Breastfeeding, Solid Food Introduction and Wheeze

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1 Total breastfeeding and wheeze

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 wheeze risk. There were a total of 105 studies of which one was a cluster randomised controlled trial, 68 were prospective cohort studies (2 of which were parental studies to a cross-sectional (CS) and to a nested case-control study), 3 retrospective cohorts, 10 case-control, 2 nested case-control, and 19 cross-sectional studies. The majority of studies (n=57) are from Europe – others are from the Asia-Pacific region (n=18) and North America (n=17), 5 from South America, 3 from Africa, 1 from the Middle East (Iraq), and 1 has an unknown provenance. There are also 2 studies from the International Study of Allergies and Asthma in Childhood (ISAAC), which included multiple countries.

Overall, valid data on TBF duration in the first 2 years of life and wheeze risk were available from over 463,000 subjects. Information on wheeze was obtained solely from parental or self-reported in 25 studies, through Dr-diagnosis in 31 studies, and from the ISAAC questionnaire in 16 studies. A further 4 studies use spirometry alone. Another 27 studies used a combination of self /parental report, Doctor diagnosis, and/ or objective measures (e.g. bronchial hyper-responsiveness (BHR)). One study used an unclear method for defining wheeze.

With regards to time of outcome diagnosis, 34 studies explored the association between TBF duration and wheeze at age 0-4 years, 41 at age 5-14 years, and 14 at age 15 years or beyond. A further 15 studies investigated the association between TBF duration and wheeze at various time points between the ages of 1 and 22 years. To ascertain exposure to TBF, 64 studies used a questionnaire method, 13 used an interview, 3 used medical records, 2 used a diary, and 1 used a food frequency questionnaire (FFQ). A further 18 studies used a combination of 2 or more of these methods, whilst 3 studies had no information available on the method 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. At least half of the studies were considered to have a low risk of assessment, selection and confounding bias, with over a third of studies had a low risk of overall bias. Over a third of the studies had a high risk of overall bias, mainly due to lack of controlling for potential confounders. 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 wheeze 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 wheeze at age 1 year or 6.5 years. For observational studies, across in children aged 0-4 years, we found no consistent evidence for an association between TBF and wheeze or recurrent wheeze. There was weak evidence for an association in dose-response analysis of four studies for wheeze (Figures 4 to 6) and three studies for recurrent wheeze (Figures 28 to 30). In other analyses there was either extreme heterogeneity, or no consistent association between TBF duration and wheeze or recurrent wheeze. Heterogeneity could not always be explained, but in some cases was likely due to differences in adjustment for potential confounders. In some sensitivity analyses unadjusted data showed greater evidence of association than adjusted data.

In children aged 5-14 years old, we found limited evidence from observational studies for an association between TBF and wheeze or recurrent wheeze. Meta-analysis of data for ever vs. never breastfed showed reduced odds of wheeze, but with high heterogeneity and evidence of publication bias; inconclusive findings from dose/response analysis, and no association seen with other durations of TBF. Meta-analysis of data for ever vs. never breastfed showed reduced odds of recurrent wheeze, with moderate heterogeneity and evidence of publication bias; but supportive findings from dose-response analysis, and significant or borderline significant associations seen with other durations of TBF (3 to 4 months, 5 to 7 months, over 18 months). The evidence for an association between TBF and recurrent wheeze at age 5-14 was graded as VERY LOW (-1 publication bias).

In people aged 15 years or older, we found no consistent evidence for an association between TBF and risk of wheeze or recurrent wheeze. Data were sparse for analyses of wheeze. For analyses of recurrent wheeze, TBF 1 to 2 months or longer was associated with increased risk of recurrent wheeze in one prospective and one retrospective study (Figure 47); TBF 5 to 7 months or longer was associated with decreased risk of recurrent wheeze in one prospective study at low risk of bias (Figure 49); and analyses of TBF ever vs. never, or TBF 3 to 4 months or longer showed no significant association with recurrent wheeze.

We found no evidence for an association between TBF and atopic wheeze, or between TBF and wheeze when TBF was reported as a continuous measure (e.g. average number of months breastfed in those with and without a history of wheeze).

We found no evidence for an association between TBF and bronchial hyper-reactivity (BHR) in children aged 5 to 14 years, and no consistent evidence for an association between TBF and measures of lung function. Eight studies investigated the association between lung function outcomes and TBF in over 37,800 subjects aged 10 to 51 years old, summarised in Table 12. Outcomes reported included forced expiratory volume in 1 second (FEV_1), FEV_1 as percentage of predicted value (FEV_1%predicted), peak expiratory flow rate (PEFR), forced expiratory mid flow (FEF_{50}), FEV_1 decline, airflow obstruction ($FEV_1/FVC<0.80$), FEV_1/FVC as percentage of predicted value, and post-bronchodilator measures of FEV_1, FVC and FEV_1/FVC. One cross-sectional study reported a positive association between FEV_1% and TBF ever vs. never. A prospective cohort reported a positive association between TBF and FEF_{50}, whilst two prospective cohort studies reported a positive association between TBF and FEV_1. Two studies reported an association between TBF ever and FEV_1/FVC% and FVC. However a number of non-significant associations reported, and no measure of lung function was consistently associated with TBF across different studies.

A total of 36 studies with data on wheeze and TBF exposure were identified which did not report data in a way that could be included in meta-analyses (Table 11). There were 25 prospective cohorts, 1 retrospective cohort, 1 case-control, 1 a nested case-control, and 8 cross-sectional studies. Seven prospective cohort studies reported associations between TBF and reduced wheeze (n=1) or recurrent wheeze (n=6), and 2 cross-sectional studies reported associations between TBF and reduced recurrent wheeze. Twenty five studies showed no

evidence of an association between TBF and wheeze outcomes. Four studies reported borderline associations (P=0.05).

Overall, TBF analyses were marked by statistical heterogeneity, evidence of publication bias in 3 analyses (ever vs. never and wheeze at age 5-14; ever vs. never and recurrent wheeze at age 5-14; TBF for at least 3 to 4 months and recurrent wheeze at age 5-14) – suggesting that the relationship reported between TBF and wheeze/recurrent wheeze may be influenced by publication of studies showing a protective association, and non-publication of studies finding TBF is not associated with, or is associated with increased risk of wheeze/recurrent wheeze.

Conclusion

We found VERY LOW (-1 publication bias) evidence that longer TBF is associated with reduced risk of recurrent wheeze at age 5-14 years, and no consistent evidence for an association between TBF and other wheeze or lung function outcomes.

Table 1 Characteristics of included studies evaluating total breastfeeding and wheeze

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	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
Wright, 2002 (3)	PC	499	Q/I	Parent reported wheeze	0-1	USA	Part of a metropolitan Boston prospective birth cohort study of infants born between 1994-1996 with family history of asthma or recruited from a Boston hospital
Al-Kubaisy, 2005 (4)	CS	2262	Q	DD plus ISAAC	12	Iraq	Primary school urban and rural children
Hesselmar, 2010 (5)	PC	184	I	DD asthma (>=3 episodes of wheeze)	1.5	Sweden	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Elliott, 2008; Granell, 2012; Sherriff, 2001 (6-8)	PC	9100	Q	DD asthma PLUS current wheeze; Parent reported wheeze; BHR: (metacholine PC20)	3, 3.5, 7, 7.5	UK	ALSPAC study. Population based cohort of children born 1991-1992
Kull, 2002 (9)	PC	3790	Q	Self-reported wheeze; >=3 episodes of wheeze OR inhaled corticosteroids	2	Sweden	BAMSE study. Population based cohort of children born between 1994-1996

