BREASTFEEDING, SOLID FOOD INTRODUCTION AND RHINOCONJUNCTIVITIS

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1 Total breastfeeding and rhinoconjunctivitis

1.1 Overall characteristics of studies, risk of bias and summary of results

Table 1 describes the main characteristics of the studies that assessed total breastfeeding duration (TBF) in relation to rhinoconjunctivitis (RC) risk. A total of 1 cluster randomised controlled trial and 21 observational studies, reported the association between TBF and RC. Of these, 16 were prospective cohort studies, 5 cross-sectional studies. The majority of studies (n=17) are from Europe – others are from North America (n=2) and Japan (n=2). Overall, valid data on TBF duration in the first 2 years of life and RC risk were available from over 200,000 subjects. Information on RC was obtained solely from a medical assessment in 8 studies, and mainly via parental report in 13 studies. With regards to time of outcome diagnosis, 4 studies explored the association between TBF duration and RC at age 0-4, where allergic RC can be most difficult to distinguish from infectious RC, 10 at ages 5-14, and 7 at ages up to and beyond 15 years. Four studies used an interview, one parent diaries, and one a medical records review; in one study the method of exposure assessment was unclear and in all others a questionnaire method was used.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented, but also in some cases due to high risk of selection bias. Risk of conflict of interest was generally assessed as low.

Where data were available, five levels of comparison were used to assess the risk of RC according to TBF duration, namely 'ever vs. never', '≥1-2 months vs. <1-2 months', '≥3-4 months vs. <3-4 months', '≥5-7 months vs. <5-7 months', and '≥8-12 months vs. <8-12 months'.

Main Findings

In the single intervention trial there was no evidence of a relationship between breastfeeding promotion and risk of allergic rhinoconjunctivitis. For observational studies, across all cut-offs where data were available, there was no clear evidence of a relationship between risk of

RC and initiation or prolongation of BF. In general there were only small numbers of studies with available data for individual meta-analyses, although the number of participants in some of the relevant studies was large. For RC at age 0-4 there was a trend to reduced risk with TBF ever and ≥5-7 months, but this was not statistically significant. For RC at older ages the large study sizes mean that we can be more confident of having excluded at least a large reduction in RC risk with increased initiation or duration of TBF.

Table 1 Characteristics of included studies evaluating TBF duration and rhinoconjunctivitis

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 2001 (1); Kramer, 2007 (2)	8865/8181	Cluster RCT	Belarus	-	SPT-Aero	6.5	Breastfeeding promotion program based on the WHO/UNICEF baby friendly hospital initiative, versus standard local breastfeeding policies
Kull, 2002 (3)	3790/262	PC	Sweden	Q	Parent reported RC symptoms	2	BAMSE study. Population based cohort of children born between 1994-1996
Butland, 1997 (BCS58 and BCS70) (4)	20582/3631	PC	UK	I	Parent reported current AR	16	British Cohort Study (two samples): infants born in England, Wales, and Scotland in 1958 and 1970
Taylor, 1983 (BSC70) (5)	10781/452	PC	UK	I	Parent reported RC	5	CHES study. Population based cohort of children born in England, Scotland, and Wales in 1970
Burr, 1993 (6)	453/117	PC	UK	Q	Parent reported AR	7	Infants with family history of allergy born in 1982

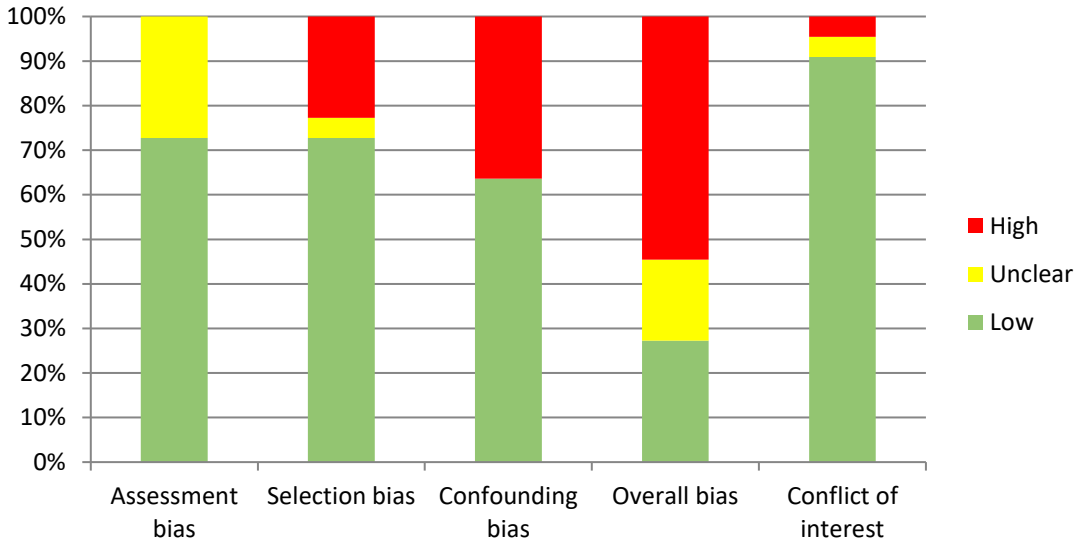
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Businco, 1987 (7)	244/3	PC	Italy	I	Physician assessment	8	Infants of atopic parents recruited from hospital and born in 1985-1988
Larsson, 2008 (8)	4779/573 (in 2000), 975 (in 2005)	PC	Sweden	Q	DD; ISAAC - current AR	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005
Devereux, 2006 (9)	1253/54	PC	UK	Q	ISAAC	5	Population based birth cohort of infants born in 1998
Virtanen, 2010 (10)	1288/185	PC	Finland	Q	Modified ISAAC questionnaire	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study 1998-2000
Farooqi, 1998 (11)	1453	PC	UK	R	DD	16	Representative sample of general practice born in 1975-84
Gruskay 1982 (12)	908/22	PC	USA	Unclear	Parent reported AR	3, 5, 15	Children born in 1961-1966 seen in a private pediatric practice
Marini, 1996	359/	PC	Italy	Q	Physician	3	Infants with family history of

