BREASTFEEDING, SOLID FOOD INTRODUCTION AND RISK OF ECZEMA

ROBERT J BOYLE[1], VANESSA GARCIA-LARSEN[2], DESPO IERODIAKONOU[3], JO LEONARDI-BEE[4], TIM REEVES[5], JENNIFER CHIVINGE[6], ZOE ROBINSON[6], NATALIE GEOGHEGAN[6], KATHARINE JARROLD[6], ANDREW LOGAN[6], ANNABEL GROOME[6] , EVANGELIA ANDREOU[7], NARA TAGIYEVA-MILNE[8], ULUGBEK NURMATOV[9], SERGIO CUNHA[10]

[1]Clinical Senior Lecturer, Section of Paediatrics, Imperial College London; [2]Post-Doctoral Research Associate & Honorary Research Fellow Royal Brompton and Harefield NHS Foundation Trust, Respiratory Epidemiology, Occupational Medicine, and Public Health Group, National Heart and Lung Institute, Imperial College London; [3]Post-Doctoral Research Associate, Departments of Paediatric and Respiratory Epidemiology and Public Health Group, Imperial College London. [4]Associate Professor of Community Health Sciences, University of Nottingham; [5]Research Support Librarian, Faculty of Medicine, Imperial College London; [6]Undergraduate medical students, Imperial College London; [7]Research Associate, Imperial Consultants; [8]Research Fellow, University of Aberdeen; [9]Research Fellow, University of Edinburgh; [10]Research Associate, Respiratory Epidemiology and Public Health, National Heart and Lung Institute, Imperial College London

Imperial Consultants,

58 Princes Gate,

Exhibition Road,

London SW7 2PG

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1 Total breastfeeding duration and eczema

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 eczema/atopic dermatitis (AD) risk. In this report AD or eczema refers to any eczema/atopic dermatitis, and 'atopic AD' refers to eczema in association with evidence of IgE sensitisation to dietary or inhalant allergens. A total of 1 cluster randomised controlled trial and 57 observational studies, reported the association between TBF and AD. Of these, 43 were prospective cohort studies, 1 retrospective cohort study, 1 nested case-control study, 3 case control studies, and 9 cross-sectional studies. The majority of studies (n=40) are from Europe – others are from Asia (n=7), North America (n=3) and Australasia (n=3), Africa (n=1), Middle East (n=1) and worldwide (n=2). Overall, valid data on TBF duration in the first 2 years of life and AD risk were available from over 250,000 subjects. Information on AD was obtained from a medical assessment (n=23), parental report (n=15), Hanifin and Rajka criteria or modifications of these (n=8), the ISAAC questionnaire (n=9), self-report (n=1) and unclear methodology (n=1). With regards to time of outcome diagnosis, 33 studies explored the association between TBF duration and AD at age 0-4, 18 at ages 5-14, and six at age 15 and over. For assessment of TBF duration, 10 studies used an interview, 8 parent diaries, and 4 a medical records review; in one study the method of exposure assessment was unclear and in all others (n=24) 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. Approximately 30% of studies had a high risk of bias due to lack of adjustment for confounding bias i.e. no adjusted data presented, and a further 10-15% had a 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 AD 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 LOW certainty evidence (-1 imprecision; -1 inconsistency) of a relationship between breastfeeding promotion and reduced risk of AD in the first year of life; OR 0.54 (95% CI 0.31, 0.95). This effect was not seen at later follow up at age 6-7 years. For observational studies, across all cut-offs where data were available, there was no consistent evidence of a relationship between risk of AD and initiation or prolongation of BF. There was weak evidence that ever BF may be associated with increased AD risk at age 0-4 years; OR 1.15 (1.00, 1.32; I^2=57%). This was not the case in the subgroup of studies with low risk of bias, prospective study design, or adjusted data analysis. Studies which could not be included in meta-analysis, which represented over 16,000 participants in 16 studies, almost universally found no evidence of a relationship between TBF duration and AD.

Table 1 Characteristics of included studies evaluating TBF duration and eczema

Study	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
Hesselmar, 2010 (3)	184	PC	Sweden	I	UK Working Party Criteria	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Abd, 2012 (4)	Unclear	PC	UK	Q	Visible flexural dermatitis; Parent reported eczema	3.5, 7.5	ALSPAC study. Population based cohort of children born 1991-1992.
Purvis, 2005(5)	550	PC	New Zealand	Q	UK Working Party Criteria	3.5	Auckland Birthweight Collaborative study. Birth cohort with representative sample of babies born in 1996-1997
Kull, 2002(6)	3790	PC	Sweden	Q	Parent reported OR DD eczema	2	BAMSE study. Population based cohort of children born between 1994-1996
Berth-Jones, 1997 (7)	413	PC	UK	Q	Physician assessment	1	Infants born in 1992 and registered with the two major Leicester obstetric units
Taylor, 1984 (8)	14498	PC	UK	I/Q	Parent reported eczema	5, 6, 7	British Cohort Studies of children born in England and Wales in 1946; England, Scotland and Wales in 1958 and 1970

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Taylor, 1983 (9)	10886	PC	UK	I	Parent reported eczema	5	CHES study. Population based cohort of children born in England, Scotland, and Wales in 1970
Burr, 1989; Burr, 1993; Burr, 1993 (b) (10-12)	483	PC	UK	D, Q	Physician assessment	1, 7	Infants with family history of allergic diseases in South Wales
Businco, 1987(13)	244	PC	Italy	I	Physician assessment	8	Infants of atopic parents recruited from hospital and born in 1985-1988
Mihrshahi, 2007 (14)	516	PC	Australia	I	Visible flexural dermatitis OR DD eczema	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Bisgaard, 2009 (15)	354	PC	Denmark	Q	Hanifin and Rajka criteria	3	COPSAC study. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001.
Larsson, 2008 (16)	4779	PC	Sweden	Q	ISAAC	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Devereux, 2006 (17)	1704	PC	UK	Q	ISAAC	5	Population based birth cohort of infants born in 1998
Nwaru, 2013(18)	3109	PC	Finland	D	ISAAC	0.5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Farooqi, 1998 (19)	1453	PC	UK	R	DD	16	Representative sample of general practice born in 1975-84
Forster, 1990(20)	145	PC	Germany	Q	Parental report	1.5	Babies hospitalised in 1985
Harris, 2001(21)	622	PC	UK	I	UK Working Party Criteria	2	Population based birth cohort of children born between 1993 and 1995 in three general practices in Ashford
Hikino, 2001(22)	21766	PC	Japan	Q	Physician assessment	1.5	All children born in 1993-1995 attending Well-baby check-ups funded by Fukuoka City
Howie, 1990(23)	618	PC	UK	R/D	Physician assessment	1	Population based birth cohort of infants born between 1983 and 1986 in Dundee
Gruskay, 1982 (24)	908	PC	USA	Q	Physician assessment	3, 5, 15	Children born in 1961-1966 in a private paediatric practice
Alm, 2008 (25)	4941	PC	Sweden	Q	Parent reported eczema	1	Infants of Western Sweden. Population birth cohort of infants born in 2003
Morales, 2012 (26)	467	PC	Spain	Q/I	Parent reported eczema	1	INMA project. Population based birth cohort of infants born 2004-2006

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kemeny, 1991(27)	180	PC	UK	Unclear	Unclear	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Snijders, 2007; Snijders, 2008(28, 29)	2510/ 783	PC	Netherlands	Q	Parent reported eczema	2	KOALA study. Population based birth cohort of infants born between 2000-2002 (conventional and anthroposophic lifestyle)
Wetzig, 2000(30)	475	PC	Germany	Q	Physician assessment	1	LARS study. High allergy risk or low birth weight children born within one year in the City and District of Leipzig
Marini, 1996 (31)	279	PC	Italy	Q	Physician assessment	1	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Miskelly, 1988(32)	482	PC	UK	D	Physician assessment	1	Infants from antenatal clinics with family history of allergy randomised into a dietary intervention program
Moore, 1985(33)	475	PC	UK	D/I	Physician assessment	0.25	Infants born in a hospital in 1979-1980 with family history of eczema or asthma, participating in a dietary intervention program
Morgan, 2004; Morgan, 2004 (b) (34, 35)	257	PC	UK	I	Parent reported eczema; Physician assessment	1, 1.5	Infants from five prospective randomised dietary trials conducted in the UK between 1993 and 1997. One LBW, 2 premature and 2 appropriate weight/gestation cohorts
Bergmann, 2000; Bergmann,	1314	PC	Germany	Q/I	Physician assessment; Hanifin and Rajka criteria	6, 7	MAS study. Atopic risk enriched cohort of infants born in 1990 in 5 German cities

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
2002(36, 37)							
Silvers, 2009 (38)	987	PC	New Zealand	Q	Parent reported eczema	1	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Miyake, 2009(39)	763	PC	Japan	Q	Physician assessment	2	OMCHS study. Population based birth cohort of infants born in 2002-2003
Kerkhof, 2003(40)	304	PC	Netherlands	Q	UK Working Party Criteria	1	PIAMA: population-based born in 1996-1997 (normal risk of disease)
Porch, 1998(41)	130	PC	USA	D	ISAAC - current AD	1	Infants recruited from prenatal services with family history of allergy (high risk of disease)
Pratt, 1984(42)	198	PC	UK	D/I	DD; Physician assessment	4.5, 5	Recruited in antenatal clinics, normal risk of disease
Rothenbacher, 2005(43)	803	PC	Germany	Q/I	DD	2	Recruited from university service, born in 2000-2001 (normal risk of disease)
Ruiz 1992(44)	39	PC	UK	Unclear	Hanifin and Rajka criteria	1	Recruited from hospital and family history of atopy (high risk of disease)

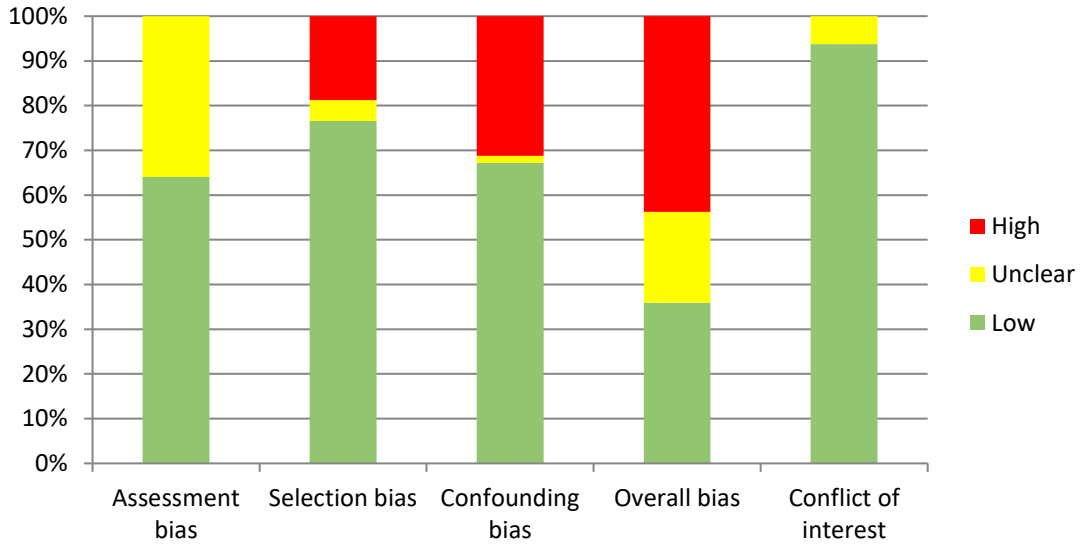
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Saarinen, 1995(45)	150	PC	Finland	R	Parent reported OR DD eczema	5, 17	Recruited from hospital and born in 1975 (normal risk of disease)
Chuang, 2011(46)	18773	PC	Taiwan	R/I	Physician assessment	1.5	Taiwan Birth Cohort Study: population representative sample born in 1995 (normal risk of disease)
Hide, 1981(47)	843	PC	UK	D/Q	DD	1	The Isle of Wight study: born in 1977-1978 (normal risk of disease)
Wang, 2007(48)	1760	PC	Taiwan	Q	DD	0.5	Tiawan National Birth Cohort Study: population representative sample born in 2003 (normal risk of disease)
Zutavern, 2004(48)	604	PC	UK	I	DD	5.5	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Hagendorens, 2005; Sariachvili, 2007(49, 50)	976	PC	Belgium	Q	Parent reported eczema	1	PIPO study: recruited from university service, born 1997-2001 (normal risk of disease)
Sariachvili 2010 (51)	557	NCC	Belgium	Q	ISAAC	4	PIPO: nested case control study within the PIPO cohort
Monego, 1989(52)	144	RC	Italy	D	DD	4	144 Italian infants retrospectively followed to examine association between breastfeeding and allergic diseases