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Lewis, 1996 (BCS58) (10)	PC	9820	I	Parent reported current wheeze	16	UK	British Cohort Study: Infants born in England, Wales, and Scotland England, Scotland and Wales in 1958
Lewis, 1995; Lewis, 1996 (BCS70) (10, 11)	PC	12835	Q, I	Parent reported wheeze ever/ current wheeze	5, 16	UK	British Cohort Study: sample of all infants born in 1970 in Britain
Burr, 1989; Burr, 1993; Burr, 1993 (b) (12-14)	PC	483	D, Q	Parent reported wheeze; Wheeze ever, DD	1, 6.7, 7	UK	Infants with family history of allergic diseases in South Wales
Alper, 2006 (15)	CS	858	Q	Parent reported wheeze classified using Martinez criteria	7	Turkey	7 years old children randomly selected from seven primary schools in Bursa in 1999
Businco, 1987 (16)	PC	244	I	DD asthma (>=3 episodes of wheeze)	8	Italy	Infants of atopic parents recruited from hospital and born in 1985-1988
Camara, 2003 (17)	CC	91	Q	DD (wheezing that required therapy with inhaled β2-agonists as judged by the attending physician)	12	Brazil	Cases and control were children who sought ED care

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Midodzi, 2010 (18)	PC	8499	Q	DD	5	Canada	Canadian Early Childhood Development Cohort Study- part of NLSCY. Longitudinal surveys of children representative of the Canadian population
Taylor, 1983 (19)	PC	12608	I	Parent reported wheeze; DD	5	UK	CHES study. Population based cohort of children born in England, Scotland, and Wales in 1970
Mihrshahi, 2007 (20)	PC	516	I	DD PLUS current wheeze	5	Australia	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Simon, 2008 (21)	PC	372	R/I	Transient wheezing: wheezing in the last 12 months at ages of 1,2 and/or 4 years but not at age of 6 years	6	USA	CAS study. Middle class mother-infant pairs enrolled in a health maintenance organisation in 1987-89
Larsson, 2008 (22)	PC	4779	Q	DD	9	Sweden	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Devereux, 2006 (23)	PC	1704	FFQ	ISAAC	5	Scotland, UK	Population based birth cohort of infants born in 1998
Nwaru, 2013 (24)	PC	3675	D	DD plus ISAAC; DD plus ISAAC (+/- sIgE)	5	Finland	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000
Wilson, 1998 (25)	PC	545	Q	Self-reported wheeze; DD	7	UK	Dundee infant feeding study. Population based cohort of infants born between 1983-1986

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Ehrlich, 1996 (26)	CS	620	Q/I	ISAAC	9	South Africa	Second year elementary school (7- 8 years) children. All black
Visser, 2010 (27)	CS	1115	Q	Parent reported wheeze ever; >=3 episodes of wheeze	1	Netherlands	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Munro, 2011 (28)	PC	700	Q	Parent reported wheeze	1	UK	EuroPrevall-UK. Population based birth cohort of infants born in 2008
Farooqi, 1998 (29)	PC	1453	R	DD (recurrent episodes of wheeze after the age of two years)	16	UK	Representative sample of general practice both in 1975-84
Friday, 2000 (30)	RC	94	NA	Physician assessed asthma	10?	no data	Unclear
Fredriksson, 2007 (31)	PC	1933	Q	ATS questionnaire: wheezing apart from colds or wheezing most days or nights during the past year; DD	15	Finland	Population-based study of children born between 1984 and 1989
Tanaka, 2009(32)	CS	1957	Q	ISAAC	3	Japan	Fukuoka Child Health Study. All 3-year old children who had the examination at public public health centers in Fukuoka city
van der Voort, 2012 (33)	PC	5368	Q	ISAAC	1, 4	Netherlands	Generation R study. Population-based multicultural birth cohort of infants born between 2002 and 2009

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Gruskay 1982 (34)	PC	328 FH+/ 580 FH-	NA/Q	Physician assessment (recurrent wheezing)	3, 5, 15	USA	Children born in 1961-1966 in a private pediatric practice
Guida, 2009 (35)	PC	3041	Q	Parent reported wheeze	1	France	Population based birth cohort of infants born in 2003
Gustafsson, 1999 (36)	PC	94	Q	>=3 episodes of physician diagnosed wheezing	8	Sweden	Children with atopic dermatitis attending allergic clinic or referred by child welfare clinics
Halken, 1991(37)	PC	276	Q	>=2 episodes of physician diagnosed wheeze	1.5	Denmark	Population based birth cohort of children born in 1985
Han, 2009 (38)	CS	21371	Q	ISAAC	15	Taiwan	Elementary and middle school children aged 6-15 years old in 2004
Puig, 2010 (39)	PC	368	Q	DD	6	Spain	Part of AMICS. Population based cohort of infants born in 1996-1998 in Barcelona
Soto-Ramirez, 2013 (40)	PC	2833	Q	Parent reported current wheeze	1	USA	Population based birth cohort selected from nationally distributed consumer opinion panel of 500 000 household between 2005-2007
Oddy, 2003 (41)	PC	243	Q	Parent reported wheeze ever	1	USA	Birth cohort of infants participating in the Infant Immune Study in Tucson, Arizona.

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Infante-Rivard, 1993(42)	CC	914	I	DD	3.5	Canada	Cases were 3- and 4-year-old children with a first-time diagnosis of asthma made by a paediatrician 1988-90. Age and area matched controls chosen from computerized family allowance files for the target region.
Alm, 2008; Goksor, 2009 (43, 44)	PC	4987	Q, Q/FFQ	Wheeze ever; >=3 episodes of wheeze in past year	1.4, 4.5	Sweden	Infants of Western Sweden. Population birth cohort of infants born in 2003
Morales, 2012 (45)	PC	467	Q/I	Parent reported wheeze	1	Spain	INMA project. Population based birth cohort of infants born 2004-2006
Nagel, 2009 (46)	CS	31579	Q	Parent reported current wheeze; Parent reported asthma (+/- SPT); Spirometry; BHR:hypertonic saline PC1	12	Worldwide	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries
Björkstén, 2011 (47)	CS	103716	Q	ISAAC	7	Worldwide	ISAAC Phase 3: Schoolchildren aged 6-7 years from different countries and geographic regions
Awasthi, 2004 (48)	CS	2471	Q	ISAAC	7	India	ISAAC Phase 3-India: Schoolchildren aged 6-7 and 13-14 years old from India
Karmaus, 2008 (49)	PC	1336	Q	ISAAC PLUS DD asthma	10	UK	Isle of Wight Prevention Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Juca, 2012 (50)	CC	590	Q	ISAAC	14	Brazil	Adolescents age 13-14 years old in Mato Grosso State, Brazil
Karino, 2008 (51)	CS	9615	Q	Self-reported asthma	18	Japan	University freshmen students aged 18–19 years enrolled from 2003 through 2005.
Karunasekera, 2001 (52)	CC	582	Q	Physician assessment	10	Sri Lanka	Hospital-based cases aged 1-10 years old with age matched controls from inpatient clinics
Kaufman, 1976 (53)	PC	94	NA	DD	2	USA	Birth cohort of infants from allergic mothers
Kemeny, 1991(54)	PC	180	NA	>=2 episodes of wheeze	1	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Klinnert, 2001(55)	PC	145	Q	DD	8	USA	Birth cohort of infants at increased risk for atopy born between 1985 and 1987
Snijders, 2007; Snijders, 2008 (56, 57)	PC	2505	Q	>=4 episodes of wheeze	2	Netherlands	KOALA study. Population based birth cohort of infants born between 2000-2002 (consisting of cohorts with conventional and alternative lifestyle)
Galbally, 2013 (58)	PC	4507	I	Parent reported wheezing >=4 nights per week	1	Australia	Longitudinal Study of Australian Children. Population based study of infants born between March 2003 and February 2004 and were enrolled in the Australian Medicare database