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
(13)					assessment		allergy who participated in an allergy prevention program
Miskelly, 1988 (14)	468/204	PC	UK	D	Physician assessment	1	Infants from antenatal clinics with family history of allergy enrolled in a dietary intervention trial
Strachan, 1996 (15)	11765/1932	PC	UK	I	DD	16	Population based cohort born in 1975
Hide, 1981 (16)	843/198	PC	UK	D/Q	Parent reported rhinitis symptoms	1	Isle of Wight study: infants born in 1977-1978
Wright, 1994 (17)	747/313	PC	USA	Q	Parent reported AR	6	Tuscon Children's Respiratory Study: recruited from local health maintenance organisation born in 1980-1984
Bergmann, 2000; Kulig, 2000(18, 19)	587/88	PC	Germany	Q/I	Physician assessment; Parent reported AR ever	6, 7	MAS study. Atopic risk enriched cohort of infants born in 1990 in 5 German cities

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Björkstén, 2011 (20)	103716/unclear	CS	Worldwide	Q	ISAAC - AR ever	7	ISAAC Phase 3: Schoolchildren age 6-7 from different countries
Miyake, 2003 (21)	5614/1340	CS	Japan	Q	ISAAC - current AR	15	12-15 year old children from all public junior high schools in Suita, Japan
Karino, 2008 (22)	9615/4038	CS	Japan	Q	DD	18	University students aged 18–19 years enrolled from 2003-2005
Kurt, 2007 (23)	25843/4618	CS	Turkey	Q	Parent reported current AR	6-15	Prevalence and Risk Factors of Allergies in Turkey. Representative sample of children aged 6-15
Selcuk, 1997(24)	5412/271	CS	Turkey	Q	Parent reported RC ever	7-12	Children aged 7-12 at 18 primary schools

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DD: doctor diagnosis of RC, in contrast to 'Physician assessment' where RC diagnosis was always made by a study physician as part of the study protocol.

Figure 1 Risk of bias in studies of TBF duration and rhino conjunctitis



1.2 TBF and rhinoconjunctivitis

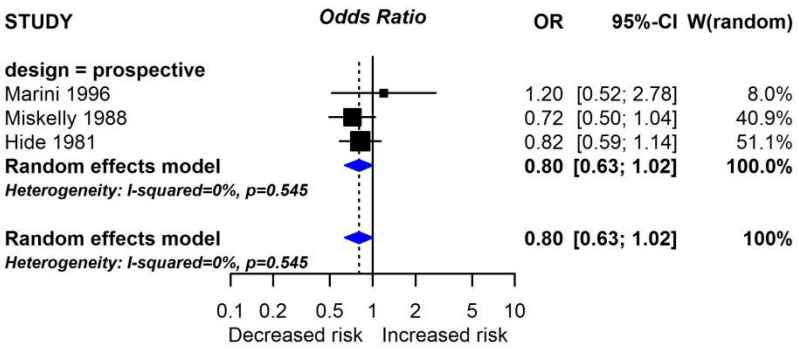
The single intervention trial of a breastfeeding promotion intervention was rated as having a low risk of bias on all domains, and a low risk of conflict of interest. Kramer found no significant difference in odds of ever having hayfever by the age of 6.5 years – cluster adjusted odds ratio 1.1 (95% CI 0.6, 1.9), or hayfever in the past 12 months at the same age OR 1.0 (0.6, 1.8). All other evidence was derived from observational studies.

1.2.1 TBF duration and risk of RC in children aged 0-4 years

1.2.1.1 TBF Ever vs. Never

Figure 2 shows the outcomes of 3 eligible observational studies including over 600 children with RC. The data show reduced odds of RC in breastfed infants, but do not reach statistical significance. There is no statistical heterogeneity (I^2=0%). All three studies are prospective cohort studies – the study of Marini reported adjusted data at age 3 and had overall unclear risk of bias due to unclear assessment bias; the other two studies reported unadjusted data at age 1, and are therefore at high risk of confounding bias. Thus the data do not show strong evidence of a relationship between breastfeeding ever and risk of RC.

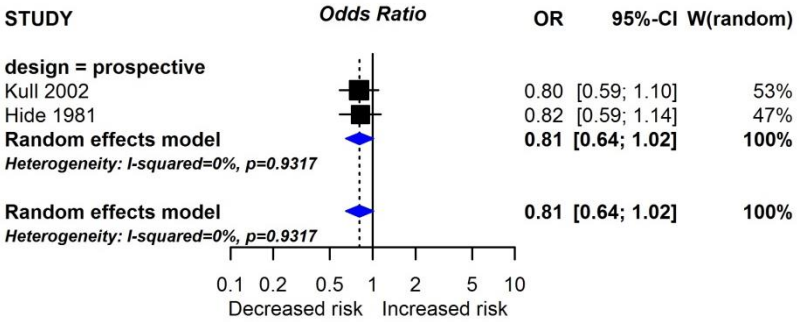
Figure 2 TBF Ever vs. Never and RC at age 0-4 years



1.2.1.2 TBF ≥5-7 months vs. <5-7 months

Two prospective cohort studies reported data that could be used to calculate OR for RC at age 0-4 with TBF ≥ 6 months compared to <6 months and found reduced odds of RC with longer breastfeeding duration, which did not reach statistical significance. There was no statistical heterogeneity (I^2=0%). The study of Hide assessed infants at 1 year and reported unadjusted data, so carries a high risk of bias. The study of Kull assessed infants at 2 years and reported adjusted data – there was unclear risk of assessment bias but low risk of bias on other parameters.

Figure 3 TBF ≥5-7 months vs. <5-7 months and risk of RC at age 0-4 years



1.2.2 TBF duration and risk of RC in children aged 5-14 years

1.2.2.1 TBF Ever vs. Never

Four prospective cohort studies and two cross-sectional surveys reported data that could be used to calculate OR for RC at age 5-14 with TBF ever vs. never and found no association between breastfeeding duration and odds of RC (Figure 4). There was high statistical heterogeneity (I^2=72.2%). The studies of Selcuk and Bjorksten reported adjusted data and were judged to be at low overall risk of bias. Other studies reported unadjusted data and were therefore at high risk of confounding bias. Subgroup analyses (Table 2) did not identify a

clear explanation for the statistical heterogeneity between studies, but there was no heterogeneity between the two studies reporting adjusted data.

Analysis of 'dose response' using a reference group of 'never BF' with comparison groups of short TBF (≥1-3; Figure 5), medium TBF (≥4-6; Figure 6) and long TBF (≥7-12; Figure 7) were limited by small numbers of eligible studies reporting only unadjusted data, and did not show evidence of a dose response relationship.