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 1981 (53)	470	CC	Canada	I	Hanifin and Lobitz criteria	<20	Cases and controls were1 month to 20 years old children attending dermatology clinics visits
Ghaderi, 2014 (54)	200	CC	Iran	I	DD	5	Unclear source of population. Sex and age matched controls
Haileamlak, 2005 (55)	732	CC	Ethiopia	I	ISAAC	5	Children age 1- 5 years. Cases were defined according to the ISAAC criteria for AD and confirmed by clinical examination
Flohr, 2011 (56)	51, 119	CS	Worldwide	Q	Parent reported eczema	12	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries
Civelek, 2001(57)	1533	CS	Turkey	Q	ISAAC	11	Representative sample of schoolchildren in 5 cities
Nakamura, 1999(58)	3850	CS	Japan	Q	DD	3	All 3 year old children participating in a health check-up in 1997
Tanaka, 2009(59)	1957	CS	Japan	Q	ISAAC - current AD	3	Fukuoka Child Health Study. All 3-year old children examined at public public health centre's in Fukuoka city
Girolomoni,2003(60)	1369	CS	Italy	Q	UK Working Party Criteria	9	Representative sample of children attending the fourth grade at elementary school

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Björkstén, 2011(61)	103716	CS	Worldwide	Q	ISAAC - AD ever	7	ISAAC Phase 3: Schoolchildren aged 6-7 years from different countries and geographic regions
Karino, 2008(62)	9615	CS	Japan	Q	Self-reported AD	18	University students aged 18–19 years enrolled from 2003 through 2005.
Kurt, 2007 (63)	25843	CS	Turkey	Q	Parent reported current eczema	15	Prevalence and Risk Factors of Allergies in Turkey (PARFAIT): population representative sample of children aged 9-15 years old (normal risk of disease0
Selcuk, 1997 (64)	5412	CS	Turkey	Q	Parent reported current eczema	12	Children 7-12 yrs. from 18 primary schools (normal risk of disease)

Q: questionnaire, I: interview, R: medical records, D: diary, PC: prospective cohort, RC: retrospective cohort, NCC: nested case-control, CC: case-control, CS: Cross-sectional, AD: eczema, DD: doctor diagnosis of AD, in contrast to 'Physician assessment' where AD 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 eczema



1.2 Total breastfeeding duration and eczema

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 reduced odds of AD at age 1 year – cluster adjusted odds ratio 0.54 (95% CI 0.31, 0.95). This outcome was an unblinded assessment of AD by study paediatricians, and the authors reported poor agreement between sites in the outcome measure. The effect on AD was not seen at later follow-up in the same trial at age 6.5 years (OR 1.0 95% CI 0.50, 1.80). Certainty of evidence was downgraded for imprecision (wide confidence intervals) and for inconsistency with later outcome data and with the findings of observational studies. All other evidence was derived from observational studies.

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

1.2.1.1 TBF Ever vs. Never

Figure 2 shows the outcomes of 20 eligible observational studies reporting OR for TBF never vs ever and AD. The pooled data show increased risk of AD in breastfed infants, with borderline statistical significance and high heterogeneity (I^2=57%). The outlier study of Purvis had very few participants in the reference group of never breastfed (n=26, including just 3 cases of AD), which may account for the extreme OR and wide confidence intervals.

A Funnel plot to explore publication bias is shown in

Figure 3, and shows no clear evidence of publication bias.

Subgroup analyses are shown in Table 2. Here we did not find clear subgroup differences, but there was a trend to different outcome according to risk of allergic disease. Those children with no increased risk of allergic disease (i.e. not selected for family history of allergic problems) had the strongest association between TBF initiation and increased AD. Heterogeneity was high (I^2=53%).

Analysis of dose-response relationship, using studies with short, medium or long duration/cut-off for the exposed group, with 'never BF' as reference group, showed some evidence of a dose-response relationship between TBF and AD although with moderate to high heterogeneity in each analysis (Figure 4 and 5).

Figure 2 TBF Ever vs. Never and risk of eczema at age 0-4 years

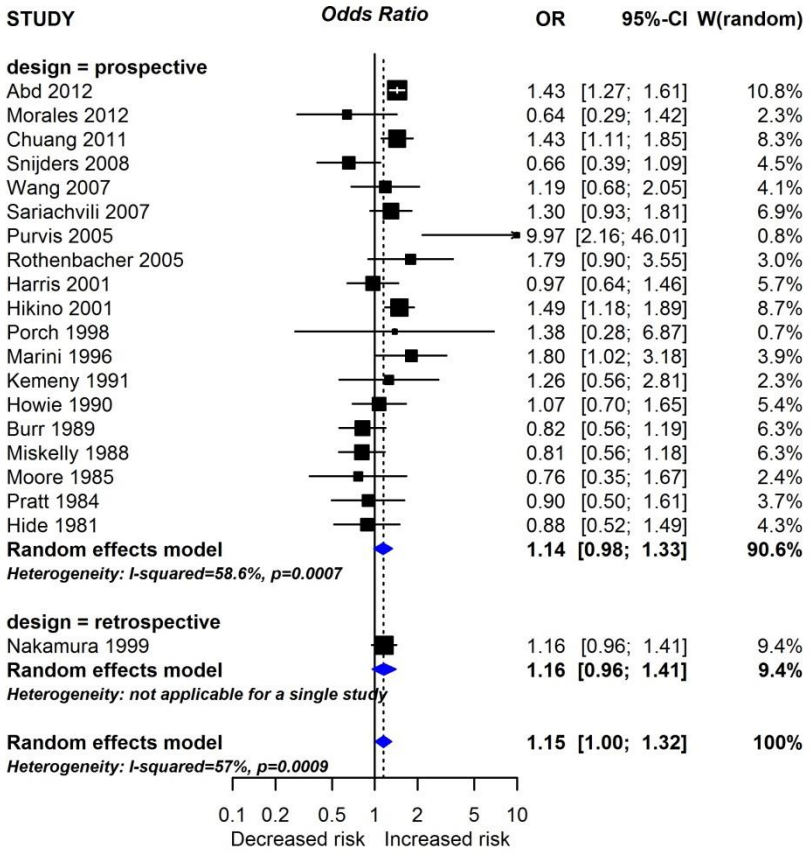
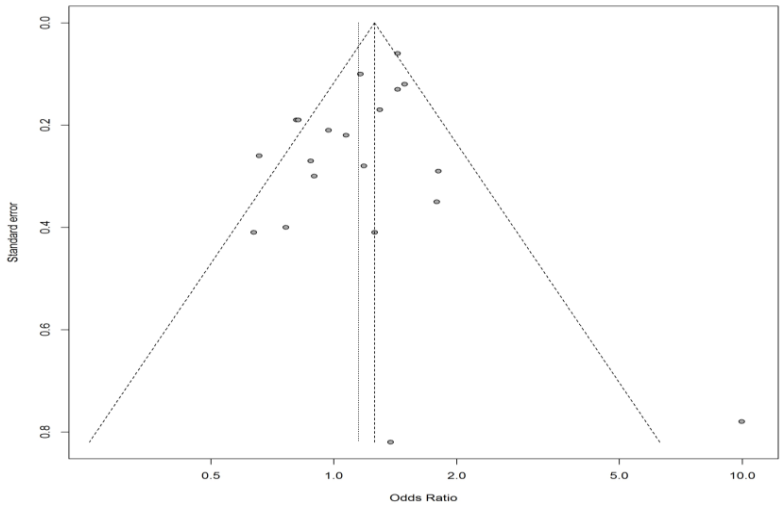


Figure 3 Risk of publication bias in studies investigating TBF Ever vs. Never and risk of eczema in children aged 0-4 years



Egger's test p-value = 0.116

Table 2 Subgroup Analyses of risk of atopic dermatitis and TBF Ever vs. Never in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between group difference
Overall	20	1.15 [1.00; 1.32]	57.0	
Adjusted	7	1.17 [0.87; 1.57]	70.1	Not tested
Unadjusted	19	1.78 [1.03; 1.35]	58.3	
Study Design – Prospective	19	1.14 [0.98; 1.33]	58.6	0.90
Study Design – Retrospective	1	1.16 [0.96; 1.41]	-	
Risk of disease – High	5	0.97 [0.70; 1.34]	40.0	0.22
Risk of disease – Normal	15	1.21 [1.05; 1.39]	53.0	
Risk of bias – Low	7	1.02 [0.80; 1.32]	55.8	0.23
Risk of bias – High/Unclear	13	1.22 [1.04; 1.44]	54.3	

Figure 4 TBF short duration (1-3 months) vs. never and risk of eczema at age 0-4 years

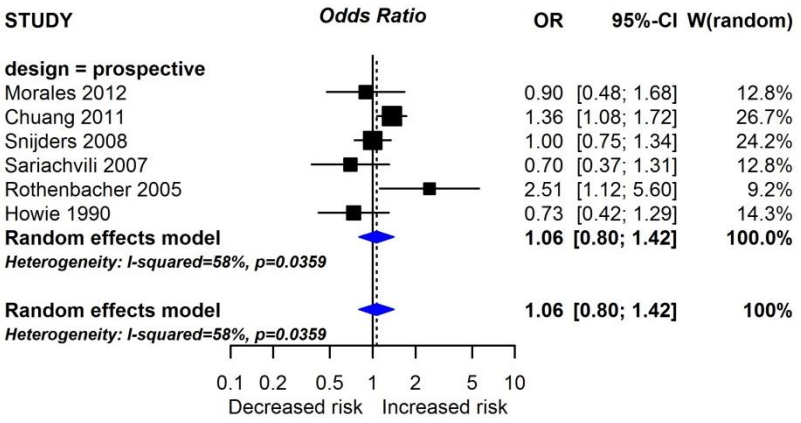


Figure 5 TBF medium duration (4-6 months) and risk of eczema at age 0-4 years

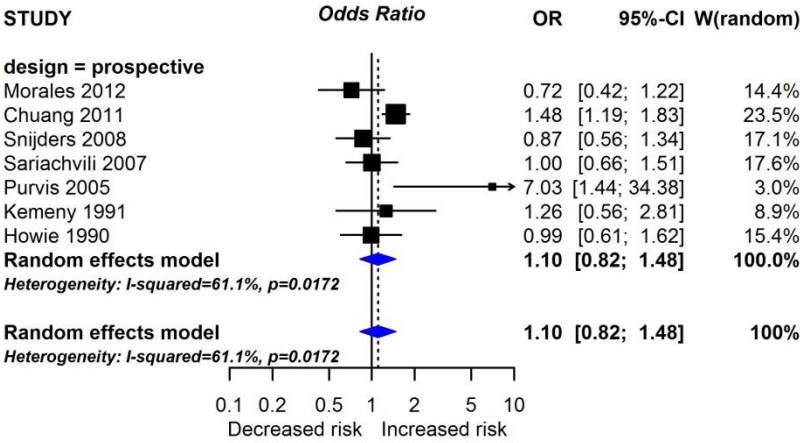
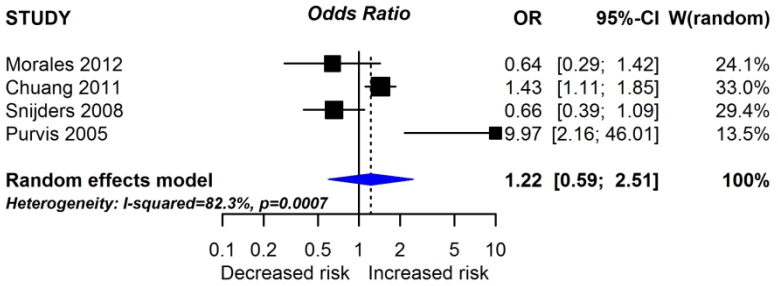


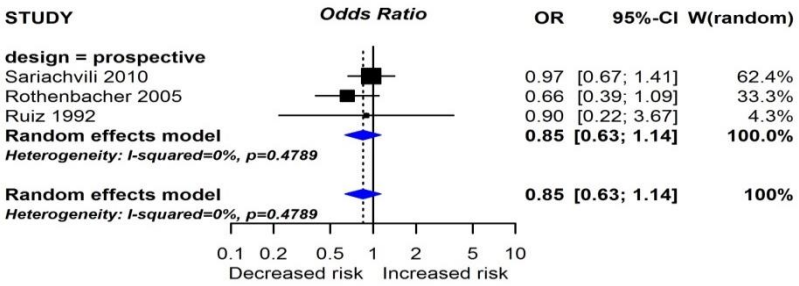
Figure 6 TBF long duration (≥7-12 months) and risk of eczema at age 0-4 years



1.2.1.2 TBF ≥3-4 months vs. <3-4 months

One nested case control study and two prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with TBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 7. They show no evidence of association between TBF and AD risk, with low statistical heterogeneity. All studies report unadjusted data, so carry a high risk of confounding bias.