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Marini, 1996 (59)	PC	Unclear	Q	Physician assessment (>=3 episodes of wheeze)	3	Italy	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Martel, 2008 (60)	NCC	1578	Q	DD PLUS asthma medication	<10	Canada	Data originating from 3 interlinked administrative health databases on children health in the first 10 years of life
Burgess, 2006 (61)	PC	4964	Q	Parent reported asthma	14	Australia	Mater-University of Queensland Study of Pregnancy. Population based birth cohort of infants born 1981-1984
Mavale-Manuel, 2003 (62)	CC	199	Q/I	DD PLUS asthma medication	8	Mozambique	Children aged between 18 months and 8 years attending pediatrics clinic with history of asthma with age-match controls attending the clinic immediately after selection of the index case
McConnochie, 1986(63)	RC	223	R/I	ATS guideline: wheezing with and without colds or most days or nights; DD (ATS guideline)	8	USA	Historical cohort with subjects were drawn from the patient population of a five-paediatrician group practice in a suburb of Rochester, New York
Miskelly, 1988 (64)	PC	482	D	Parent reported wheeze	1	UK	Infants from antenatal clinics with family history of allergy randomised into a dietary intervention program
Miyake, 2003 (65)	CS	6845	Q	ISAAC	15	Japan	12-15 years old children from all public junior high schools in Suita, Japan.
Morgan, 2004 (66)	PC	1600	I	DD	1.5	U.K.	Infants from five prospective randomised dietary trials conducted in the UK 1993-1997. Two term infant trials; one LBW infant trial; two preterm infant trials.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Mann, 1992 (67)	PC	2139	Q	Self-reported wheeze; Spirometry	36	UK	MRC National Survey of Health and Development. Birth cohort of infants to wives of non-manual and agricultural workers, and one in four of all single, legitimate infants to wives of manual workers in England, Wales, or Scotland
Muiño, 2008 (68)	PC	897	Q	Parent reported current wheeze; Persistent wheeze: parent reported wheeze at 1, 4 and 8-10 year assessments; Early transient wheeze: parent reported	12	Brazil	Population based cohort of infants born in 1993
Bergmann, 2000 (69)	PC	1314	Q/I	Physician assessment	6	Germany	MAS study. Atopic risk enriched cohort of infants born in 1990 in 5 German cities
Rust, 2001(70)	CS	6783	I	DD; DD asthma ever	<6	USA	NHANES III survey. Children ages 2 months to 5 years from noninstitutionalized U.S. population
Evenhouse, 2005 (71)	CS	16903	Q	Unclear	12-18	USA	National Longitudinal Study of Adolescent Health (Add Health). Nationally representative samples of adolescents from 80 school districts, since 1994
Dell, 2001; Midodzi, 2008 (72, 73)	PC; CS	2711	NA; Q	>=2 episodes of wheeze; Preschool wheeze: <5 years but not beyond 6 years; Parent reported wheeze; DD	2,9	Canada	National Longitudinal Survey of Children and Youth (NLSCY). First of longitudinal surveys of 12-24 months old children representative of the Canadian population
Milner, 2004 (74)	PC	8071	Q	DD	3	USA	National Maternal and Infant Health Survey and Longitudinal Follow Up. Representative US population born in 1988. Black, low socioeconomic status, and premature infants intentionally overrepresented

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Silvers, 2009; Silvers, 2011 (75, 76)	PC	987	Q	DD PLUS current wheeze; Parent reported wheeze	1, 5	New Zealand	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Ronmark, 1999 (77)	NCC	258	Q	DD plus ISAAC; Physician assessment (+/-sensitisation)	8	Sweden	Obstructive Lung Disease in Northern Sweden Study. 7-8 years old children enrolled in school in 1996 in northern Sweden (born 1988-1989) (77)
Oliveti, 1995 (78)	CC	262	Q	DD PLUS asthma medication	9	USA	Cases and age matched controls were identified using rosters of patients followed during the previous year. he majority of children from each group were insured by Medicaid (low income)
Miyake, 2008 (79)	PC	763	Q	ISAAC	2	Japan	OMCHS study. Population based birth cohort of infants born in 2002-2003
da Costa Lima, 2003; Menezes, (80, 81)	PC	4297	I, Q/I	ISAAC	18, 22	Brazil	Pelotas Birth Cohort. Population based birth cohort of infants born in 1982 in the city of Pelotas
Perez Tarazona, 2010 (82)	PC	620	Q	Parent reported wheeze	1	Spain	Population based birth cohort of infants born in 2007-2008 in Valencia
Caudri, 2013; Scholtens, 2009 (83, 84)	PC	3115	Q	Current wheeze; Parent reported wheeze; Parent reported wheeze ever (+/- sIgE); ISAAC; BHR: metacholine PC20	8	Netherlands	PIAMA: population-based born in 1996-1997 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kerr, 1981(85)	PC	269	I	Parent reported wheeze	0.5	New Zealand	Birth cohort hospital based, born 1977-1978 (normal risk of disease)
Porro, 1993 (86)	CC	465	Q	Parent reported wheeze	<1.6	Italy	Hospital based study with matched controls (normal risk of disease)
Kurt, 2008(87)	CS	25843	Q	Current wheeze; Parent reported current wheeze	15	Turkey	Prevalence and Risk Factors of Allergies in Turkey (PARFAIT): population representative sample of children aged 9-15 years old (normal risk of disease0
Schonberger, 2005 (88)	PC	443	D/Q	ISAAC	2	Netherlands	PREVASC study: cohort born in 1997-2000 with family history of asthma (high risk of disease)
Hagendorens, 2005 (89)	PC	693	Q	Parent reported current wheeze	1	Belgium	PIPO study: recruited from university service, born 1997-2001 (normal risk of disease)
Alho, 1990 (90)	PC	2130	Q	DD Wheeze	2	Finland	Birth cohort, population representative sample born 1985-1986 (normal risk of disease)
Rhodes, 2001(91)	PC	63	Q	Current wheeze AND BHR	22	UK	Hospital based, born 1976-1977, family history of allergy (high risk of disease)
Rona, 2005 (92)	RC	1213	R	ECRHS questionnaire; ECRHS questionnaire AND SPT AND BHR; BHR: metacholine PC_{20}	27	Chile	Infants born in a hospital in 1974-1978 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Rosas Vargas 2002 (93)	CC	148	Q	DD	3	Mexico	Hospital-based study, cases born in 2000 (normal risk of disease)
Rothenbacher, 2005(94)	PC	803	Q/I	DD	2	Germany	Recruited from university service, born in 2000-2001 (normal risk of disease)
Rusconi, 1999; Rusconi, 2005 (95, 96)	CS	16933	Q	Parent reported persistent wheezing: >=1 in first 2 years, and in past 12 months; Transient early wheeze: wheeze in first 2 years but not past 12 months; ISAAC	7	Italy	SIDRIA survey of a representative sample of children aged 6-7 years old
Saarinen, 1995 (97)	PC	150	R	Physician assessment	5, 17	Finland	Recruited from hospital and born in 1975 (normal risk of disease)
Selcuk, 1997 (98)	CS	5412	Q	Parent reported wheeze ever; Parent reported current asthma	12	Turkey	Children 7-12 ys of 18 primary schools (normal risk of disease)
Sunyer, 2006 (99)	PC	462	Q	DD	6.5	Spain	Population representative sample born in 1997-1998 (normal risk of disease)
Sunyer, 2001(100)	PC	596	Q	ISAAC	4	Tanzania	Cohort born in 1995-1996 in urban area (normal risk of disease)
Hide, 1981(101)	PC	843	D/Q	Wheeze ever; Parent reported wheeze	1	UK	The Isle of Wight Prevention study: born in 1977-1978 (normal risk of disease)