Figure 4 TBF Ever vs. Never and risk of RC at age 5-14 years

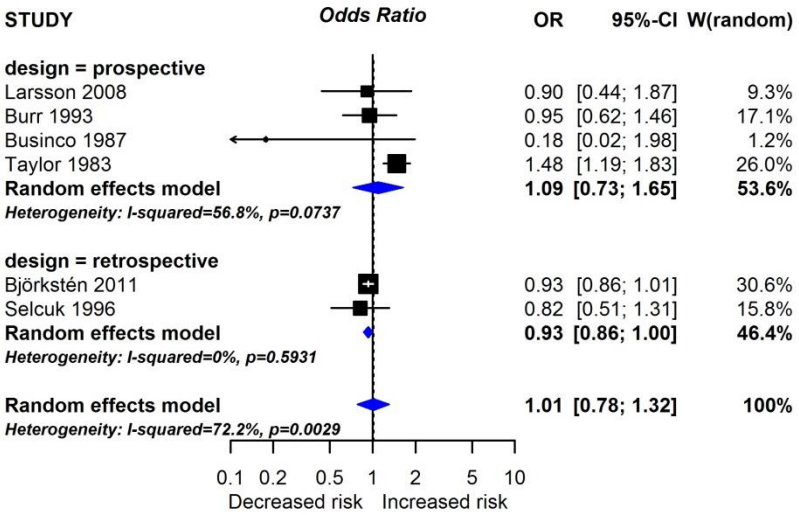


Figure 5 TBF short duration (≥1-3 months) vs. never and risk of RC at age 5-14 years

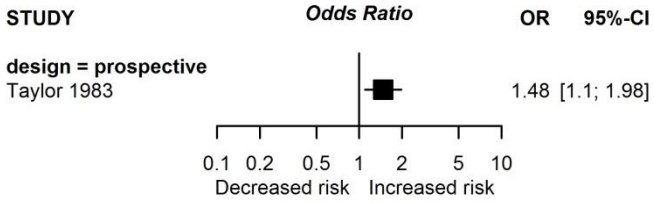


Figure 6 TBF medium duration (≥4-6 months) vs. never and risk of RC at age 5-14 years

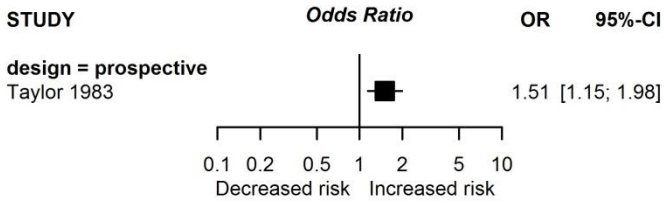


Figure 7 TBF long duration (≥7-12 months) vs. never and risk of RC at age 5-14 years

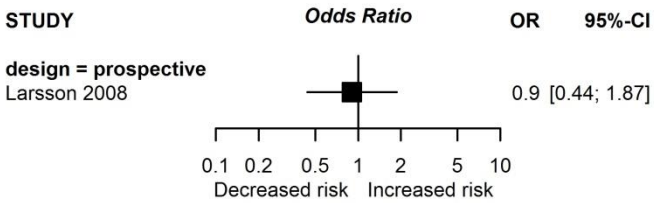


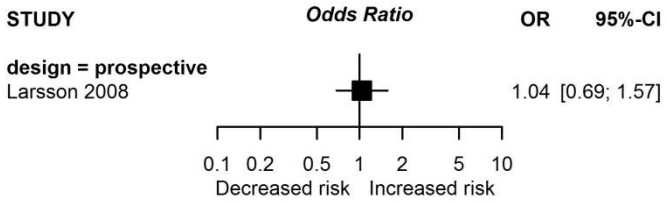
Table 2 Subgroup Analyses of risk of RC and TBF ever vs. never in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)				
Adjusted	2	0.93 [0.86; 1.00]	0.00	Not tested
Unadjusted	4	1.10 [0.73; 1.65]	56.8	
Study Design – Prospective	4	1.00 [0.62; 1.62]	58.6	0.44
Study Design – Retrospective	2	0.93 [0.86; 1.00]	0.00	
Risk of disease – High	2	0.64 [0.16; 2.59]	44.7	0.50
Risk of disease – Normal	4	1.00 [0.76; 1.43]	81.3	
Risk of bias – Low	4	1.00 [0.76; 1.43]	81.3	0.50
Risk of bias – High/Unclear	2	0.64 [0.16; 2.59]	44.7	

1.2.2.2 TBF ≥3-4 Months vs. <3-4 months

One prospective cohort study reported data that could be used to calculate an OR for this comparison, shown in Figure 8. Unadjusted data, with a high risk of confounding bias, showed no significant association between TBF duration and risk of RC at age 5-14.

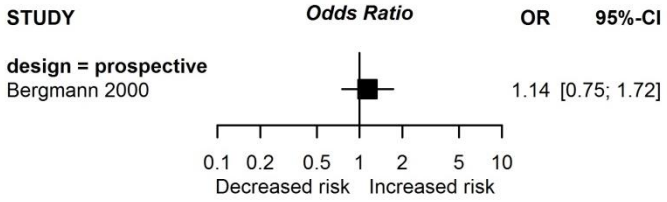
Figure 8 TBF ≥3-4 months vs. <3-4 months and RC risk at age 5-14 years



1.2.2.3 TBF ≥5-7 Months vs. <5-7 months

One prospective cohort study reported data that could be used to calculate an OR for this comparison, shown in Figure 9. Adjusted data showed no significant association between TBF duration and risk of RC at age 5-14. There was a high risk of selection bias due to loss to follow up of 33% of participants when assessed at age 6 years.

Figure 9 TBF ≥5-7 months vs. <5-7 months and risk of RC at age 5-14 years



1.2.3 TBF duration and the risk of RC in children aged 15+ years

1.2.3.1 TBF Ever vs. Never

Two cross-sectional and four prospective cohort studies reported data that could be used to calculate an OR for this comparison. Pooled data showed increased risk of RC in breastfed children at age 15+, but this did not reach statistical significance and there was high statistical heterogeneity (Figure 10). The cross-sectional studies of Miyake and Kurt, and the prospective study of Butland, reported adjusted data. The studies of Strachan and Farooqi reported unadjusted data and were therefore at high risk of confounding bias. It was not possible to identify a clear cause for the statistical heterogeneity seen in this analysis. Analysis of 'dose response' using a reference group of 'never BF' with comparison groups of short TBF (≥1-3; Figure 11) and medium TBF (≥4-6; Figure 12) were limited by small numbers of eligible studies and did not show evidence of a dose response relationship.