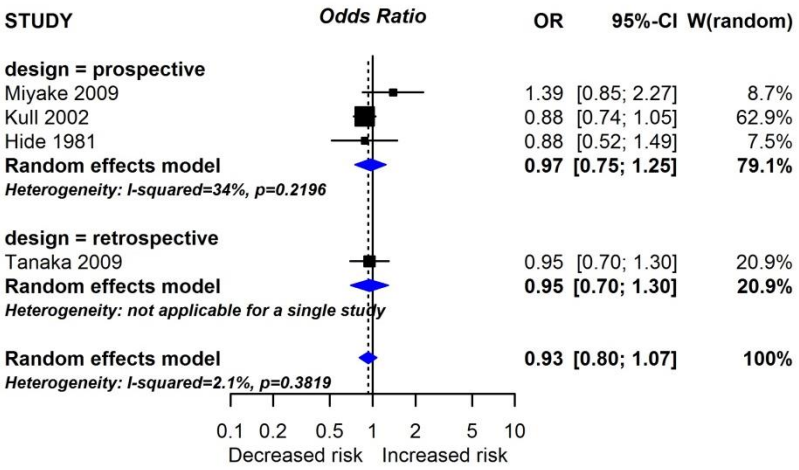
Figure 7 TBF ≥3-4 months vs. <3-4 months and risk of eczema at age 0-4 years



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

One cross-sectional and three prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with TBF for ≥5-7 months vs. <5-7 months duration and are shown in Figure 8. They show no evidence of association between TBF and AD risk, with low statistical heterogeneity. Three of the four studies report adjusted data, and the study of Hide reported unadjusted data.

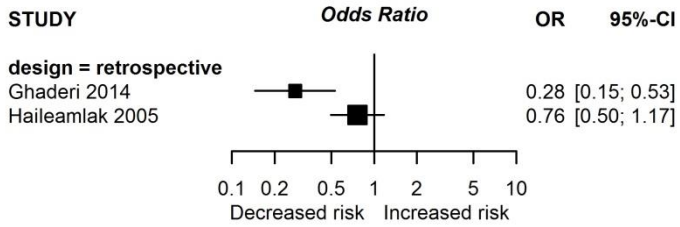
Figure 8 TBF ≥5-7 months vs. <5-7 months and risk of eczema at age 0-4 years



1.2.1.4 TBF ≥8-12 months vs. <8-12 months

Two case-control studies reported data that could be pooled to calculate OR for AD, in infants with TBF for ≥12 months vs. <12 months duration and are shown in Figure 9. Due to extreme statistical heterogeneity (I^2= 84.6%) we did not undertake pooled analysis. The study of Haileamlak reported adjusted data, and the study of Ghaderi reported unadjusted data.

Figure 9 TBF ≥8-12 months vs. <8-12 months and risk of eczema at age 0-4 years



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

1.2.2.1 TBF Ever vs. Never

Figure 10 shows the outcomes of 13 eligible observational studies reporting OR for TBF never vs ever and AD at age 5-14 years. The pooled data show association between breastfeeding and risk of AD, but with extreme statistical heterogeneity (I^2=79%). The analysis was dominated by the ISAAC phase II and III surveys published in 2011, and the British Birth Cohorts published in 1984. A Funnel plot to explore publication bias is shown in Figure 11. There is no asymmetry, and Egger's test does not suggest clear evidence of publication bias.

Subgroup analyses are shown in Table 3. Here we did not find clear subgroup differences, but of note the studies at low overall risk of bias, using prospective study design and reporting adjusted data found least evidence of an association between TBF any vs never and AD risk, compared with studies at high risk of bias, with retrospective design or reporting unadjusted data. However all subgroup analyses had moderate, high or extreme levels of statistical heterogeneity.

Analysis of dose response, with forest plots for never versus short, medium and long duration/cut-off of TBF showed no evidence of a dose-response relationship between TBF duration and risk of AD at age 5-14 years (Figure 12, Figure 13, and Figure 14).

Figure 10 TBF Ever vs. Never and risk of eczema at age 5-14 years

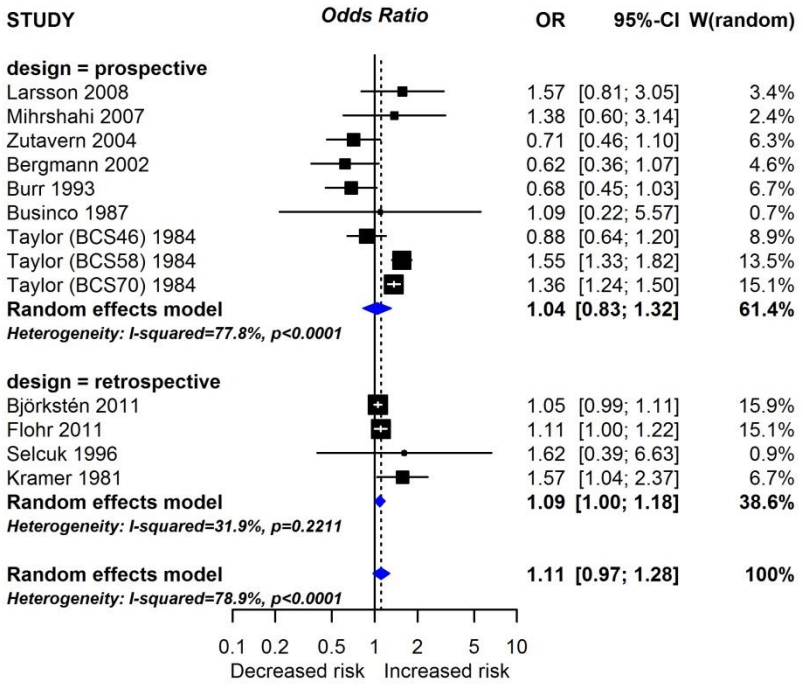
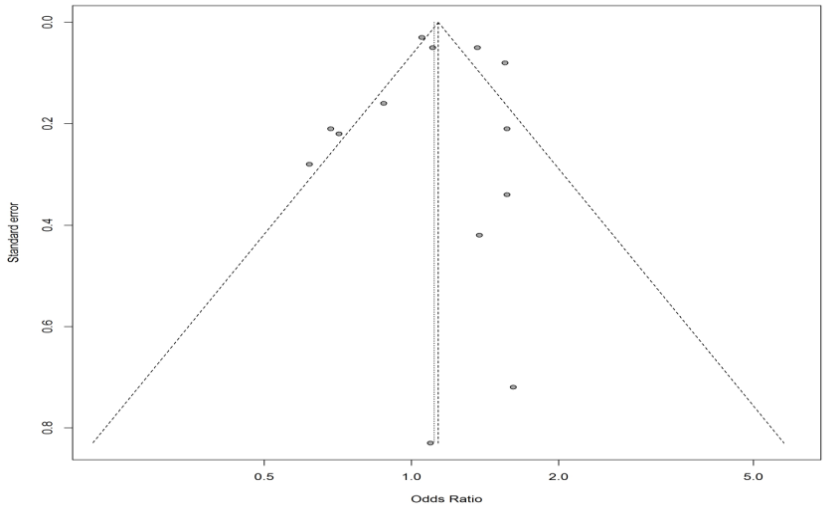


Figure 11 Risk of publication bias in studies investigating TBF and risk of eczema in children aged 5-14 years



Egger's test p-value = 0.139

Table 3 Subgroup analyses of risk of eczema 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 used)	13	1.11 [0.97; 1.28]	78.9	
Adjusted	6	1.04 [0.93; 1.15]	40.9	Not tested
Unadjusted	9	1.17 [0.94; 1.44]	75.6	
Study Design – Prospective	9	1.04 [0.83; 1.31]	77.8	0.72
Study Design – Retrospective	4	1.09 [1.00; 1.18]	31.9	
Risk of disease – High	3	0.84 [0.54; 1.31]	15.7	0.20
Risk of disease – Normal	10	1.14 [1.00; 1.32]	82.3	
Risk of bias – Low	7	0.95 [0.79; 1.17]	39.6	0.057
Risk of bias – High/Unclear	6	1.24 [1.03; 1.50]	80.6	

Figure 12 TBF short duration (1-3 months) vs. never and risk of eczema at age 5-14 years

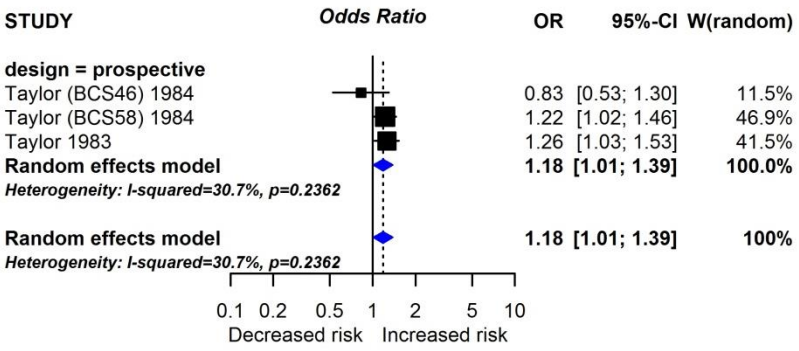


Figure 13 TBF medium duration (4-6 months) vs. never and risk of eczema at age 5-14 years

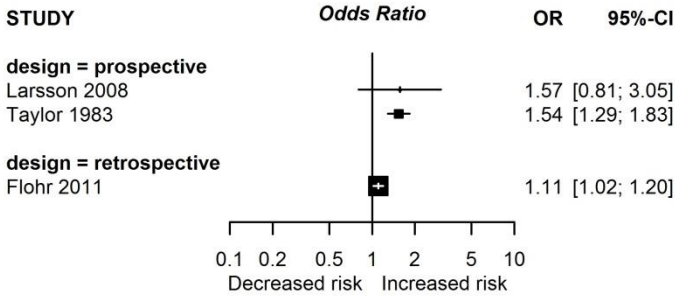
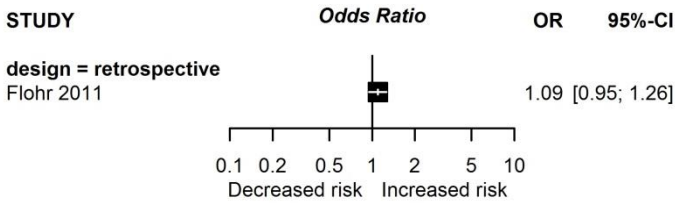


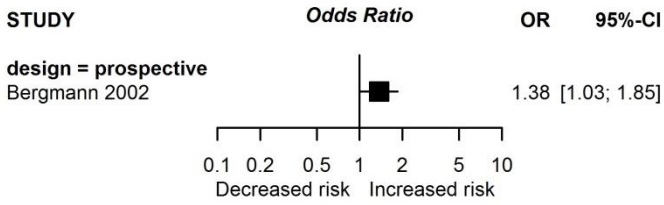
Figure 14 TBF long duration (7-12 months) vs. never and risk of eczema at age 5-14 years



1.2.2.2 TBF ≥1-2 months vs. <1-2 months

One study reported data for TBF ≥1-2 months vs. <1-2 months duration and risk of AD at age 5-14 years, and is shown in Figure 15. The study suggests increased AD risk with increased TBF duration. This is a prospective cohort study with low risk of bias in all domains, which reported adjusted data for several TBF cut-offs and found an overall significant association between increased TBF duration and increased AD risk - OR 1.03 (1.00, 1.06) for each additional month TBF P=0.034.