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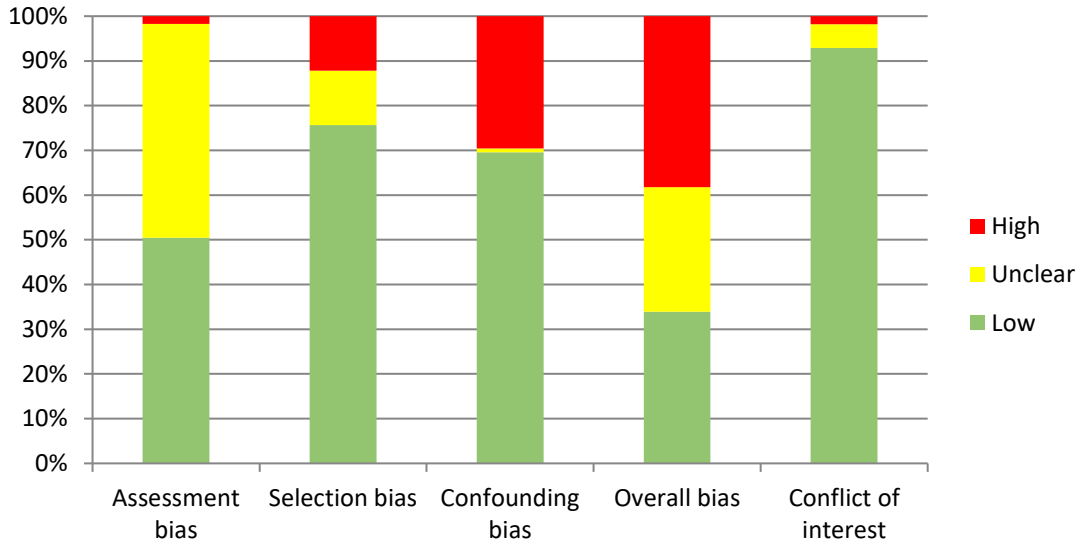
Takemura, 2002 (102)	CS	23828	Q	ATS questionnaire: DD asthma PLUS >=2 episodes of wheeze	15	Japan	The Tokorozawa Childhood Asthma and Pollinosis Study: Representative sample of children in public elementary schools (normal risk of disease)
Tian, 2009 (103)	PC	472	I	Physician assessment	2	China	Infants from urban areas born in 2004-2006 (normal risk of disease)
Yamamoto, 2011(104)	PC	1344	Q	ISAAC	3	Japan	Tokyo Children's Health Illness and Development study (T-CHILD)
Wright, 1989; Wright, 1995 (105, 106)	PC	988	Q/I	DD; >=4 episodes of wheeze in past year	1, 6	USA	Tuscon Children's Respiratory Study: Healthy newborn infants recruited from local health maintenance organisation born in 1980-1984 (normal risk of disease)
Van Beijstervelft, 2008 (107)	PC	24018	Q	DD	5	The Netherlands	Netherlands Twin Register: born in 1987-2000 (normal risk of disease)
Wang, 2006 (108)	CS	8733	Q	ISAAC	10	China	Population representative sample of children in elementary schools and nurseries (normal risk of disease)
Oddy, 1999; Oddy, 2003; Oddy, 2004 (109-111)	PC, NCC	2456	D/I, Q, D/Q	DD; DD PLUS current wheeze; Parent reported current wheeze; DD asthma PLUS >=3 episodes of wheeze	1, 6, 8	Australia	Western Australia Pregnancy Cohort: Recruited from antenatal clinics born in 1989-1992 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Wickens, 2001 (112)	CC	474	I	ISAAC	6.5	New Zealand	Population-based study (normal risk of disease)
Zhu, 2012 (113)	CC	542	Q	DD	14	China	Population-based study (normal risk of disease)
Zutavern, 2004 (114)	PC	606	I	Parent reported current wheeze	2, 5.5	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)
Ogbuanu, 2009 (115); Soto-Ramırez, 2012 (116)	PC	1033	NA, Q	Spirometry	18	UK	Isle of Wight Prevention Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990
Dogaru, 2012 (117)	PC	1458	Q	Spirometry	12	UK	Population based sample of children of white and south Asian ethnic origin born between 1993 and 1997, part of the Leicestershire cohorts
Tennant, 2008 (118)	PC	392	Q	Spirometry	50	UK	Newcastle Thousand Families Study. Population based sample of subject born in 1947 who were either traced through the National Health Service Central Register or contacted the study team in response to media publicity in the mid 1990
Suwanpromma, 2012 (119)	CS	215	Q	Spirometry; BHR:hypertonic saline PC15	18	Thailand	Schoolchildren aged 6-18 years (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Eneli, 2006 (120)	PC	536	Q	BHR:hypertonic saline PC15	10	Germany	The Child Health and Environment Cohort Study: community based in urban area, born 1994 (normal risk of disease)
Tennant, 2010 (121)	PC	122	Q	Spirometry	14, 51	UK	The Newcastle Thousand Families Study: born in 1947 (normal risk of disease)

Figure 1 Risk of bias in studies of total breastfeeding and wheeze



1.2 Total Breastfeeding and wheeze

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 recurrent wheeze at age 1 year – cluster adjusted odds ratio 0.7 (95% CI 0.29, 1.70); or at age 6.5 years – cluster adjusted odds ratio 1.2 (95% CI 0.7, 1.9). There was also no significant difference in odds of wheeze ever OR 1.1 (0.6, 1.8) or wheeze in the past 12 months OR 1.0 (0.7, 1.6) at 6.5 years. All other evidence was derived from observational studies.

1.2.1 Age at outcome measurement 0-4

1.2.1.1 Ever vs. never

Figure 2 shows the outcomes of 14 eligible observational studies evaluating TBF ever vs never and risk of wheeze. The data were not pooled due to extreme heterogeneity across studies (I^2=83.3%). Thirteen studies were prospective cohorts and one was a cross-sectional study. All studies had low or unclear risk of bias in most domains. There was no evidence of publication bias and the reason for extreme statistical heterogeneity was not clear (Figure 3). Adjusted data showed no relationship, whereas unadjusted data showed reduced wheeze with TBF. There was a significant subgroup difference in the relationship between TBF ever and wheeze, between infants with a family history of wheeze or allergic disorder, and more representative populations, with a significant association and reduced heterogeneity in the high risk infants (Table 1).

In dose-response analysis there was some evidence that increasing duration of TBF is associated with a greater reduction in risk of wheeze, in this age group (Figure 4-Figure 6). This analysis was dominated by one study Elliott, which reported appropriately adjusted OR for different durations of TBF in relation to wheeze in the first 3 years. In the same cohort there was no relationship between TBF and wheeze at older ages.

Figure 2 Total breastfeeding ever vs. never and risk of wheeze in children aged 0-4 years

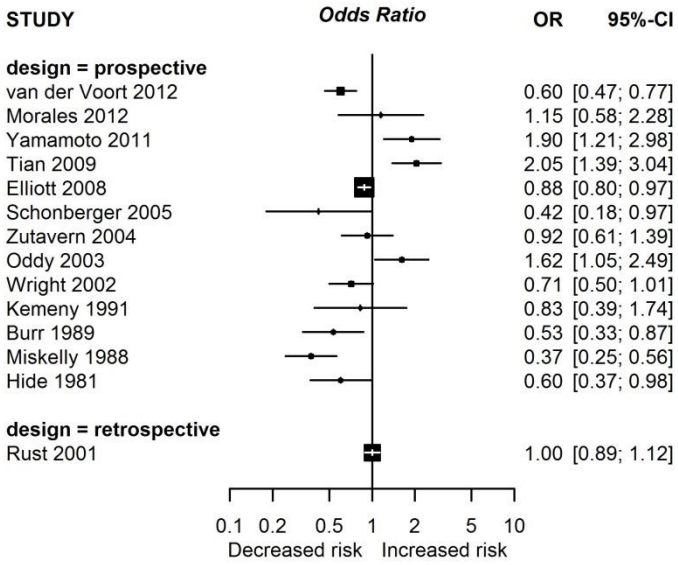
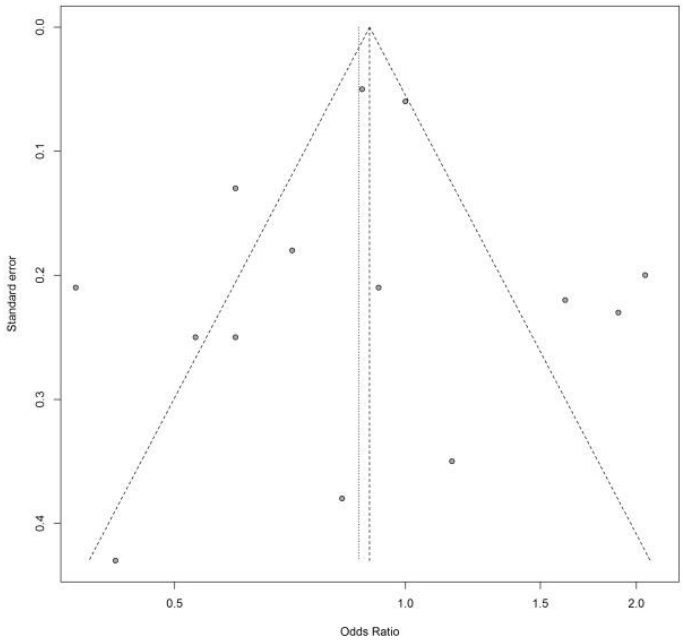