Figure 10 TBF Ever vs. Never and risk of RC at age 15+ years

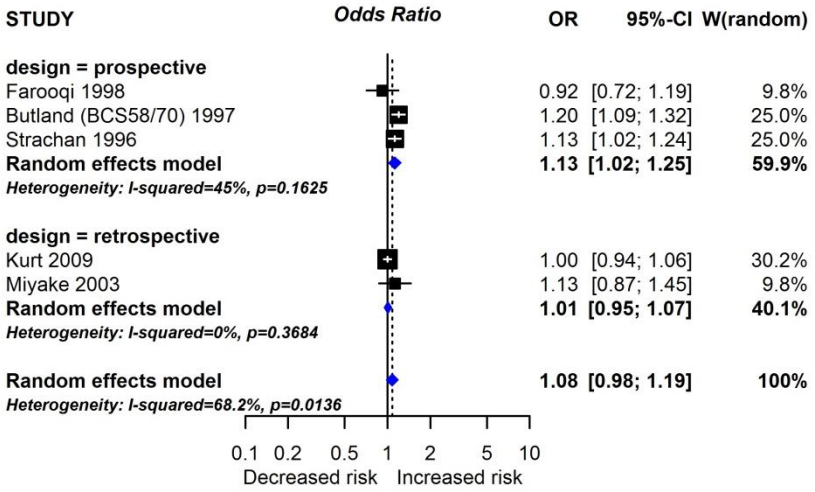


Figure 11 TBF short duration (≥1-3 months) vs. never and risk of RC at age 15+ years

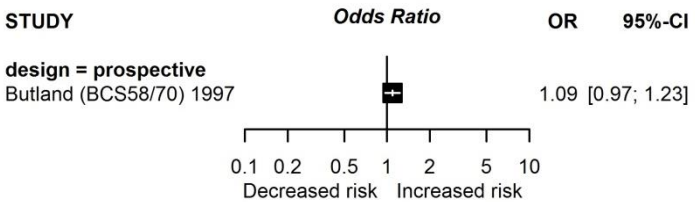
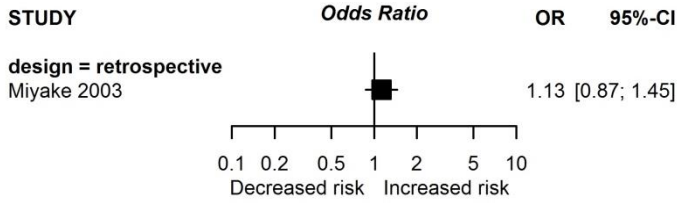


Figure 12TBF medium duration (≥4-6 months) vs. never and risk of RC at age 15+ years



1.3 TBF and Atopic RC

We also assessed the outcome 'atopic RC', where participants have the outcome if they are reported as having RC, and also have evidence of specific allergic sensitisation through skin prick or sIgE testing. This may be a more reliable measure of allergic rhinoconjunctivitis than RC alone, since infective rhinitis and conjunctivitis can be difficult to distinguish from allergic forms especially when patient or parent report is used for outcome assessment.

A single study was identified which reported TBF and atopic RC data that could be used to calculate ORs. In the study of Gruskay 6 of 782 formula fed children had RC at age 3, compared with none of 126 children who had been breastfed. At age five OR 3.51 (0.63, 19.61), at age 15 OR 1.71 (0.18, 15.80) there was no association found between TBF and atopic RC.

1.4 Data for TBF duration and RC that couldn't be meta-analysed

Meta-analyses included 10 studies, reporting data on at least 13,000 participants with RC. A further 5 studies reported relevant data which could not be reported in meta-analysis, in relation to at least 4500 participants with RC. These studies are summarised in Table 3. In all studies and analyses reported there was no association found.

Table 3 Studies investigating the association between TBF and RC which were not eligible for meta-analysis

Study	Design	Age	N/n	Data	Measure Outcome (s) P
Wright, 1994 (17)	PC	6	747/313	Continuous	No significant difference between groups in breastfeeding duration
Kulig, 2000 (19)	PC	7	587/88	Continuous	No significant difference between groups in breastfeeding duration (P=0.91; adjusted)
Devereux, 2006	PC	5	1253/54	Categorical	No significant relationship between BF ever and RC (adjusted)
Virtanen, 2010 (10)	PC	5	1288/185	Categorical	aHR (95%CI) 1.1 (0.6-1.9) for TBF <5 vs. >9.5 months
				Categorical	aHR (95%CI) 1.1 (0.6-1.6) for TBF 5-9 vs. >9.5 months
Karino, 2008 (22)	CS	18	9615/4038	Categorical	BF duration not associated with RC when classified as never/ever; more/less than 1 month, 3 months or 6 months (unadjusted)

2 Exclusive breastfeeding and rhinoconjunctivitis

2.1 Overall characteristics of studies, risk of bias and summary of results

Table 4 describes the main characteristics of the studies analysed in this report. A total of 1 systematic review which included 1 RCT analysed as a cohort study and 1 other prospective cohort study, and 13 observational studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of RC. Of these, 10 were prospective cohort studies and 3 cross-sectional studies. Over half of the studies (n=9) are from Europe – others are from Australasia (n=4), and the Middle East (n=1). Overall, valid data on EBF duration and RC risk were available from over 29,000 subjects. Information on RC was obtained mainly from a medical assessment in 6 studies, via parental report in 8 studies. With regards to time of outcome diagnosis, 5 studies explored the association between EBF duration and RC at age 0-4, where allergic RC can be difficult to distinguish from infective RC, 5 evaluated RC at age 5-14, and 4 at age 15+. Most studies used a questionnaire to assess the exposure (EBF), one study used a diary and three used an interview.

Risk of bias for the observational studies is shown in Figure 13. Over half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. Risk of conflict of interest was generally assessed as low. All included studies reported data which could be analysed as odds ratios and presented using forest plots.

Where data were available, three levels of comparison were used to assess the risk of RC according to EBF duration, namely ≥0-2 months vs. <0-2 months; ≥3-4 months vs. <3-4 months; ≥5-9 months vs. <5-9 months.