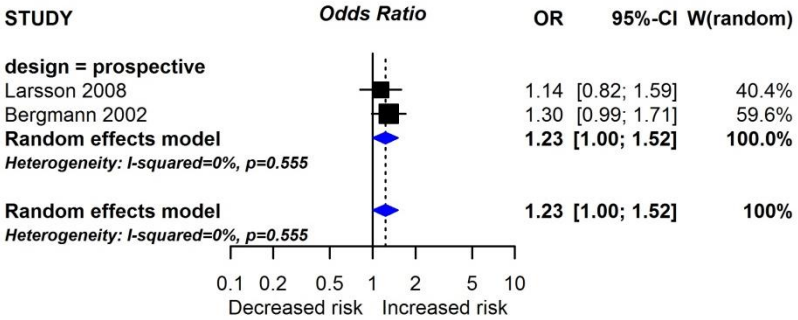
Figure 15 TBF ≥1-2 months vs. <1-2 months and risk of eczema at age 5-14 years



1.2.2.3 TBF ≥3-4 months vs. <3-4 months

Two studies reported data for TBF ≥3-4 months vs. <3-4 months duration and risk of AD at age 5-14 years, and are shown in Figure 16. They show borderline significant increase risk of AD with prolonged breastfeeding (≥3-4 months), without statistical heterogeneity. Both studies are prospective cohort studies in a normal risk population, with low risk of bias in all domains, reporting adjusted OR.

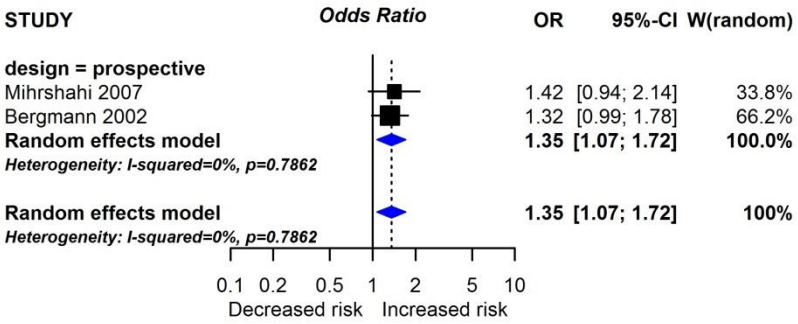
Figure 16 TBF ≥3-4 months vs. <3-4 months and risk of eczema at age 5-14 years



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

Two studies reported data for TBF ≥5-7 months vs. <5-7 months duration and risk of AD at age 5-14 years and are shown in Figure 17. They show increased risk of AD with longer TBF, with no statistical heterogeneity. Both studies are prospective cohort studies with low risk of bias in all domains, reporting adjusted OR.

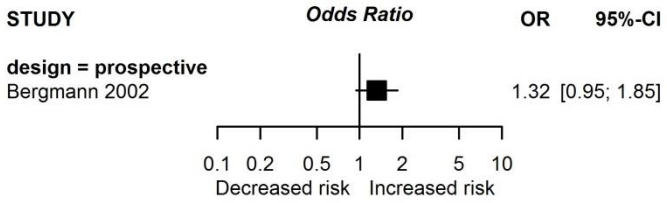
Figure 17 TBF for ≥5-7 months vs. <5-7 months and risk of eczema at age 5-14 years



1.2.2.5 TBF ≥8-12 months vs. <8-12 months

One study reported data for TBF ≥8-12 months vs. <8-12 months duration and risk of AD at age 5-14 years, and is shown in Figure 18. The study found no significant association using this cut-off. As mentioned above, the authors found an overall significant association between increased TBF duration and increased AD risk in this study.

Figure 18 TBF for ≥8-12 months vs. <8-12 months and risk of eczema at age 5-14 years

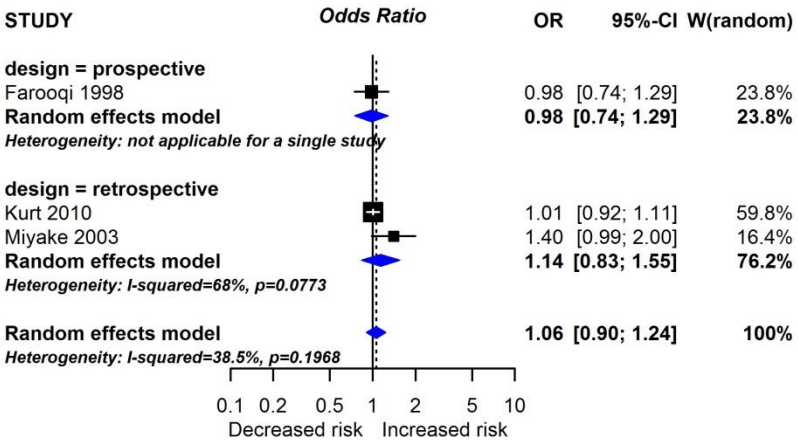


1.2.3 TBF and risk of eczema in children aged 15+ years

1.2.3.1 TBF Never vs. Any

Figure 19 shows the outcomes of 3 eligible observational studies reporting OR for TBF never vs ever and AD at age 15+ years. The pooled data show no association between breastfeeding and risk of AD, but with moderate statistical heterogeneity (I^2=38%). The studies of Miyake and Kurt report adjusted data from cross-sectional surveys; the study of Farooqi reports unadjusted data from a prospective cohort study – they do state in the manuscript that adjusted analysis showed no significant association between TBF and AD. The study of Kurt was assessed as at low risk of bias on all domains, the other two studies as at high risk of bias overall. These differences may be relevant to the statistical heterogeneity seen in the meta-analysis.

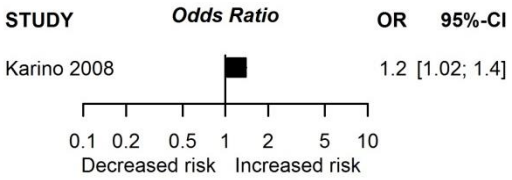
Figure 19 TBF Never vs. Any and risk of eczema at age 15+ years



1.2.3.2 TBF ≥3-4 months vs. <3-4 months

One study reported data for TBF ≥3-4 months vs. <3-4 months duration and risk of AD by age 18 years in a cross sectional survey reporting adjusted data. As shown in Figure 20, there was an association between longer TBF duration and increased risk of AD, with borderline statistical significance.

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



1.3 Data for TBF and risk of eczema that couldn't be analysed

A further 14 prospective cohort studies and 2 cross-sectional studies reported relevant data from over 16000 study participants, which could not be included in meta-analysis. These studies are summarised in Table 4. In one small prospective cohort study there was reduced AD associated with TBF ≥5 months. In all other studies and analyses reported there was no association found between TBF and AD.

Table 4 Studies investigating the association between TBF duration and eczema which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n	Data	Measure	TBF in AD	TBF in No AD	P
Berth-Jones, 1997 (7)	PC	AD	1	413	Continuous	Average	6.2	5.7	NS
Hesselmar, 2010 (3)	PC	AD	1.5	184	Continuous	Median (IQR)	6.7 (6, 9)	7.2 (4, 10)	0.82
Forster, 1990 (20)	PC	AD	1.5	145	Continuous	No significant association between TBF duration and AD risk			
Alm, 2008 (25)	PC	AD	1	4941	Continuous	No significant association between TBF duration and AD risk			
Morgan, 2004 (35)	PC	AD	1	257	Continuous/ Categorical	No significant association between TBF duration and AD risk			
Kerkhof, 2003 (40)	PC	AD	1	304	Continuous	No significant association between TBF duration and AD risk			
Nwaru, 2013 (18)	PC	AD	5	3109 / 476	Continuous	No significant association between TBF duration either as a categorical or continuous variable in adjusted analyses, and risk of AD up to age 5. Median TBF 7 (4, 11) AD; 7 (4, 11) no AD. P=0.57			

Study	Design	Outcome	Age	N/n	Data	Measure	TBF in AD	TBF in No AD	P
Silvers, 2009 (38)	PC	AD	1	987	Continuous	No significant association between TBF duration and AD. Adjusted OR 1 (0.98-1.03) per month increase in TBF. P=0.79			
Bisgaard, 2009 (15)	PC	AD	3	354	Continuous	No significant association between TBF duration and AD. Adjusted OR 2.8 (0.9-9.0) per year increase in TBF. P=0.10			
Hagendorens, 2005 (49)	PC	AD	1	669	Categorical	No significant association between TBF ever vs never, and AD. OR>1, data in graphical form. NS			
Monego 1989 (52)	PC	AD	4	144	Categorical	No significant association between TBF duration >1 month and AD.			
Wetzig, 2000(30)	PC	AD	1	323	Categorical	Significantly reduced risk of AD with TBF >5 vs <5 months			
Civelek, 2001(57)	CS	AD	11	1533 /743	Continuous	No significant association between TBF duration and AD risk. Mean duration 11.0 months AD, 11.7 months No AD			
Devereux 2006 (17)	PC	AD	5	1704	Categorical	No significant relationship between TBF ever vs never and AD risk			
Girolomoni,2003 (60)	CS	AD	9	1369	Categorical	No significant relationship between TBF ever vs never and AD risk			

Study	Design	Outcome	Age	N/n	Data	Measure	TBF in AD	TBF in No AD	P
Saarinen, 1995(45)	PC	AD	5	150	>1	No significant relationship between TBF <1 month, 1-6 months, >6 months and AD at 5 or 17 years			

2 Exclusive Breastfeeding Duration and Eczema

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

Table 5 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 45 observational studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of AD. Of these, 37 were prospective cohort studies, 3 case-control studies and 5 cross-sectional studies. Most studies (n=30) are from Europe – others are from Australasia (n=6), Asia (n=5), North America (n=3), Middle East (n=2) and worldwide (n=1). Overall, valid data on EBF duration and AD risk were available from over 100,000 subjects. Information on AD was obtained mainly from a medical assessment in 21 studies, using Hanifin and Rajka criteria or adaptations of these (n=12), via parental report (n=7), using the ISAAC questionnaire (n=5), and by unclear methodology in 2 studies. With regards to time of outcome diagnosis, 25 studies explored the association between EBF duration and AD at age 0-4 years, when most AD begins, 17 evaluated AD at age 5-14 years, and five at age 15-44 years. Most studies used a questionnaire to assess the exposure (EBF), 11 used an interview, 6 used a diary, one medical records and in 3 studies the method was unclear.

Risk of bias is shown in Figure 21. 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. Over half of studies had unclear risk of assessment bias, mainly due to unclear method for assessing/classifying EBF duration. Risk of conflict of interest was generally assessed as low.

Where data were available, three levels of comparison were used to assess the risk of AD 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. Across all cut-offs there was no consistent evidence of a lower risk of AD if EBF was prolonged. In general, there were only small numbers of studies with available data in each analysis, and a significant number of studies and participants could only be analysed in narrative form due to the way the data were presented (Table 9). The relatively large number of observational studies and participants did not suggest that there is likely to be an association between EBF duration and AD risk. We did

however find some evidence for gene-environment interaction in the relationship between EBF duration and AD risk.

