Figure 36: Peanut introduction ≤5-7 months and wheeze at ≤4, OR



6.2. Conclusions: nut introduction and wheeze

Data for this comparison were sparse, with just one study contributing to the assessment.

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

7. Timing of cereal introduction

7.1. Timing of cereal introduction and risk of wheeze/ recurrent wheeze

Figures 37 to 41 show the outcomes of 4 eligible observational studies reporting OR or HR for wheeze at age ≤4 or 5-14. The data show no evidence of a relationship between timing of cereal introduction and risk of wheeze or recurrent wheeze. Tromp 2011 reported the same comparison at age 2 (in Figure 38) and also at ages 3 and 4, where there was no significant association between cereal introduction before 6 months and odds of wheeze.

Figure 37: Cereal introduction ≤3-4 months and wheeze at ≤4, OR

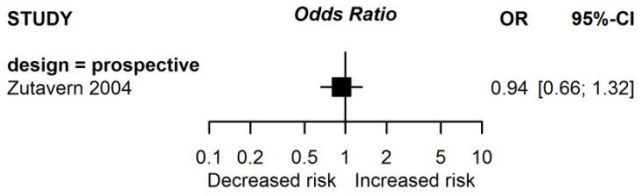


Figure 38: Cereal introduction ≤5-7 months and wheeze at ≤4, OR

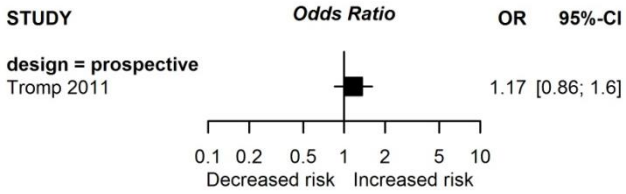


Figure 39: Cereal introduction ≤3-4 months and wheeze at 5-14, OR

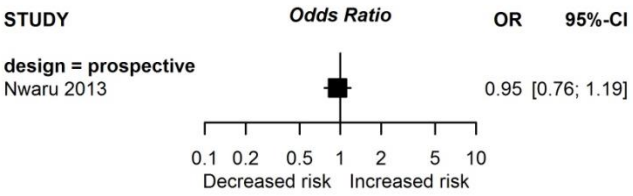


Figure 40: Cereal introduction ≤3-4 months and recurrent wheeze at 5-14, OR

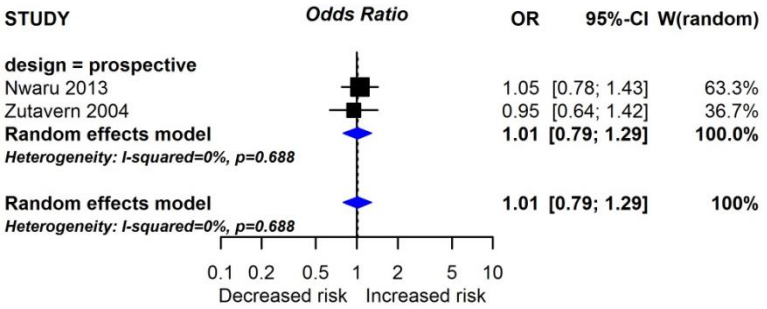
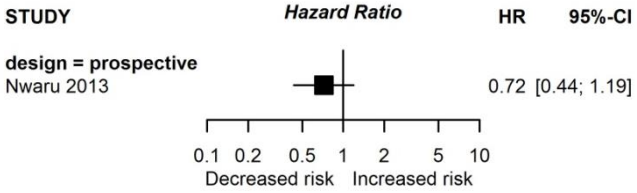


Figure 41: Cereal introduction ≤5-7 months and recurrent wheeze at 5-14, HR



7.2. Studies of cereal introduction and wheeze which could not be included in meta-analysis

Two further studies reported the relationship between timing of cereal introduction to the infant diet, and risk of wheeze. **Miskelly 1988** reported that infants with a history of parent-reported wheeze in the first year of life had earlier introduction of wheat or rye protein into their diet (P<0.05, unadjusted), but did not present numerical data. **Goksor 2013** reported no significant difference in risk of current wheeze at age 8 years, in relation to timing of gluten introduction but did not present numerical data.

7.3. Conclusions: cereal introduction and wheeze

Overall 6 prospective cohort studies assessed the relationship between timing of introduction of cereal, and wheeze or recurrent wheeze. One study reported an unadjusted association between early wheat/rye introduction and increased risk of parent-reported wheeze, but the other 5 studies reported no association.

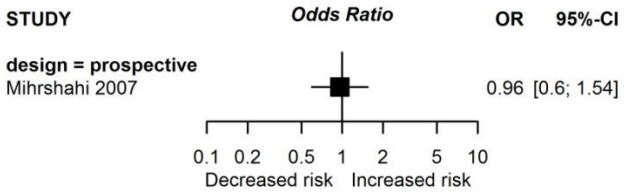
Overall we found no evidence that timing of cereal introduction influences risk of wheeze or recurrent wheeze.

8. Timing of any allergenic food introduction

8.1. Timing of allergenic food (AF) and risk of wheeze/ recurrent wheeze

Figure 42 shows the outcomes of 1 eligible observational study reporting OR for wheeze 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 recurrent wheeze risk at age 5 years compared with later introduction of AF.

Figure 42: AF introduction ≤8-12 months and recurrent wheeze at 5-14, OR



8.2. Conclusions: any AF introduction and wheeze

One study assessed the relationship between timing of introduction of any allergenic food and recurrent wheeze. No association was found.

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

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