Main Findings

There was no consistent evidence of an association between EBF and risk of RC. In general there were only small numbers of studies with available data for each analysis, and several analyses were restricted to studies with high risk of bias. Two prospective RCT showed inconsistent and non-significant findings. We did find some evidence from observational studies that EBF ≥3-4 months may reduce odds of RC at age 0-4 OR 0.77 (0.60, 0.99) with no statistical heterogeneity (I^2=0%), but this was not supported by other data. One large

cohort study suggested increased odds of hayfever by age 44 in those EBF ≥3 months however such an effect was not supported by shorter term observations in intervention studies or cohort studies.

Table 4 Characteristics of included studies evaluating EBF duration and rhinoconjunctivitis

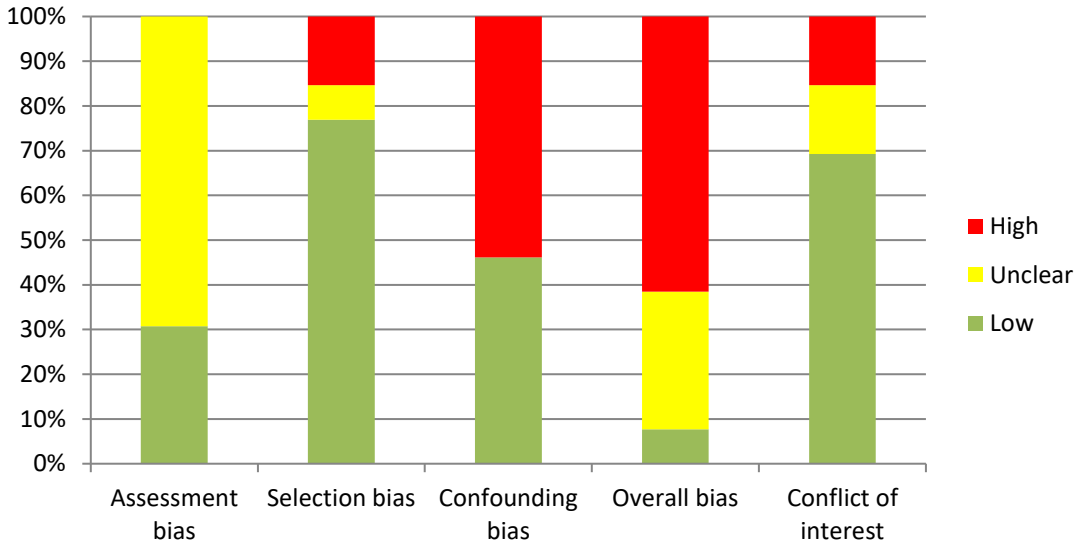
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer (25)	3584	SR of PC nested in RCTs	Finland/Belarus	-	ISAAC – current AR	5-7	Study #1: Infants of atopic parents Study #2: Healthy, term, breastfed newborns participating in a breastfeeding promotion trial.
Kajosaari, 1991(26)	135	PC	Finland		Parent report of pollen allergy	5	Solid food introduction at 6 months versus 3 months, in exclusively breastfed infants
Kellberger, 2012 (27)	3785/314	PC	Germany	Q	ISAAC - ever AR	9-18	SOLAR. Community based random sample of all pupils aged 9-11 years in 1995-1996 as part of ISAAC study, with follow-up survey 2002-2003
Kull, 2002 (3)	3791/263	PC	Sweden	Q	Parent reported RC symptoms	2	BAMSE. Population based cohort of children born between 1994-1996
Kramer, 2009 (28)	13889/455	PC nested in RCT	Belarus	I	ISAAC - current AR	6.5	PROBIT. Born 1996-1997
Siltanen,2003 (29)	285/53	PC	Finland	Q	Physician assessment	4	Infants recruited from maternal hospital born in 1994-1995

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Strachan, 1996 (15)	11765/1932	PC	UK	I	DD	16	Population representative sample born in 1975
Matheson, 2007 (30)	5729/2610	PC	Australia	Q	Physician assessment	44	Tasmanian Asthma Study: population based cohort born in 1961
Van Asperen, 1983 (31)	79/44	PC	Australia	I	Physician assessment	1	Cohort recruited from medical service, born in 1980-1981 with family history of atopy
Arshad, 1992 (32)	1167/38	PC	UK	D/Q	Physician assessment	1	Isle of Wight Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Marini, 1996 (13)	359	PC	Italy	Q	Physician assessment	3	Infants with family history of allergy whose mother agreed to participate in an allergy prevention program
Erkkola, 2012 (33)	2441/359	PC	Finland	D	ISAAC - current AR	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study 1998-2000
Ehlayel, 2008 (34)	1278	CS	Qatar	Q	ISAAC - AR ever	5	Children 0-5 years old attending primary healthcare centers for routine immunisation

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Liu 2012 (35)	8733/397	CS	China	Q	ATS questionnaire	8	Sample of children from kindergarten and elementary schools in Shenyang
Miyake, 2003 (21)	6845/1340	CS	Japan	Q	ISAAC - current AR	15	12-15 year old children from all public junior high schools in Suita, Japan

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DD: doctor diagnosis of RC, in contrast to 'Physician assessment' where RC diagnosis was always made by a study physician as part of the study protocol.

Figure 13 Risk of bias in studies of EBF duration and rhinoconjunctivitis



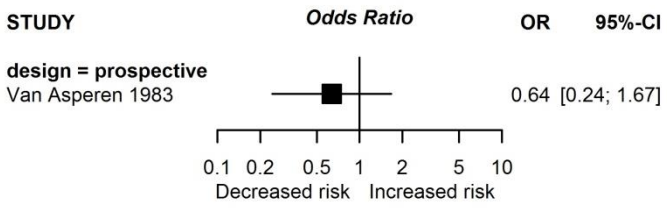
2.2 EBF duration and risk of rhinoconjunctivitis

2.3 EBF duration and risk of RC in children aged 0-4 years

2.3.1.1 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for RC in the first year, in infants with EBF for ≥2 months vs. <2 months duration and is shown in Figure 14. The study found no significant association. The data are unadjusted, so carry a high risk of bias.