Table 5 Characteristics of included studies evaluating EBF duration and eczema

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer 2012 (65)	3618	SR of PC	Finland/Belarus	-	#1 Hanifin and Rajka #2 ISAAC	1, 5-6.5	Study #1: Infants of atopic parents Study #2: Healthy, term, breastfed newborns participating in a breastfeeding promotion intervention trial
Kajosaari, 1991 (66)	135	PC	Finland	Unclear	Hanifin and Rajka	1, 5	Solid food introduction at 6 months versus 3 months, in exclusively breastfed infants
Ludvigsson, 2005 (67)	8346	PC	Sweden	Q	Parent reported eczema	1	ABIS study. Population based study of babies born between Oct 1997 and Oct 1999.
Hesselmar 2010 (3)	184	PC	Sweden	I	UK Working Party Criteria	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Purvis, 2005 (5)	550	PC	New Zealand	Q	UK Working Party Criteria	3.5	Auckland Birthweight Collaborative study. Birth cohort with representative sample of babies born in 1996-1997
Kull, 2002; Kull, 2005; Kull, 2009 (6, 68, 69)	3791	PC	Sweden	Q	Parent report OR DD eczema (+/- sIgE)	2, 4, 8	BAMSE study. Population based cohort of children born between 1994-1996

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Besednjak-Kocijancic, 2010 (70)	408	PC	Slovenia	Unclear	Unclear	1, 5	Infants with a positive history of parental allergy
Peters, 1987 (71)	11920	PC	UK	Q	Parent reported eczema	5	British Cohort Study: sample of all infants born in 1970 in Britain
Mihrshahi, 2007 (14)	516	PC	Australia	I	Visible flexural dermatitis OR DD eczema	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Fergusson, 1982; Fergusson 1990 (72)	1175	PC	New Zealand	R/D/I	DD eczema; DD eczema for >=3 years needing medication	1, 10	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Cogswell, 1987 (73)	73	PC	UK	D	Physician assessment (+ SPT)	5	Birth cohort of infants with family history of hay fever or asthma
Giwercman, 2010 (74)	306	PC	Denmark	I	Hanifin and Rajka criteria	2	COPSAC study. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001.
Benn, 2004; Linneberg, 2006 (75, 76)	34793	PC	Denmark	Q/I	Physician assessment; Parent reported eczema	1.5	DNBC. Population based birth cohort of children born between 1997-2002

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Nwaru, 2013 (18)	3109	PC	Finland	D	ISAAC	5	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study 1998 - 2000
Laubereau, 2003 (77)	2251	PC	Germany	I	DD	3	GINI study. Term newborn infants born 1995-8 were recruited from 2 regions of Germany to participate into an intervention program
Arshad, 1992 (78)	1167	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
Jedrychowski, 2011 (79)	469	PC	USA and Poland	I	Physician assessment	1	Birth cohort of full-term infants born between 2001 and 2004
Kemeny, 1991 (27)	180	PC	UK	Unclear	Unclear	1	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Kitz, 2006 (80)	131	PC	Germany	D	Hanifin and Rajka criteria	1	Birth cohort of infants at increased risk for atopy participate in RCT on infant feeding intervention
Marini, 1996 (31)	359	PC	Italy	Q	Physician assessment	1	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Midwinter, 1987 (81)	455	PC	UK	Unclear	DD	5	Children born to parents with a family history of atopy in 1979-1981

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Gruber 2010 (82)	300	PC	Netherlands, Austria, Switzerland, Italy, Germany	Q	Hanifin and Rajka criteria	1	MIPS-1 study. Infants born in 2006 without family history of allergy, randomised to intervention if fully formula fed < 8 weeks
Moore, 1985 (33)	475	PC	UK	D/I	Physician assessment	0.25	Infants born in a hospital in 1979-1980 with family history of eczema or asthma (high risk of disease)
Nentwich, 2009 (83)	121	PC	Germany	Q/I	DD	0.5	Newborns with a hereditary risk for atopy
Silvers, 2009 (38)	987	PC	New Zealand	Q	Parent reported eczema	1	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Miyake, 2009 (39)	763	PC	Japan	Q	Physician assessment	2	OMCHS study. Population based birth cohort of infants born in 2002-2003
Pesonen, 2006 (84)	160	PC	Finland	I	Physician assessment	5, 20	Population based birth cohort of infants born in 1981
Kerkhof, 2003 (40)	304	PC	Netherlands	Q	UK Working Party Criteria	1	PIAMA: population-based born in 1996-1997 (normal risk of disease)
Pratt, 1984 (42)	198	PC	UK	D/I	Physician assessment	5	Recruited in antenatal clinics, normal risk of disease

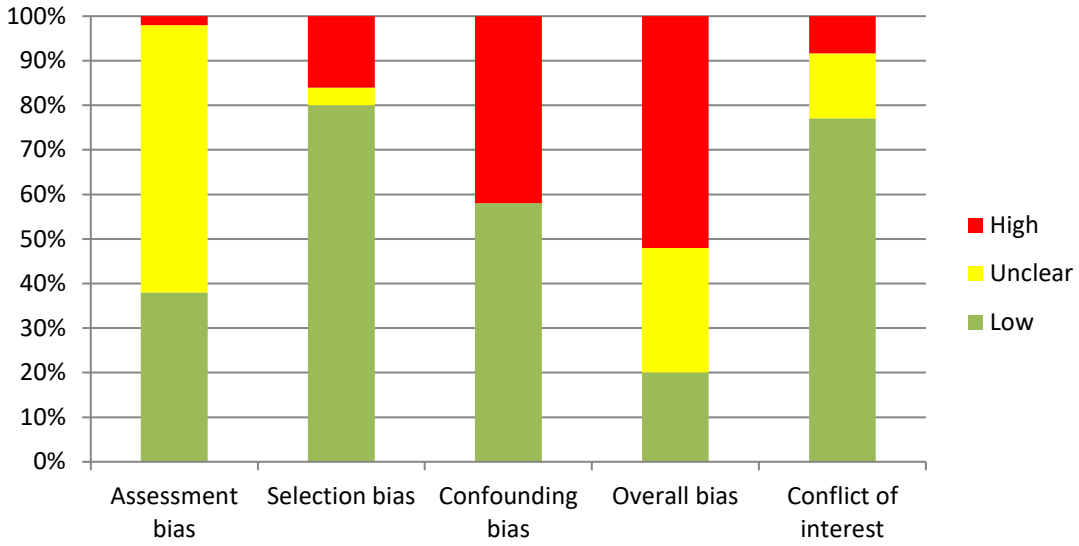
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Kramer, 2003; Kramer, 2009 (85, 86)	2951	PC	Belarus	I	Physician assessment// ISAAC	1, 6.5	PROBIT study: recruited in hospitals , born 1996-1997 (normal risk of disease)
Moore, 2004 (87)	1005	PC	USA	Q	DD	0.5, 6.5	PROJECT VIVA: hospital based and born 1998-2002 (normal risk of disease)
Saarinen, 1979 (88)	177	PC	Finland	Q	Physician assessment	1	Recruited from hospital and born in 1975 (normal risk of disease)
Siltanen,2003 (89)	285	PC	Finland	Q	Hanifin and Rajka criteria	4	Infants recruited from maternal hospital born in 1994-1995 (normal risk of disease)
Shohet, 1985 (90)	368	PC	Israel	I	Hanifin and Lobitz criteria	0.5	Cohort born in 1980 (normal risk of disease)
Dunlop, 2006 (91)	1326	PC	Slovakia	Q	Physician assessment	1	Recruited from hospital, born 1997-1999 (normal risk of disease)
Matheson, 2007 (92)	5729	PC	Tasmania	Q	Parent reported eczema	44	Tasmanian ASTHMA Study: population based born in 1961 (normal risk of disease)
Wang, 2007 (48)	1760	PC	Taiwan	Q	DD	0.5	Tiawan National Birth Cohort Study: population representative sample born in 2003 (normal risk of disease)
Van Asperen, 1983 (48)	79	PC	Australia	I	Physician assessment	1	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
							disease)
Zutavern 2004 (93)	604	PC	UK	I	DD	5.5	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Amri 2012 (94)	343	CC	Saudi Arabia	Q	Hanifin and Rajka criteria	<15	Cases from hospital, source of control unknown
Sahakyan, 2006 (95)	240	CC	Armenia	Q	UK Working Party Criteria	7	Hospital-based study with matched controls (low risk of disease)
Kramer, 1981 (31)	142	CC	Canada	I	Hanifin and Lobitz criteria	<20	Cases and controls were1 month to 20 years old children attending dermatology clinics visits
Tanaka, 2009 (59)	1957	CS	Japan	Q	ISAAC - current AD	3	Fukuoka Child Health Study. All 3-year old children examined at public health centres in Fukuoka city
Civelek, 2001 (57)	1533	CS	Turkey	Q	ISAAC	11	Representative sample of schoolchildren in 5 cities
Ehlayel, 2008 (96)	1278	CS	Qatar	Q	Parent reported eczema	5	Children 0-5 years old attending primary healthcare centres for routine immunisation
Flohr,2011(56)	51 119	CS	Worldwide	Q	Parent reported eczema	12	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Miyake, 2003 (97)	6845	CS	Japan	Q	ISAAC - current AD	15	12-15 years old children from all public junior high schools in Suita, Japan.

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

Figure 21 Risk of bias in studies of exclusive breastfeeding duration and eczema



2.2 Exclusive breastfeeding duration and eczema

2.2.1 EBF duration and risk of eczema in children aged 0-4 years

2.2.1.1 EBF ≥0-2 months vs. <0-2

Seven prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 20. They show no association between EBF duration and AD risk, with high statistical heterogeneity. Most studies in this meta-analysis were at high risk of bias due to reporting unadjusted data, including those with most extreme OR, which may account for some of the statistical heterogeneity. Subgroup analysis (Table 6) did not identify significant differences by subgroup in this outcome.

Figure 22 EBF ≥0-2 months vs. <0-2 months and risk of eczema at age 0-4 years

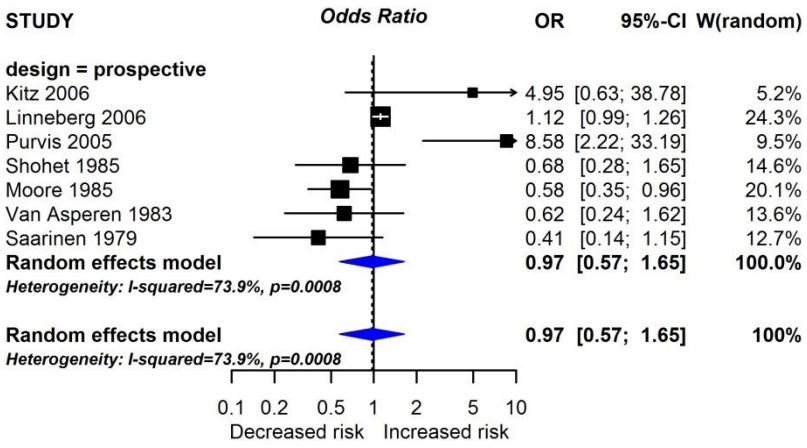


Table 6 Subgroup Analyses EBF duration ≥0-2 vs. <0-2 months and risk of AD at 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	7	0.97 [0.57; 1.65]	73.9	
Adjusted	1	1.12 [0.99; 1.26]	--	Not tested
Unadjusted	6	1.01 [0.47; 2.19]	72.6	
Study Design – Prospective	7	0.97 [0.57; 1.65]	73.9	1.00
Study Design – Retrospective	0	-	-	
Risk of disease – High	3	0.77 [0.35; 1.72]	49.5	0.51
Risk of disease – Normal	4	1.14 [0.50; 2.60]	77.9	
Risk of bias – Low	1	0.58 [0.35; 0.96]	--	0.11
Risk of bias – High/Unclear	6	1.13 [0.59; 2.17]	70.6	

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

1.1.1.1 Systematic reviews and intervention trials

As shown in Table 7, the single systematic review found no evidence that exclusive/predominant breastfeeding for 6 months, compared with exclusive/predominant breastfeeding for 3 months, influenced risk of AD at 1 or 5 years. There was evidence of reduced AD at 1 year with prolonged EBF, from the study of Kajosaari, but the study of Kramer found no relationship, yielding significant statistical heterogeneity between the 2 studies. Of note, the study of Kramer separately reported reduced AD at 12 months in centres randomised to a breastfeeding promotion programme (OR 0.54 95% CI 0.30, 0.95), as discussed under 'TBF' in this report. The study of Kajosaari reported no effect on AD at age 5 years (Table 7), and the study of Kramer separately reported no effect on AD at age 6.5 years (OR 1.0 95% CI 0.50, 1.80).

Table 7 EBF for 6 months versus 3 months and risk of RC

Study	Outcome measure	No. participants (studies)	Outcome (95% CI)
Kramer 2012 (98) Kajosaari (66) Kramer 2007 (2)	AD at 1 year	3618 (2)	RR 0.73 (0.49, 1.08) I^2=78%
Kramer 2012 (98) Kajosaari (66)	AD at 5 years	3584 (2)	RR 0.97 (0.50, 1.89)

Data shown are from analyses of the trials of Kramer and Kajosaari in the 2012 Cochrane review of Kramer (98).

1.1.1.2 Observational studies

Eighteen observational studies reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥3-4 months vs. <3-4 months duration and are shown in Figure 22. They show reduced risk of AD with increased EBF duration, of borderline statistical significance, with moderate statistical heterogeneity. The Funnel plot (Figure 24) was not symmetrical, but Egger's test was >0.05 suggesting no clear evidence of publication bias. Subgroup analyses (Table 8) suggested that the statistical heterogeneity may be explained by family disease risk – children at high risk of allergic disease had less AD where EBF ≥3-4 months, whereas for children without high risk of allergic disease there was no association. It is notable that two other large observational studies reported effect modification by family history, for EBF and AD, whereby children from non-allergic families had increased AD with increased EBF duration, but this was not seen from children from allergic families (75, 76, 97). Other studies have suggested important gene environment interactions between EBF duration and allergic sensitisation, at least to foods (99).