Figure 3 Risk of publication bias in studies investigating total breastfeeding ever vs. never and risk of wheeze in children aged 0-4 years



Egger's test p-value =0.736

Table 2 Subgroup and stratified analysis of TBF ever and risk of wheeze 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	0.87 [0.71; 1.06]	83.3	
Adjusted	7	0.98 [0.72; 1.35]	76.8	Not tested
Unadjusted	12	0.79 [0.63; 0.99]	87.7	
Study Design – Prospective	13	0.85 [0.66; 1.10]	83.6	0.26
Study Design – Retrospective	1	1.00 [0.89; 1.12]	--	
Risk of disease – High	4	0.51 [0.37; 0.72]	48.7	< 0.001
Risk of disease – Normal	10	1.04 [0.85; 1.28]	81.7	
Risk of bias – Low	6	0.75 [0.54; 1.05]	74.8	0.25
Risk of bias – High/Unclear	8	0.96 [0.74; 1.25]	86.2	

Figure 4 Total breastfeeding (dose response) short vs. never and risk of wheeze in children aged 0-4 years

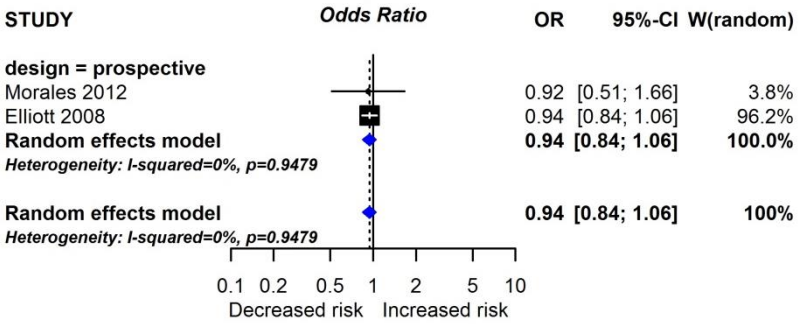


Figure 5 Total breastfeeding (dose response) medium vs. never and risk of wheeze in children aged 0-4 years

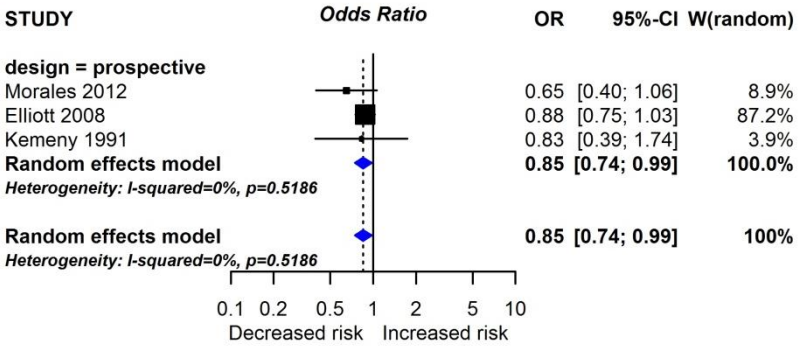
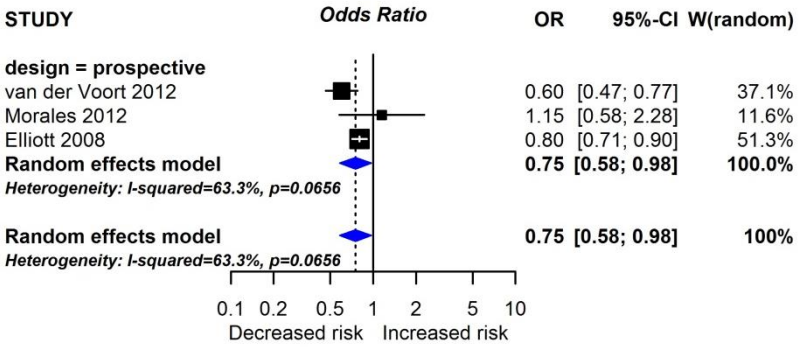


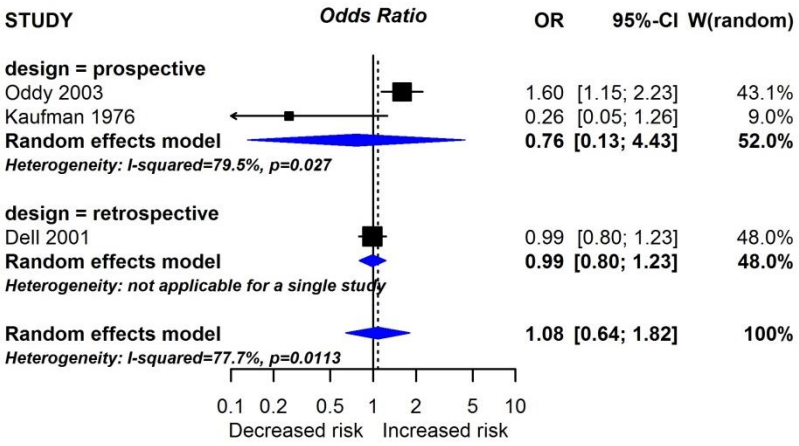
Figure 6 Total breastfeeding (dose response) long vs. never and risk of wheeze in children aged 0-4 years



1.2.1.2 1-2 Months

Figure 7 shows the pooled estimates of three studies which assessed risk of wheeze and TBF for ≥1-2 months vs. <1-2 months, suggesting no association, with very high heterogeneity between studies (I^2=77.7%). The study of Oddy and Dell provided adjusted odds ratios, whilst the study of Kaufman provided unadjusted estimates, and therefore carried a high risk of bias.

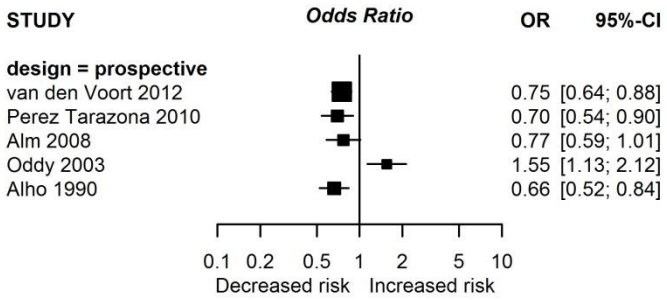
Figure 7 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of wheeze in children aged 0-4 years



1.2.1.3 3-4 Months

Five studies (all prospective cohorts) reported relevant data, which could not be combined in a meta-analysis due to extreme heterogeneity (I^2=81%; Figure 8). With the exception of the Oddy study, all the studies showed a tendency for a lower risk of wheeze if TBF lasted for at least 3-4 months when compared to less than this cut-off. The studies of Perez-Tarazona and Alho provided unadjusted estimates and therefore carried a high risk of bias. The other three studies had a low overall risk of bias and the source of heterogeneity is not clear.

Figure 8 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years



1.2.1.4 5-7 Months

Nine observational studies examined the association between TBF for ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 0-4 years (Figure 9). There was no association between TBF and risk of wheeze in this analysis, but with high heterogeneity across studies (I^2=72.3%). Subgroup analyses (Table 3) show no important subgroup differences, and outcomes are similar in unadjusted and adjusted analyses. Heterogeneity remains high in all analyses, and we were unable to explain the heterogeneity in outcomes between studies.