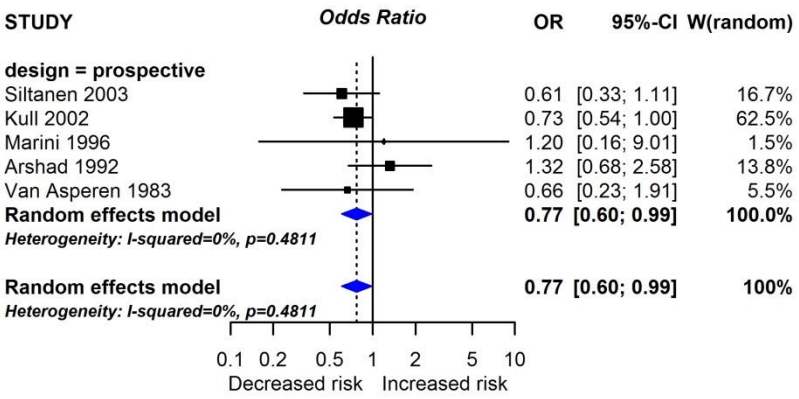
Figure 14 EBF ≥0-2 months vs. <0-2 months and RC risk at age 0-4



2.3.1.2 EBF ≥3-4 months vs. <3-4 months

Five prospective cohort studies reported data that could be used to calculate OR for RC at age 0-4, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 15. They show reduced odds of RC with longer EBF duration, with no statistical heterogeneity. The data from Arshad, Marini and Van Asperen are unadjusted, so carry a high risk of bias, but the data of Kull and Siltanen are adjusted.

Figure 15 EBF ≥3-4 months vs. <3-4 months and risk of RC at age 0-4 years



2.3.2 EBF and risk of RC in children aged 5-14 years

2.3.2.1 Systematic reviews and intervention trials

As shown in Table 5, the single systematic review found no evidence that increased duration of exclusive/predominant breastfeeding influences risk of RC at 6.5 years, although there was heterogeneity in findings, with one small study finding borderline evidence for reduced risk of RC RR 0.53 (0.28, 1.01), and a larger study showing no evidence of association.

Table 5 Promotion of increased EBF duration and risk of RC

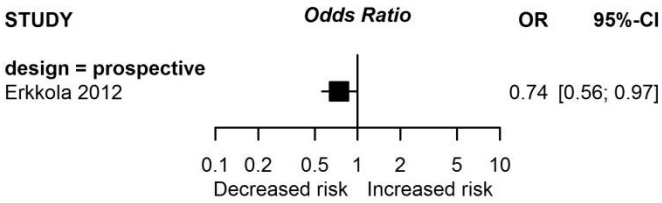
Study	Outcome measure	No. participants (studies)	Outcome (95% CI)
Kajosaari 1991 (26)	Pollen allergy at 5 years	113 (1)	RR 0.5 (0.3, 1.0)
Kramer 2007 (2)	Allergic rhinoconjunctivitis at age 6.5 years using ISAAC questionnaire	17,046 (1)	RR 1.1 (0.6, 1.9)

Data for Kajosaari 1991 are taken from the systematic review of Kramer 2012 (25).

2.3.2.2 EBF ≥0-2 months vs. <0-2 months

One prospective cohort study reported data that could be used to calculate OR for RC at age 5-14, in infants with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 16. The study found reduced odds of RC with EBF duration of >3months vs. <1 month (Figure 18) and a trend to reduced RC with longer EBF when all 3 categories (<1 month, 1-3 months, >3 months) were considered (P=0.093). The data carry a high risk of bias because they are unadjusted.

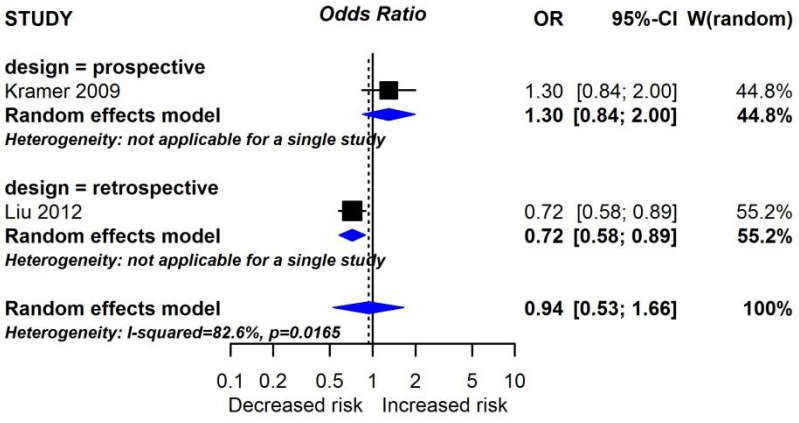
Figure 16 EBF ≥0-2 months vs. <0-2 months and risk of RC at age 5-14 years



2.3.2.3 EBF ≥3-4 months vs. <3-4 months

Two observational studies reported data that could be used to calculate OR for RC at age 5-14, in infants with EBF for ≥3-4 months vs. <3-4 months duration are shown in Figure 17. Data were not pooled due to extreme statistical heterogeneity (I^2 >80%). The cross-sectional study of Liu found reduced odds of RC with EBF duration of >3months vs. <3 months but data were unadjusted so carry a high risk of bias. The prospective cohort study of Kramer presented adjusted data showing no association when comparing EBF for >6 months with <3 months (data shown in Figure 17) but found increased odds of RC with EBF 3-6 months vs <3 months (OR 1.3 95%CI 1.1, 1.5).

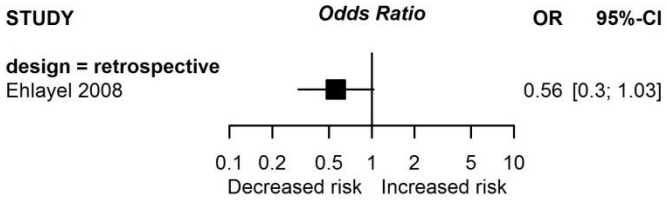
Figure 17 EBF ≥3-4 months vs. <3-4 months and risk of RC at age 5-14 years



2.3.2.4 EBF ≥5-7 months vs. <5-7 months

One cross-sectional study reported OR for RC at age 5, in children EBF for ≥6 months vs. <6 months duration and is shown in Figure 18. There were reduced odds of RC with prolonged EBF duration, but this did not reach statistical significance. The study reported unadjusted data, and therefore carries a high risk of bias.