Figure 23 EBF for ≥3-4 months vs. <3-4 months and risk of eczema at age 0-4 years

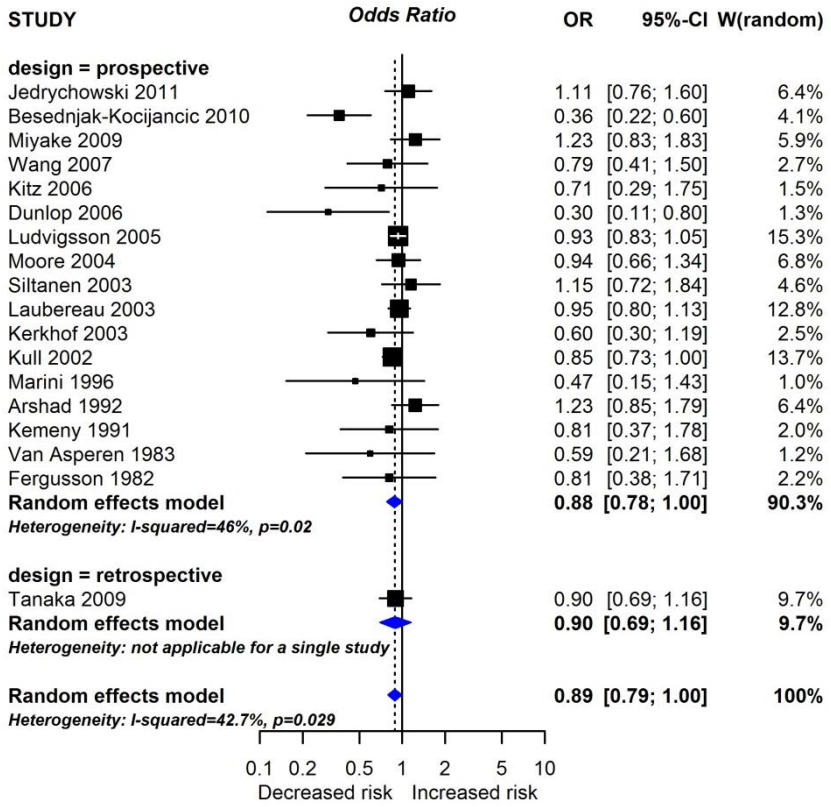
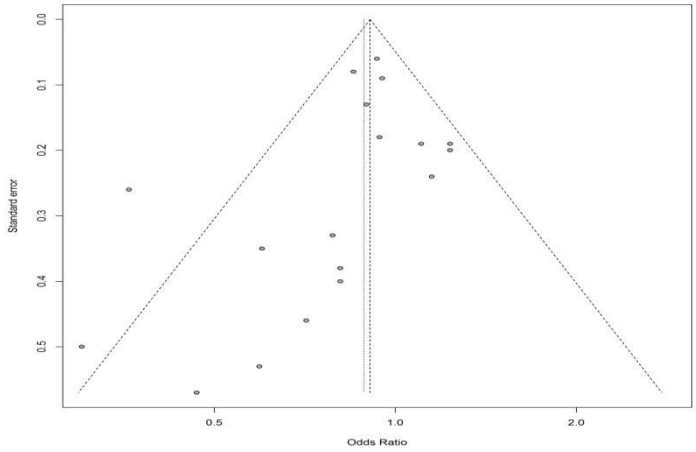


Figure 24 Risk of publication bias in studies investigating EBF duration for ≥3-4 months vs. <3-4 months and risk of eczema in children aged 0-4 years



Egger's test p-value = 0.141

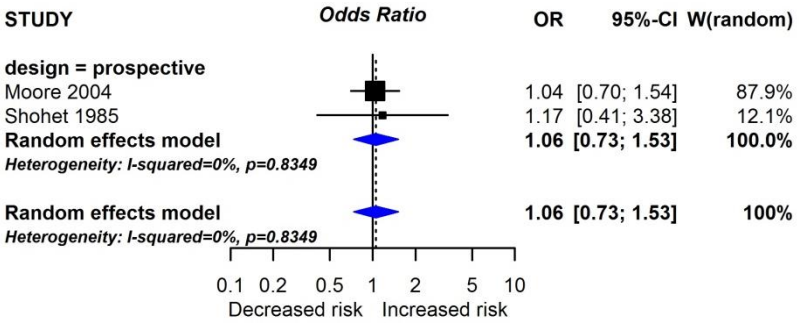
Table 8 Subgroup Analyses of risk of atopic dermatitis and EBF duration ≥3-4 months vs. <3-4 months in children aged 0-4 years

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	18	0.89 [0.79; 1.00]	42.7	
Adjusted	6	0.92 [0.85; 0.99]	0	Not tested
Unadjusted	16	0.89 [0.78; 1.03]	47.8	
Study Design – Prospective	17	0.88 [0.78; 1.00]	46	0.92
Study Design – Retrospective	1	0.90 [0.69; 1.16]	--	
Risk of disease – High	4	0.45 [0.31; 0.66]	0	0.00
Risk of disease – Normal	14	0.93 [0.86; 1.01]	9.2	
Risk of bias – Low	1	0.95 [0.80; 1.14]	--	0.45
Risk of bias – High/Unclear	17	0.87 [0.76; 1.00]	45.5	

2.2.1.3 EBF for ≥5-9 months vs. <5-9 months

Three prospective cohort studies reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥5-9 months vs. <5-9 months duration and are shown in Figure 25. They show no association between EBF duration and AD risk, with no statistical heterogeneity.

Figure 25 EBF ≥5 -9months vs. <5-9 months and risk of eczema at age 0-4 years

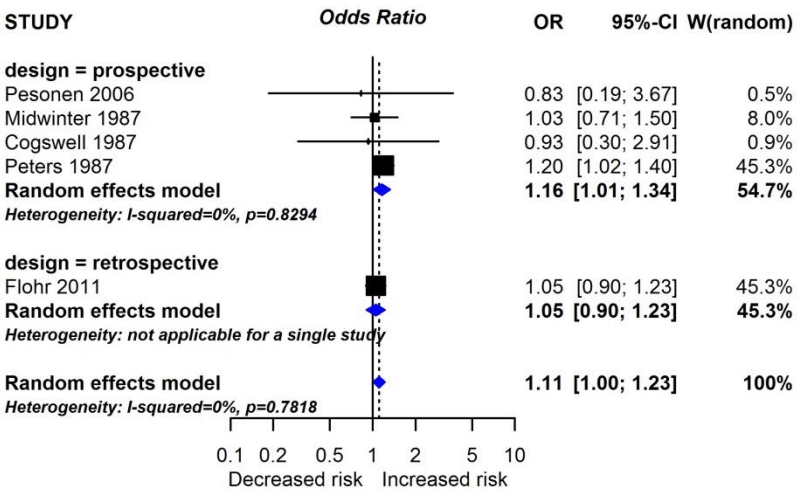


2.2.2 EBF duration and the risk of eczema in children aged 5-14 years

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

Four prospective cohort studies and one cross-sectional study reported data that could be pooled to calculate OR for AD, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 26. They show increased AD with increasing duration of EBF, with borderline statistical significance but no statistical heterogeneity (I^2=0%). Two of the studies presented adjusted data including the cross-sectional study of Flohr, and three presented unadjusted data including the significant study of Peters.

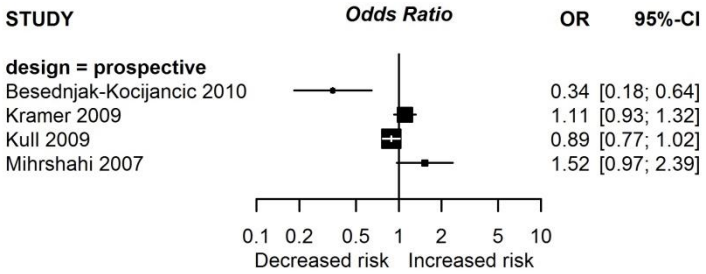
Figure 26 EBF ≥0-2 months vs. <0-2 months and risk of eczema at age 5-14 years



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

Four prospective cohort studies reported OR for AD, in infants with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 27. The studies could not be pooled due to extreme statistical heterogeneity (I^2=83%). The studies of Mihrshahi and Besednjak-Kocijancic were in populations at high risk of allergic outcomes, the latter study reported unadjusted data; the former adjusted. The studies of Kramer and Kull were in normal risk populations and reported adjusted data. Overall the data do not support an association between EBF ≥0-2 months vs. <0-2 months duration and altered AD risk.

Figure 27 EBF for ≥3-4 months vs. <3-4 months and risk of eczema at age 5-14 years

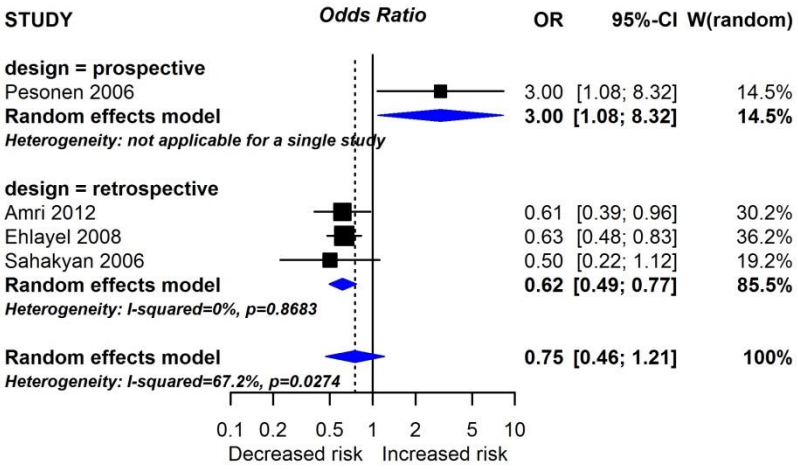


2.2.2.3 EBF ≥5-9 months vs. <5-9 months

Four observational studies reported OR for AD, in infants with EBF for ≥5-9 months vs. <5-9 months duration and are shown in Figure 28. The pooled OR show no association, with high statistical heterogeneity (I^2=67%). The studies of Amri and Ehlayel were retrospective studies reporting unadjusted data and thus carry a high risk of confounding bias. The study of Pesonen compared EBF duration ≥9 vs <9 months which is an unusual duration of EBF and

this analysis included relatively small numbers hence the wide confidence intervals. The study of Sahakya is a case-control study which reported adjusted OR and was judged as low or unclear risk of bias in all domains.

Figure 28 EBF for ≥5 months vs. <5 months and risk of eczema at age 5-14 years

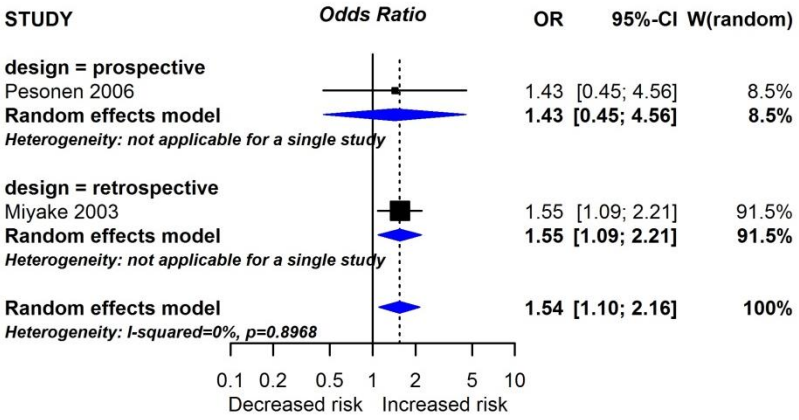


2.2.3 EBF duration and risk of eczema in children aged 15+ years

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

Two observational studies reported data that could be pooled to calculate OR for AD, in people aged 15+ years with EBF for ≥0-2 months vs. <0-2 months duration and are shown in Figure 29. They show increased AD with increasing duration of EBF, with no statistical heterogeneity (I^2=0%). The study of Pesonen compared EBF duration ≥9 vs <9 months which is an unusual duration of EBF and this analysis included relatively small numbers hence the wide confidence intervals. The study of Miyake is a cross-sectional survey using the ISAAC questionnaire, which reported adjusted data. The same authors found a similar effect for partial BF in the first 3 months, as for EBF.

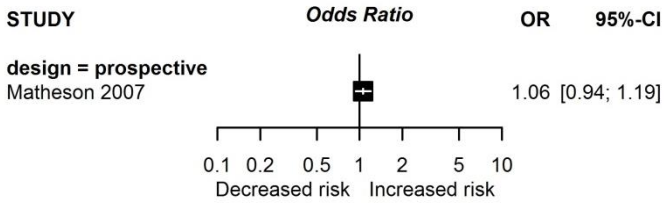
Figure 29 EBF for ≥0-2 months vs. <0-2 months and risk of eczema at age 15+ years



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

One prospective cohort study reported OR for AD, in adults aged 44 years with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 30. There was no evidence of an association.