Figure 9 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 0-4 years

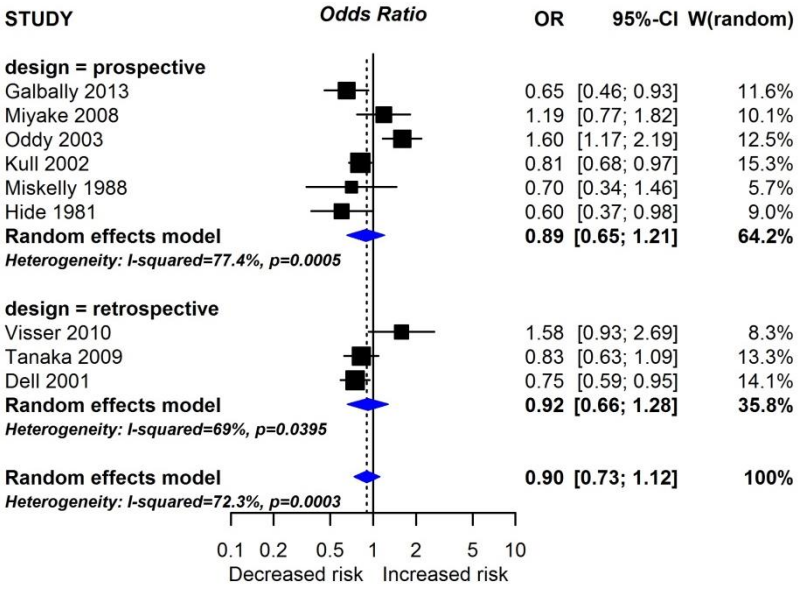


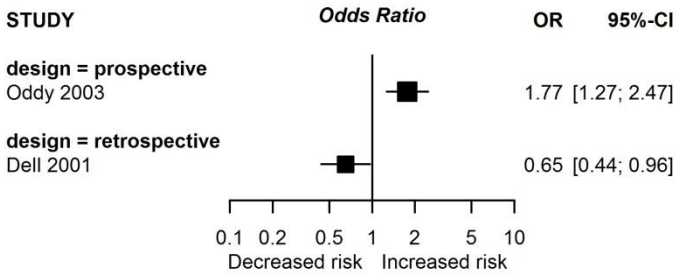
Table 3 Subgroup Analysis of risk of wheeze and total breastfeeding ≥5-7 months vs. <5-7 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	9	0.91 [0.73; 1.12]	72.3	
Adjusted	7	0.96 [0.76; 1.22]	77.1	Not tested
Unadjusted	8	0.89 [0.63; 1.27]	89.3	
Study Design – Prospective	6	0.89 [0.65; 1.21]	77.4	0.89
Study Design – Retrospective	3	0.92 [0.66; 1.28]	69	
Risk of disease – High	1	0.71 [0.34; 1.46]	--	0.49
Risk of disease – Normal	8	0.92 [0.73; 1.15]	75.5	
Risk of bias – Low	3	0.94 [0.59; 1.51]	88.6	0.78
Risk of bias – High/Unclear	6	0.88 [0.69; 1.12]	54.3	

1.2.1.5 8-12 Months

Two prospective cohort studies had eligible data that could be pooled to calculate OR for wheeze in infants with TBF for ≥8-12 months vs. <8-12 months and are shown in Figure 10. Data could not be pooled due to extreme statistical heterogeneity (I^2=93.1%). The overall risk of bias in the Oddy study was assessed as low and that of Dell unclear.

Figure 10 Total breastfeeding for ≥8-12 months vs. <8-12 months and risk of wheeze in children aged 0-4 years

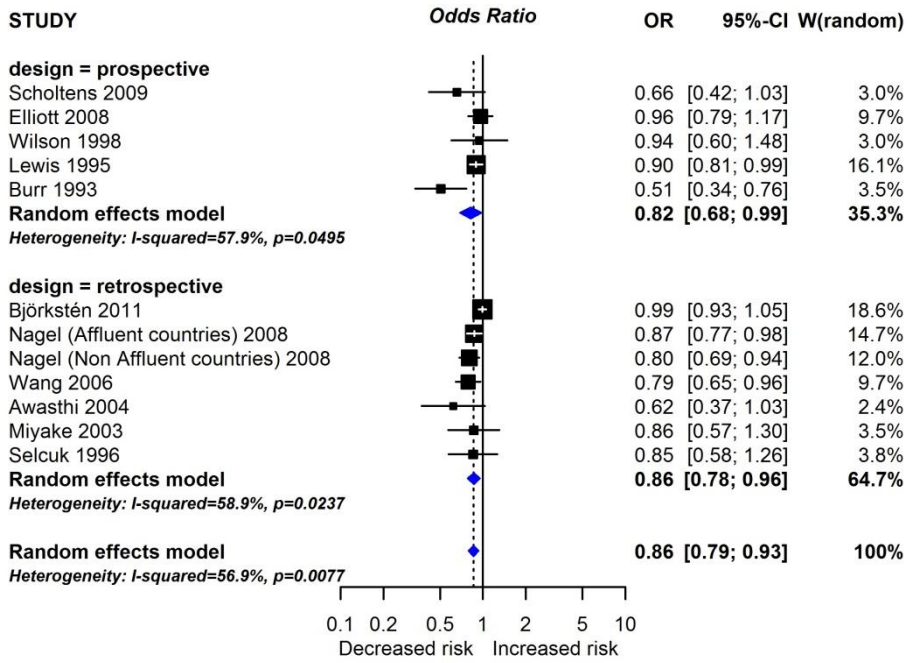


1.2.2 Age at outcome measurement 5-14

1.2.2.1 Ever vs. never

Figure 11 illustrates the pooled OR from 12 studies for risk of wheeze in children aged 5-14 years who ever initiated TBF vs. those who never did, suggesting an association between ever BF and reduced risk of wheeze. The statistical heterogeneity between studies was high (I^2=56.9%). Five studies were prospective cohorts, two of which had an overall low risk of bias, one had an unclear risk of bias due to unclear selection method, and two had unadjusted estimates (Wilson and Lewis), which carried a high risk of confounding. There were 7 case-control studies, five of which were considered to have a low or unclear overall risk of bias, whilst the studies of Nagel (affluent and non-affluent countries) and Miyake were considered to have a high risk of bias due to the selection of participants.

Figure 11 Total breastfeeding ever vs. never and risk of wheeze in children aged 5-14 year

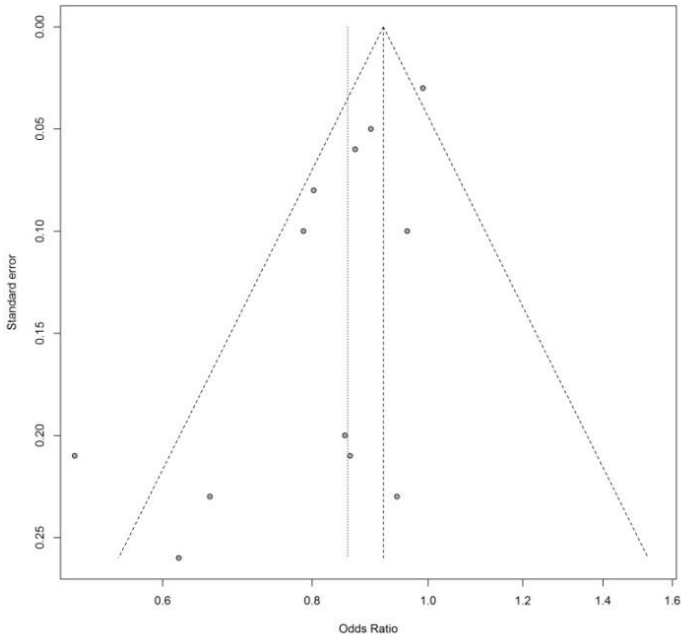


A Funnel plot to explore publication bias is shown in Figure 12. The plot is not symmetrical, and the Egger's test for asymmetry reaches statistical significance suggesting evidence of publication bias.

Subgroup and stratified analyses (Table 4) did not show clear subgroup differences, other than a difference for risk of disease based on one study (Burr 1993); and findings were similar in adjusted and unadjusted analyses.