Figure 18 EBF ≥5-7 months vs. <5-7 months and risk of RC at age 5-14 years

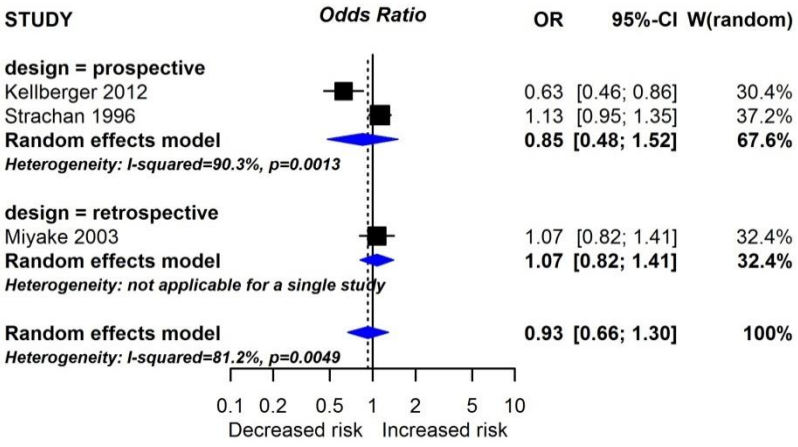


2.3.3 EBF and risk of RC in children aged 15+ years

2.3.3.1 EBF ≥0-2 months vs. <0-2 months

Two prospective cohort studies (Strachan, Kellberger) and one cross-sectional study reported OR for RC at age 15+, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 19. Data were not pooled due to extreme heterogeneity (I^2 >80%). The study of Kellberger reported adjusted data showing reduced odds of RC with prolonged EBF beyond 2 months; the studies of Miyake and Strachan reported adjusted and unadjusted data respectively, showing no association between EBF duration and RC risk.

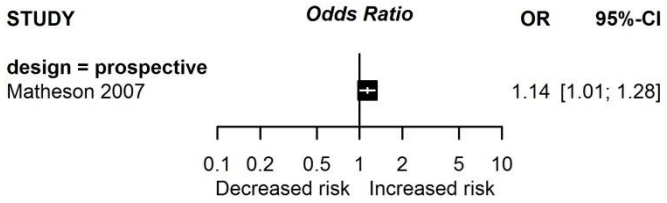
Figure 19 EBF ≥0-2 months vs. <0-2 months and risk of RC in children aged 15+ years



2.3.3.2 EBF ≥3-4 months vs. <3-4 months

One prospective cohort study reported data that could be used to calculate OR for RC at age 44, in infants with EBF ≥3-4 months vs. <3-4 months duration and is shown in Figure 20. There were significantly increased odds of self-reported hayfever in adults who had received longer duration of EBF. The data were appropriately adjusted, but the study was considered at unclear risk of bias due to inadequate definition of EBF, which was assessed retrospectively through parental report at aged 7 years.

Figure 20 EBF ≥3-4 months vs. <3-4 months and risk of RC at age 15+ years



2.4 Data for EBF duration and RC that couldn't be meta-analysed

All included studies reported OR that have been presented as forest plots – there were no further data of note for EBF duration and RC risk.

3 Solid Food Introduction and Rhinoconjunctivitis

3.1 Overall characteristics of studies, risk of bias and summary of results

Table 6 describes the main characteristics of the studies analysed in this report. A total of 6 prospective cohort studies and no intervention studies, reported the association between timing of solid food introduction (SF) and risk of RC. The studies were from Europe (n=4), USA (n=1) and Australia (n=1). Overall, valid data on SF and RC risk were available from over 8000 subjects. Information on RC was obtained from a medical assessment in 3 studies, via parental report in 3 studies. With regards to time of outcome diagnosis, 3 studies explored the association between SF and RC in the first 4 years of life, when allergic RC can be difficult to distinguish from infectious RC, and 3 studies assessed at age 5-14. Five studies used a questionnaire +/- diary to assess the exposure (SF), 1 used an interview.

Risk of bias is summarised in Figure 21. Half of studies had a high risk of bias, due to lack of adjustment for confounding bias i.e. no adjusted data presented. Four of six studies had unclear risk of assessment bias. Risk of conflict of interest was generally assessed as low.

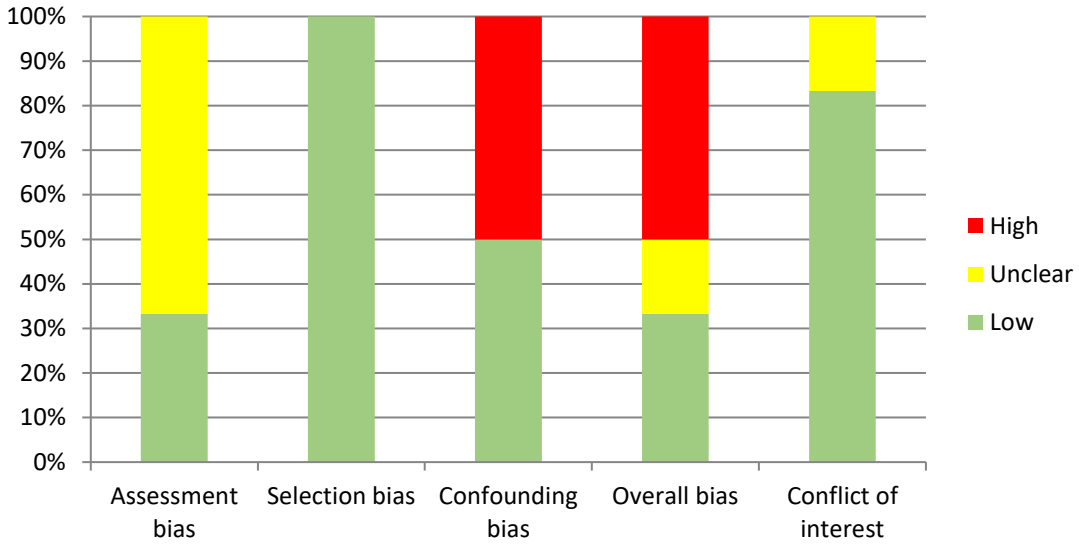
The risk of RC according to SF was categorised as ≥3-4 months vs. <3-4 months. Overall the evidence base was limited due to small numbers of included studies. We found no evidence that the timing of solid food introduction is associated with risk of RC, based on the available data.