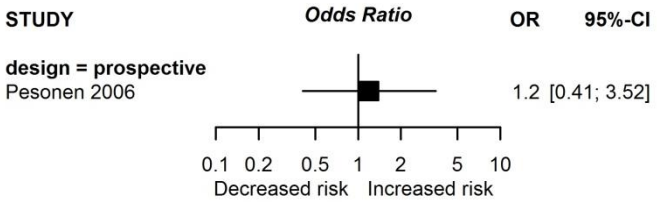
Figure 30 EBF ≥3-4 months vs. <3-4 months and risk of eczema at age 15+ years



2.2.3.3 EBF 5-9 months vs. <5-9 months

One prospective cohort study reported OR for AD, in adults aged 44 years with EBF for ≥5-9 months vs. <5-9 months duration and is shown in Figure 31. There was no evidence of an association.

Figure 31 EBF ≥5 months vs. <5 months and risk of eczema at age 15+ years



2.3 Exclusive breastfeeding duration and atopic eczema

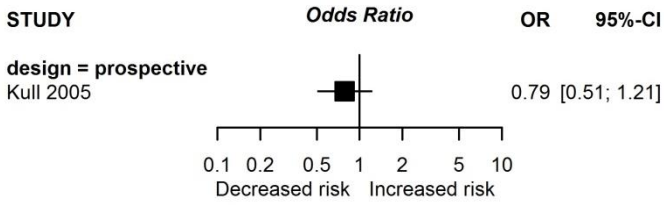
We also evaluated associations between EBF duration and eczema associated with atopy (i.e. a positive SPT or sIgE test). Relatively few included studies reported this outcome.

2.3.1 EBF and atopic eczema in children aged 0-4 years

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

One prospective cohort study reported OR for atopic-AD, in infants with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 32. There was no evidence of an association.

Figure 32 EBF ≥3-4 months vs. <3-4 months and risk of atopic eczema at age 0-4 years

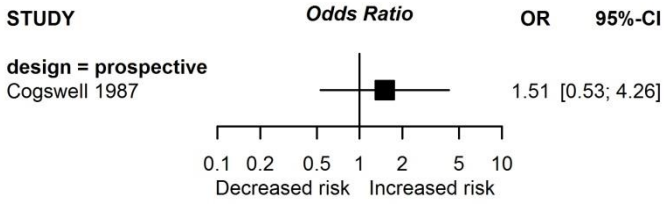


2.3.2 EBF and atopic eczema in children aged 5-14 years

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

One large cross-sectional study reported separately for affluent and non-affluent countries, calculated OR for atopic-AD, in children with EBF for ≥0-2 months vs. <0-2 months duration and is shown in Figure 33. There was no evidence of an association, with low statistical heterogeneity.

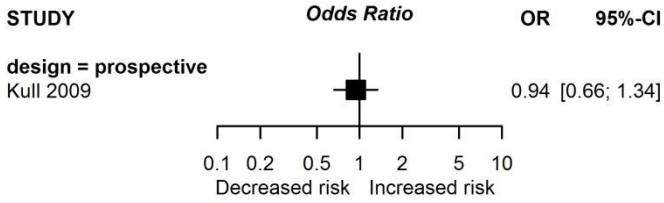
Figure 33 EBF ≥0-2 months vs. <0-2 months and risk of atopic eczema at age 5-14 years



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

One prospective cohort study reported OR for atopic-AD, in children with EBF for ≥3-4 months vs. <3-4 months duration and is shown in Figure 34. There was no evidence of an association.

Figure 34 EBF for ≥3-4 months vs. <3-4 months and risk of atopic eczema at age 5-14 years



2.4 Data for TBF and risk of eczema that couldn't be analysed

A further 11 prospective cohort studies, 1 case-control and 1 cross-sectional study reported relevant data from over 35000 study participants, which could not be included in meta-analysis. These studies are summarised in Table 9. In one prospective cohort study there was increased AD associated with increased EBF duration. In all other studies reported there was no association found between EBF and AD.

Table 9 Studies investigating the association between EBF duration and eczema which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	EBF in AD	EBF in no AD	P
Hesselmar, 2010 (3)	PC	AD	1.5	184	Continuous	Median (IQR)	4 (3.2, 4.5)	4 (3.9, 4.5)	0.63
Giwercman, 2010 (74)	PC	AD	2	306	Categorical	Risk of AD increased with increasing duration of EBF in analyses adjusted for allergy risk factors and filaggrin genotype HR 2.1 (1.2-3.8) P=0.016			
Gruber, 2010 (82)	PC	AD	1	543/47	Categorical	Cumulative incidence 7.3% (SE1.6%) with EBF>2 months vs 9.7% (SE1.5%) with EBF <2 months. Not adjusted. No statistical comparison.			
Ludvigsson, 2005 (67)	PC	AD	1	8346/ unclear	Categorical	Cumulative incidence of AD to 1 year in EBF ≥4 vs <4 months was not significantly different. Adjusted HR 1.0 (0.95, 1.06)			
Kramer, 2003 (86)	PC	AD	1	3483/96	Categorical	Cumulative incidence of AD to 1 year in EBF ≥6 vs 3-5 months was not significantly different. Adjusted OR 1.1 (0.65, 2.0)			
Benn, 2004 (75)	PC	AD	1.5	15430	Categorical	Cumulative incidence of AD to 1.5 years in EBF ≥4 vs <4 months was not significantly different. Adjusted HR 1.1 (0.98-1.28) NB The authors found significantly increased AD with EBF ≥4 months where there was no parental allergy, but not if parents were allergic			
Nentwich, (83)	PC	AD	2	106	Categorical	At 2 and 6 months of age there were more atopic symptoms in EBF group, but differences disappeared after 6 months			

Study	Design	Outcome	Age	N/n cases	Data	Measure	EBF in AD	EBF in no AD	P
Silvers, 2009 (38)	PC	AD	1	987	Categorical	No association between duration of EBF and AD to 1 year. Adjusted OR 0.96 (0.9-1.03)			
Nwaru, 2013 (18)	PC	AD	5	3109	Categorical; Continuous	No significant association between EBF duration either as a categorical or continuous variable in adjusted analyses, and risk of AD up to age 5. Median EBF 1.8 (0.2, 3.5) AD; 1.5 (0.2, 3.5) no AD			
Kramer, 1981 (53)	CC	AD	<20	142/ unclear	Categorical	No significant association between EBF >2 months and AD risk			
Zutavern, 2004 (93)	PC	AD	5.5	604	Categorical	No significant association between EBF ≥2 months and AD risk, in adjusted analysis			
Fergusson, 1990 (72)	PC	AD	10	1067	Categorical	No significant association between EBF ≥4 months and AD risk, in adjusted analysis. P>0.80			
Civelek, 2001 (57)	CS	AD	11	1533/743	Continuous	No significant association between EBF duration and AD risk, in adjusted analysis			

3 Solid food introduction and atopic eczema

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

Table 10 describes the main characteristics of the studies analysed in this section of the report. A total of 25 observational studies including 21 prospective cohort studies, 1 retrospective cohort study, 1 nested case-control study and 2 case-control studies, reported the association between timing of solid food introduction (SF) and risk of AD. The studies were mainly from Europe (n=17), but also Australasia (n=3), Asia (n=3), USA (n=1) and Africa (n=1). Overall, valid data on SF and AD risk were available from over 45,000 subjects. Information on AD was obtained from a medical assessment in 11 studies, via parental report in 6 studies, using Hanifin and Rajka criteria or modified versions of the criteria in 4 studies, and ISAAC questionnaire in 4 studies. With regards to time of outcome diagnosis, 19 studies explored the association between SF and AD in the first 4 years of life, and 6 studies assessed at age 5-14 years. Eleven studies used a questionnaire to assess the exposure (SF), 3 diary, 10 interview and 1 used medical record review.

Risk of bias is summarised in Figure 35. Just over 40% of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented. Risk of conflict of interest was generally assessed as low.

The risk of AD according to SF was categorised as ≥3-4 months vs. <3-4 months. Overall the evidence base was limited by some unexplained statistical heterogeneity in both meta-analyses, but the available data do not suggest any relationship between timing of solid food introduction and AD risk.

Table 10 Characteristics of included studies evaluating solid food introduction and eczema

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Hesselmar, 2010 (3)	184	PC	Sweden	I	UK Working Party Criteria	1.5	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Mihrshahi, 2007 (14)	516	PC	Australia	I	Visible flexural dermatitis OR DD eczema	5	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Fergusson, 1981 (100); Fergusson, 1982 (100)	1175	PC	New Zealand	R/I	DD	1, 2	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Larsson, 2008 (16)	4779	PC	Sweden	Q	ISAAC	9	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Forsyth, 1993 (101)	455	PC	UK	D/I	Parent reported eczema	2	Dundee infant feeding study. Population based cohort of infants born between 1983-1986
Filipiak, 2007; Schoetzau, 2002 (102-104)	4753	PC	Germany	Q, D	DD; Physician assessment	1, 4	GINI study. Term newborn infants born 1995-8 in 2 regions of Germany referred to an intervention program according to risk of allergy
Harris, 2001 (21)	622	PC	UK	I	UK Working Party Criteria	2	Population based birth cohort of children born between 1993 and 1995 in three general practices in Ashford

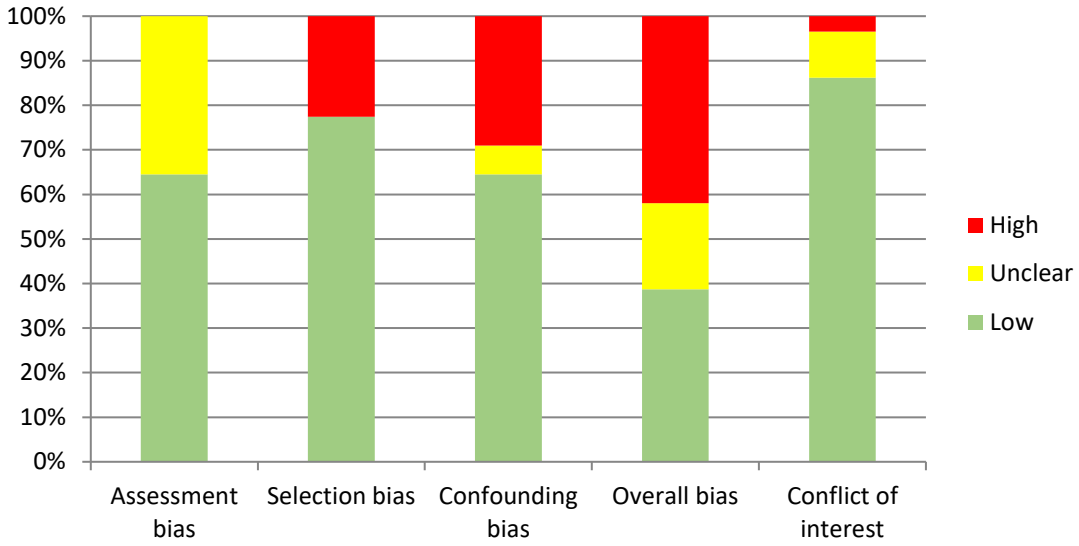
Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Huang, 2013 (105)	684	PC	China	Q	ISAAC	2	Mother-infant pairs registered in Putuo District, Changzheng Town Community Health Service Center Child Health Clinic, 2008
Alm, 2008 (25)	4941	PC	Sweden	Q	Parent reported eczema	1	Infants of Western Sweden. Population birth cohort of infants born in 2003
Snijders, 2008 (28)	822	PC	Netherlands	Q	Parent reported eczema	2	KOALA study. Population based birth cohort of infants born 2000-2002 (including a cohort with anthroposophic lifestyle)
Brockow, 2008; Zutavern 2006 ; Zutavern, 2008 (106-108)	2474	PC	Germany	I, Q	DD; Parent reported eczema	2, 6	LISA study. Population based birth cohort of infants born between 1997-9 at selected maternity hospitals in 4 German cities
Marini, 1996 (31)	359	PC	Italy	Q	Physician assessment	1	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Moore, 1985 (33)	470	PC	UK	D/I	Physician assessment	1.0	Infants born in a hospital in 1979-1980 with family history of eczema or asthma (high risk of disease)
Morgan, 2004; Morgan, 2004 (b) (34, 35)	257	PC	UK	I	Parent reported eczema; Physician assessment	1, 1.5	Infants from five prospective randomised dietary trials conducted in the UK 1993-7. Two term infants, one LBW infants, two premature infants