Dose response analysis (Figure 13-Figure 15) did not show evidence of a dose response effect of increasing durations of TBF compared with never TBF on risk of wheeze.

Figure 12 Risk of publication bias in studies investigating breastfeeding ever vs. never and risk of wheeze in children aged 5-14 years



Egger's test p-value = 0.007

Table 4 Subgroup Analysis of risk of wheeze and total breastfeeding never vs. ever 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)	12	0.86 [0.79; 0.93]	56.9	
Adjusted	10	0.88 [0.82; 0.95]	48.3	Not tested
Unadjusted	9	0.84 [0.77; 0.91]	33.9	
Study Design – Prospective	5	0.82 [0.69; 0.99]	57.9	0.65
Study Design – Retrospective	7	0.86 [0.78; 0.96]	58.9	
Risk of disease – High	1	0.51 [0.34; 0.77]	--	0.01
Risk of disease – Normal	11	0.88 [0.82; 0.95]	42.6	
Risk of bias – Low	4	0.76 [0.55; 1.05]	77.5	0.43
Risk of bias – High/Unclear	8	0.87 [0.82; 0.92]	0.0	

Figure 13 Total breastfeeding (dose response) short vs. never and risk of wheeze in children aged 5-14 years

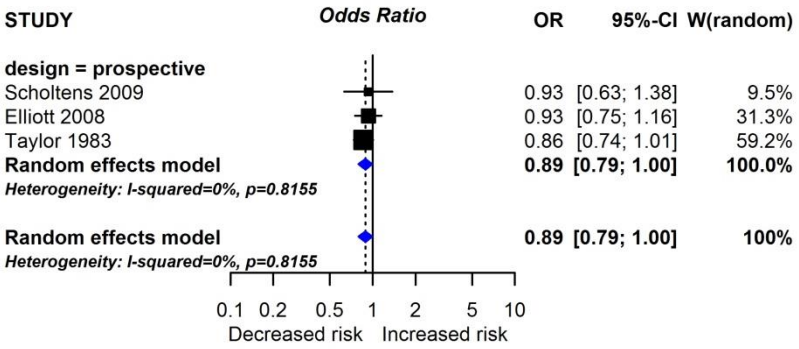


Figure 14 Total breastfeeding (dose response) medium vs. never and risk of wheeze in children aged 5-14years

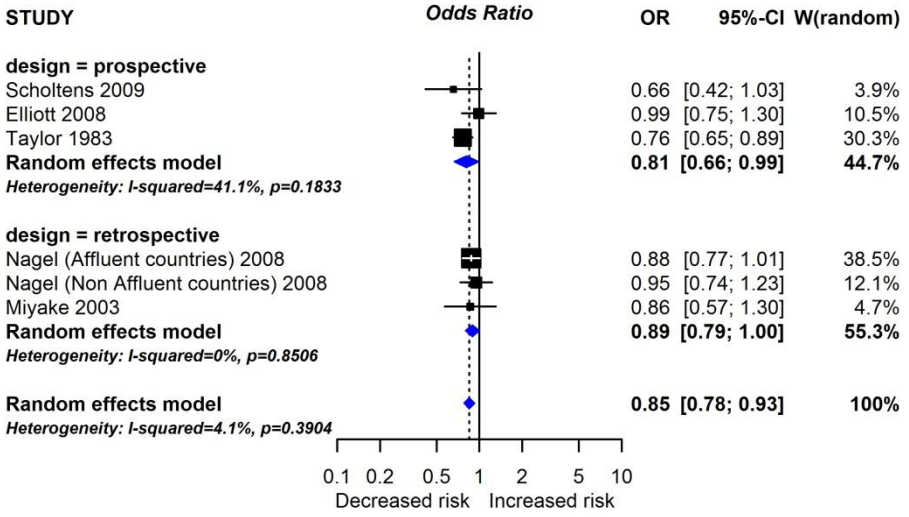
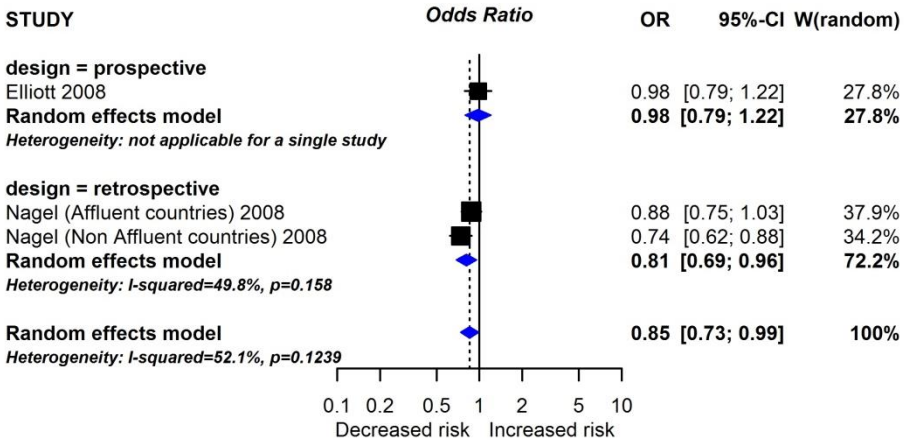


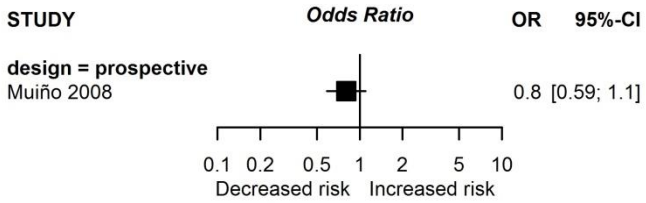
Figure 15 Total breastfeeding (dose response) long vs. never and risk of wheeze in children aged 5-14 years



1.2.2.2 1-2 Months

A cohort study of 897 infants born in Brazil showed no evidence of association between TBF for ≥1-2 months vs. <1-2 months in children aged 5-14 year (Figure 16). The study had an overall high risk of bias due to not controlling for relevant potential confounders.

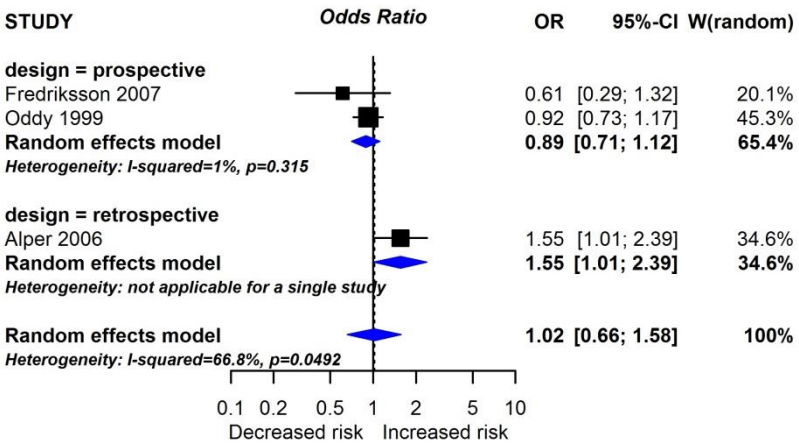
Figure 16 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of wheeze in children aged 5-14 years



1.2.2.3 3-4 Months

Two prospective cohort studies and one case-control study had eligible data to calculate a combined OR of wheeze in infants who had TBF for ≥3-4 months vs. <3-4 months at age 5-14 years, showing no clear evidence of an effect (Figure 17). There was high statistical heterogeneity between studies (I^2=66.8%). Two studies had an unclear risk of bias and the study of Oddy had a low risk of bias.