Table 6 Characteristics of included studies evaluating SF introduction and rhinoconjunctivitis

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Larsson, 2008 (8)	4779/573 (in 2000), 975(in 2005)	PC	Sweden	Q	ISAAC - current AR	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Zutavern, 2008 (36)	2073/83	PC	Germany	Q	DD	6	LISA study. Population based birth cohort of infants born 1997-1999 at selected maternity hospitals in 4 German cities
Marini, 1996 (13)	359	PC	Italy	Q	Physician assessment	3	Infants with family history of allergy whose mother agreed to participate in an allergy prevention program
Hide, 1981 (16)	843/198	PC	UK	D/Q	Parent reported rhinitis symptoms	1	The Isle of Wight study: born in 1977-1978
Wright, 1994 (17)	747/313	PC	USA	Q	Parent reported AR	6	Tuscon Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984
Van Asperen, 1983 (31)	79/44	PC	Australia	I	Physician assessment	1.3	Cohort recruited from medical service, born in 1980-1981 with family history of atopy

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control, DD: doctor diagnosis of RC, in contrast to 'Physician assessment' where RC diagnosis was always made by a study physician as part of the study protocol.

Figure 21 Risk of bias in studies of SF introduction and rhinoconjunctivitis

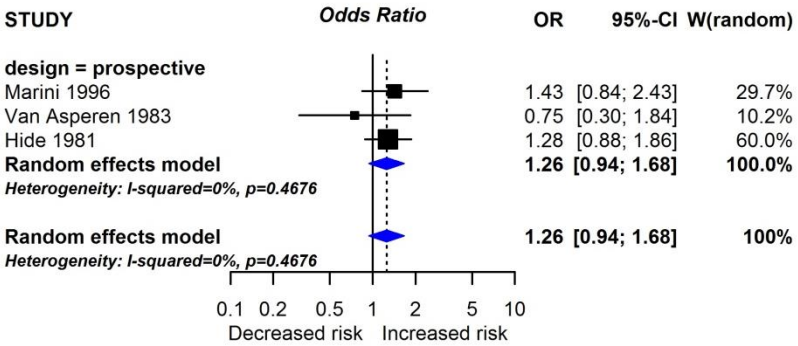


3.2 SF introduction and risk of rhinoconjunctivitis

3.2.1 SF introduction and risk of RC in children aged 0-4 years

Three prospective cohort studies reported OR for RC at age 0-4, in infants with SF ≥3-4 months vs. <3-4 months and are shown in Figure 22. There was no significant association found. The study of Marini reported adjusted data at age 3 and had overall unclear risk of bias due to unclear assessment bias; the other two studies reported unadjusted data at age 1, and are therefore at high risk of confounding bias.

Figure 22 SF ≥3-4 months vs. <3-4 months and RC risk at age 0-4

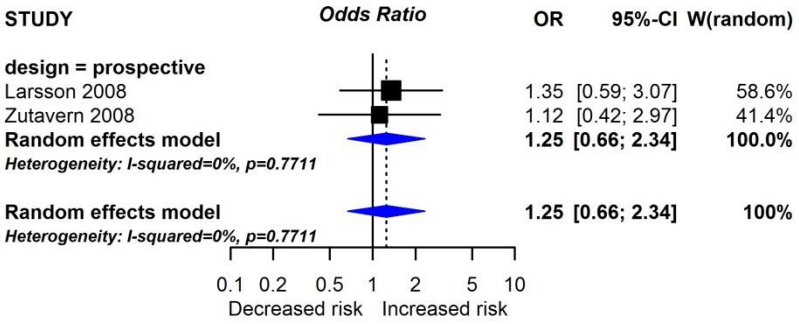


3.2.2 SF introduction and risk of RC in children aged 5-14 years

Two prospective cohort studies reported OR for RC at age 5-14, in infants with SF ≥3-4 months vs. <3-4 months and is shown in Figure 23. There was no significant association found. The study of Zutavern reported adjusted data at age 6 and had overall low risk of bias;

the study of Larsson reported unadjusted data but also stated that there was no significant relationship between SF introduction and RC in adjusted analyses, and had overall low risk of bias.

Figure 23 SF ≥3-4 months vs. <3-4 months and RC risk at age 5-14 years



3.3 Data for SF introduction and RC that couldn't be meta-analysed

Meta-analyses included 5 studies, reporting data on ~ 900 participants with RC. One further study reporting RC in over 300 participants reported no relationship between timing of SF introduction and RC (Table 7).

Table 7 Studies of SF introduction and RC which were not eligible for meta-analysis

Study	Design	Age	N/n cases	Data	Measure	TBF in no AR	TBF in AR	P
Wright, 1994 (17)	PC	6	747/313	Continuous	No relationship between timing of solid food introduction and RC			

4 Conclusion

This report summarises the results of 26 studies investigation the association between total and exclusive breastfeeding duration, timing of solid food introduction and risk of rhinoconjunctivitis. The majority of studies were prospective cohort studies, with one systematic review and one intervention trial. Overall we found no clear evidence to support an association between TBF duration, and RC risk at any age. The data from the intervention trial showed no evidence that promotion of longer TBF duration influences risk of RC – OR 1.1 (95% CI 0.6, 1.9),.One meta-analysis of observational studies found reduced risk of RC at ages 0-4 years associated with EBF ≥3-4 months vs <3-4 months with no statistical heterogeneity, based largely on 2 prospective cohort studies reporting adjusted data. However, statistical significance was borderline, and we were unable to confirm this association using other cutoffs for EBF duration. At other ages there was no association between EBF duration and RC risk. Data for timing of SF introduction and RC risk were limited, but the available data do not support an association between timing of SF introduction and RC.

The possible relationship between EBF duration and RC risk at age 0-4 years makes some physiological sense, and is consistent with findings from the systematic review of Kramer, who evaluated EBF duration in relation to a range of child health outcomes and found some evidence for reduced nasal symptoms with longer EBF duration (25). Most RC in this age group is infective rather than allergic in origin and distinction of the two can be difficult in epidemiological studies. Breastfeeding duration is known to be associated with reduced risk of respiratory and gastrointestinal infections during infancy, so the possible association here may reflect a protective effect of human breast milk through the high immunoglobulin content which is thought to mediate the effects on other infections. The quality of data was limited, especially for analysis of timing of solid food introduction in relation to RC, and more research is needed to clarify whether there is an effect of different infant feeding regimens on upper airway and ocular health.

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