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Ruiz, 1992 (44)	39	PC	UK	I	Hanifin and Rajka criteria	1	Recruited from hospital and family history of atopy (high risk of disease)
Dunlop, 2006 (91)	1326	PC	Slovakia	Q	Physician assessment	1	Recruited from hospital, born 1997-1999 (normal risk of disease)
Chuang, 2011 (46)	18773/ 1050	PC	Taiwan	R/I	Physician assessment	1.5	TaiwanBirth Cohort Study: population representative sample born in 1995 (normal risk of disease)
Joseph, 2011 (109)	594	PC	USA	I	DD	3	WHEALS STUDY: Recruited from hospital prenatal care and born in 2005 (normal risk of disease)
Zutavern, 2004 (93)	604	PC	UK	I	DD	5.5	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Hide, 1981 (47)	843	PC	UK	D/Q	DD	1	The Isle of Wight study: born in 1977-1978 (normal risk of disease)
Van Asperen, 1983 (110)	79	PC	Australia	I	Physician assessment	1.3	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of disease)
Sariachvili, 2010 (51)	557	NCC	Belgium	Q	ISAAC	4	PIPO COHORT: population representative sample, participants born in 1997-2001 (normal risk of disease)
von Geburstsreif , 1990 (20)	145	RC	Germany	Q	Parental report	1.5	Incident cases from diabetes registry and controls from schools (normal risk of disease)

Study	N/n cases	Design	Country	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Population characteristics
Haileamlak, 2005 (55)	732	CC	Ethiopia	I	ISAAC	5	Children age 1- 5 years. Cases were defined according to the ISAAC criteria for AD and confirmed by clinical examination
Sahakyan, 2006 (95)	240	CC	Armenia	Q	UK Working Party Criteria	7	Hospital-based study with matched controls (normal risk of disease)

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

Figure 35 Risk of bias in studies of solid food introduction and eczema



3.1.1 SF introduction and risk of eczema in children aged 0-4 years

3.1.1.1 SF ≥3-4 months vs. <3-4 months

Figure 36 shows the outcomes of 14 eligible observational studies evaluating SF ≥3-4 months vs. <3-4 months and risk of AD at age 0-4 years. The data show no significant relationship, with high statistical heterogeneity (I^2=70%). Chuang also reported no relationship between SF introduction at >6 months and AD, in their prospective cohort study with low overall risk of bias in a normal risk population evaluated at age 1.5 years aOR 1.08 (0.74-1.57). In an analysis of a subset of the GINI dataset reported by Filipiak, Schoetzao also found no association between SF introduction at >6 months and risk of AD in the first year – unadjusted OR 1.8 (0.8-1.7). Funnel plot is shown in Figure 37, and does not suggest obvious publication bias. In the study of Snijders a cutoff of >7 versus 3 months was used.

Subgroup analyses are shown in Table 11 and do not identify important subgroup differences or explanations for the statistical heterogeneity.

Figure 36 SF ≥3-4 months vs. <3-4 months and risk of atopic eczema at age 0-4 years

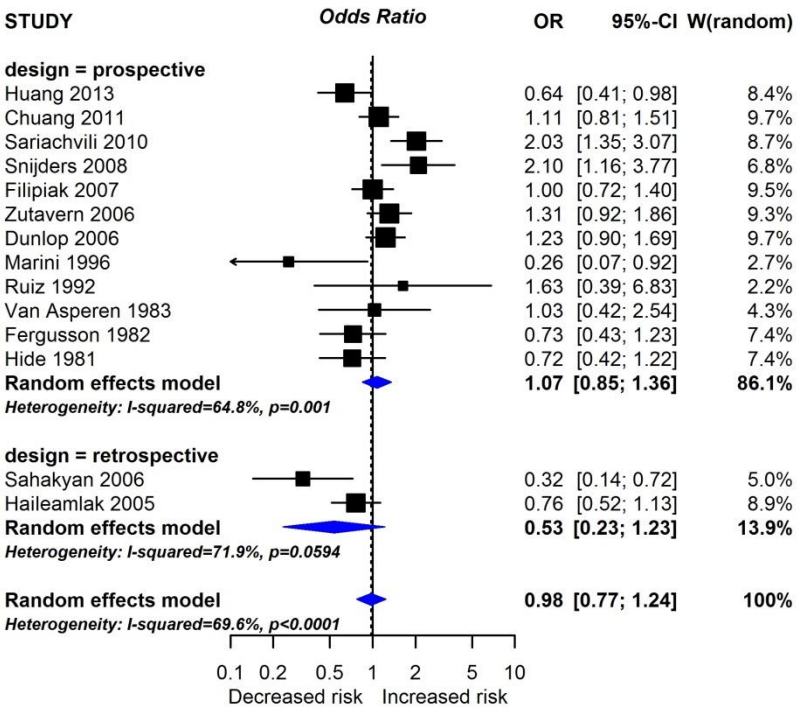
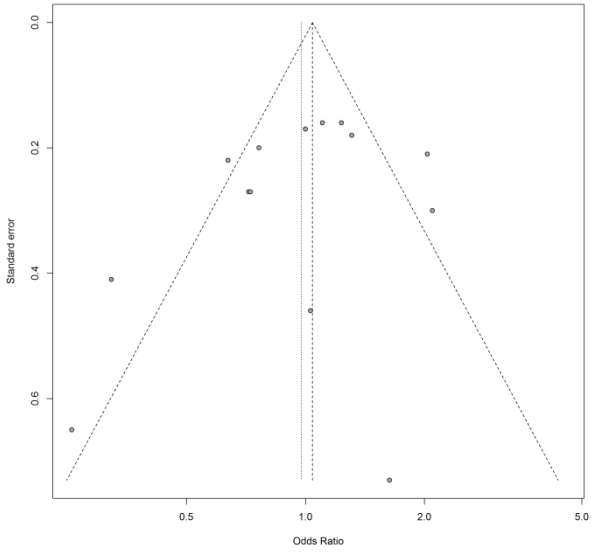


Figure 37 Risk of publication bias in studies investigating SF introduction ≥3-4 months vs. <3-4 months and risk of eczema in children aged 0-4 years



Egger's test p-value = 0.241

Table 11 Subgroup Analyses of risk of atopic dermatitis and SF ≥3-4 months vs. <3-4 months in children aged 0-4 years

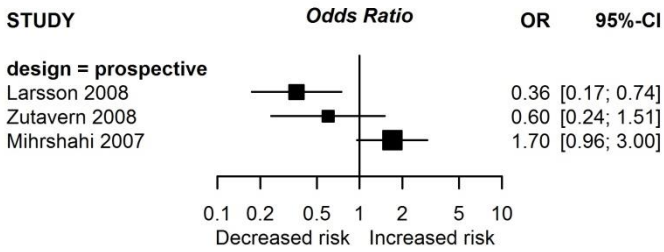
	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	14	0.98 [0.77; 1.24]	69.6	
Adjusted	8	1.03 [0.73; 1.46]	77.9	Not tested
Unadjusted	9	1.10 [0.84; 1.43]	63.3	
Study Design – Prospective	12	1.07 [0.85; 1.36]	64.8	0.11
Study Design – Retrospective	2	0.54 [0.23; 1.23]	71.9	
Risk of disease – High	3	0.76 [0.28; 2.07]	53.6	0.60
Risk of disease – Normal	11	1.00 [0.78; 1.28]	73.5	
Risk of bias – Low	6	1.20 [0.84; 1.71]	76.8	0.09
Risk of bias – High/Unclear	8	0.81 [0.62; 1.06]	44.0	

3.1.2 SF introduction and risk of eczema in children aged 5-14 years

3.1.2.1 SF ≥3-4 months vs <3-4 months

Three observational studies reported OR for SF at ≥3-4 months vs <3-4 months and risk of AD at age 5-14 years. Data were not pooled due to extreme statistical heterogeneity (I^2=83%). All 3 studies had a low risk of bias on all domains, and reported adjusted data – Zutavern at aged 6 in a normal risk population using parental report of eczema, Mihrshahi at aged 5 in a high risk population using doctor diagnosis, Larsson at aged 9 in a normal risk population using ISAAC. In the study of Larsson, there was no significant association between SF 3-6 months versus >6 months and AD OR 0.99 (0.77, 1.27). However, there was a significant association between SF >6 months vs <3 months and AD (data shown in Figure 38). We were unable to identify an explanation for the statistical heterogeneity seen between studies.

Figure 38 SF ≥3-4 months vs. <3-4 months and risk of eczema at age 5-14 years



3.2 Data for SF and risk of eczema that couldn't be analysed

A further 7 prospective cohort studies reported relevant data from over 7500 study participants, which could not be included in meta-analysis. This was due to the way the studies presented the data, either as simply a narrative in the Results section, or with estimates that were not comparable. Their characteristics and results are summarised in Table 12. The studies show no evidence of an association between SF and AD.

Table 12 Studies investigating the association between solid food introduction and eczema which were not eligible for meta-analysis

Study	Design	Outcome	Age	N/n cases	Data	Measure	SF in AD	SF in no AD	P
Hesselmar 2010 (3)	PC	AD	1.5	184/ unclear	Continuous	Median (IQR)	4 (4, 5)	4 (4, 4.6)	0.97
Moore, 1985 (33)	PC	AD	1	470	Categorical		No significant association between SF >3 vs <3 and risk of AD (adjusted analysis)		
Joseph 2011 (109)	PC	AD	3	594	Categorical		No significant association between SF >4 vs <4 and risk of AD P=0.76		
Forsyth, 1993 (101)	PC	AD	2	455	Categorical		SF >3 had less AD (8.3%) than SF 2-3 (17.0%) but more than SF <2 (5.4%) P<0.05. Adjusted analysis		
Morgan, 2004 (35)	PC	AD	1.5	257	Categorical		No significant association between SF >3 vs <3 and risk of AD (adjusted analysis)		
Alm, 2008 (25)	PC	AD	1	4941/ unclear	Categorical		No significant association between SF and risk of AD		
Harris, 2001 (21)	PC	AD	2	622/ 283	Categorical		No significant association between SF and risk of AD		

4 Conclusions

This report summarises the results of 57, 47, 25 studies of TBF, EBF and SF respectively, in relation to AD risk. Studies included over 250,000 people and AD is a common disease affecting 5-20% of most human populations. Thus we captured a significant dataset in which to explore the relationship between BF, SF and AD risk. Our search identified one high quality recent systematic review, which appraised 2 observational studies of EBF duration and AD and found no evidence for an association. One cluster RCT trial of a breastfeeding promotion intervention found reduced AD risk at 1 year (but not at 6.5 years) in centres randomised to the breastfeeding promotion intervention. Despite a large volume of data from observational studies, some analyses especially for EBF and solid food introduction were limited by small numbers of studies reporting relevant data. Overall we found no evidence from the observational studies that duration of TBF or EBF at any stage is associated with reduced risk of AD. Some analyses suggested an association in the opposite direction i.e. prolonged BF associated with increased AD – however these were not consistent between analyses, not robust to subgroup analysis, and not seen in studies which did not contribute to meta-analysis. The intervention trial evidence that breastfeeding promotion reduces risk of AD was graded at LOW certainty, due to imprecision and inconsistency with other sources of evidence. We found no association between timing of SF introduction and AD risk.

Our data suggest that breastfeeding promotion may reduce risk of AD, at least in the first year of life, but that the evidence for this is of LOW certainty. We did not find evidence that duration of EBF, or timing of SF introduction, influence AD risk. We did identify some evidence of gene-environment effects which were also seen in the 'Allergic Sensitisation' report – suggesting that human breast milk may be able to have an effect on AD risk, but that its composition or the genetic make-up of the infant are important effect modifiers. This is an unproven hypothesis with respect to AD, but needs exploration in future studies since our understanding of eczema pathogenesis may be enhanced by understanding the relationship between breast milk composition, maternal and infant genotype, and clinical outcome.

A previous overview of systematic reviews undertaken by the Cochrane Collaboration found no evidence of a relationship between these exposures and risk of eczema, but did highlight the single intervention trial which we also found, that reported reduced eczema risk in infants born in centres randomised to a breastfeeding promotion intervention (111). Our

comprehensive analysis of the observational studies literature has failed to strengthen support for this finding..

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