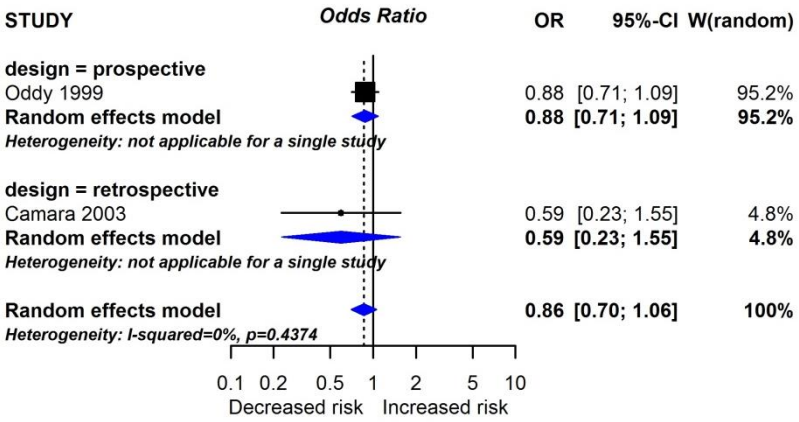
Figure 17 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 5-14 years



1.2.2.4 5-7 Months

A case-control study and a prospective cohort had data eligible for meta-analysis, and their combined effect showed no evidence of association between TBF ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 5-14 years (Figure 18). The study of Camara had a high risk of overall bias as it provided unadjusted data. There was no heterogeneity between studies (I^2=0.0%).

Figure 18 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of wheeze in children aged 5-14 years

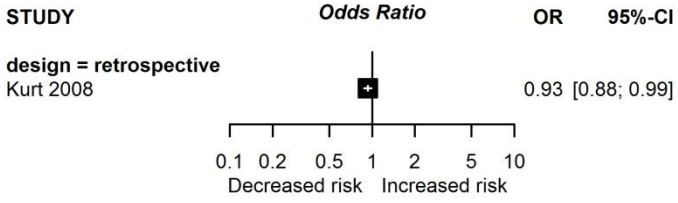


1.2.3 Age at outcome measurement 15+

1.2.3.1 Ever vs. never

One case-control study reported risk of wheeze at age 15 or beyond in infants who received any TBF compared to those who never did. The data are adjusted, the study had a low overall risk of bias, and they show a reduced risk of wheeze (Figure 19).

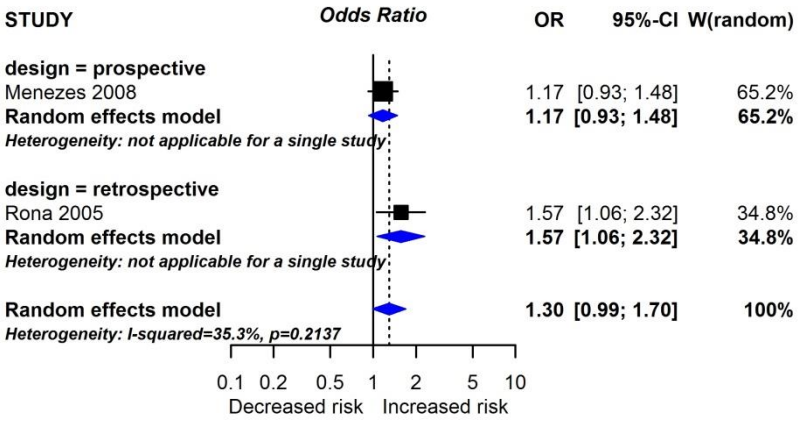
Figure 19 Total breastfeeding ever vs. never and risk of wheeze in children aged 15+ years



1.2.3.2 1-2 Months

Figure 20 illustrates the combined effect of two eligible studies, a retrospective and a prospective cohort, showing no clear evidence of an association with risk of wheeze in children at age 15 or beyond who received TBF for ≥1-2 months vs. <1-2 months. The studies had moderate statistical heterogeneity between them (I^2=35.3%) and had low or unclear overall risk of bias.

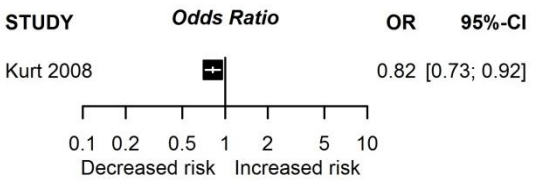
Figure 20 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of wheeze in children aged 15+ years



1.2.3.3 3-4 Months

One cross-sectional study reported the risk of wheeze at age 15 or beyond, in infants who had TBF for ≥3-4 months vs. <3-4 months, showing significantly reduced odds of wheeze with longer TBF (Figure 21). The study had a low overall risk of bias.

Figure 21 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 15+ years



1.3 Total Breastfeeding and atopic wheeze

1.3.1 Age at outcome measurement 5-14

One study reported atopic wheeze at age 5-14 in relation to TBF. The findings are shown in Figure 22, and show no association. It was also possible to assess does response using this study, and there was no evidence of a dose-response relationship (Figure 23-Figure 24).

Figure 22 Total breastfeeding (dose response) ever vs. never and risk of atopic wheeze in children aged 5-14 years

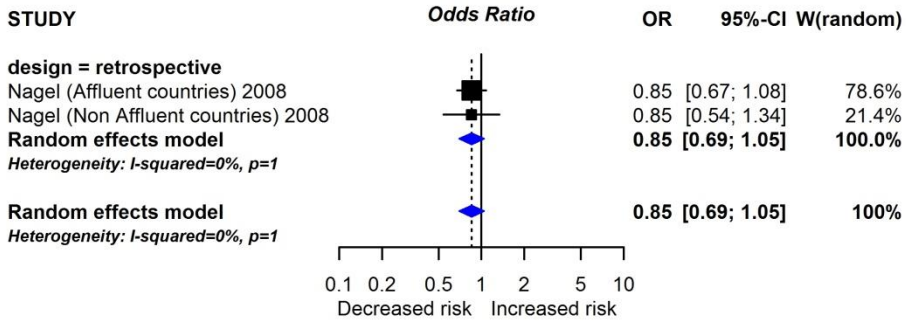


Figure 23 Total breastfeeding (dose response) medium vs. never and risk of atopic wheeze in children aged 5-14 years

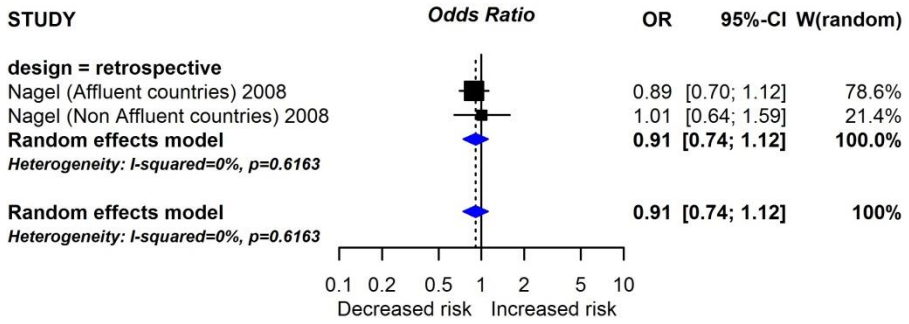
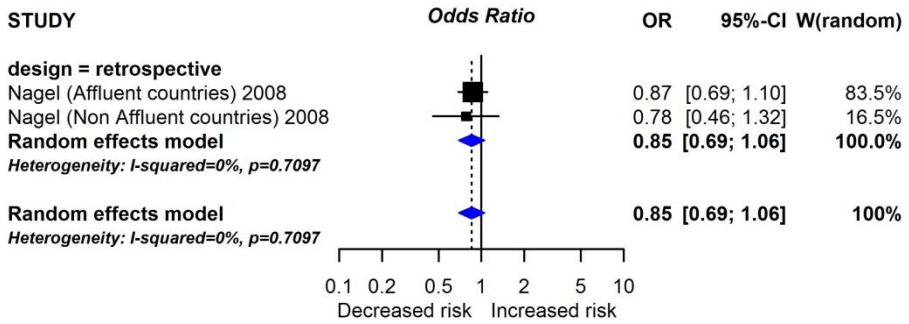


Figure 24 Total breastfeeding (dose response) long vs. never and risk of atopic wheeze in children aged 5-14 years

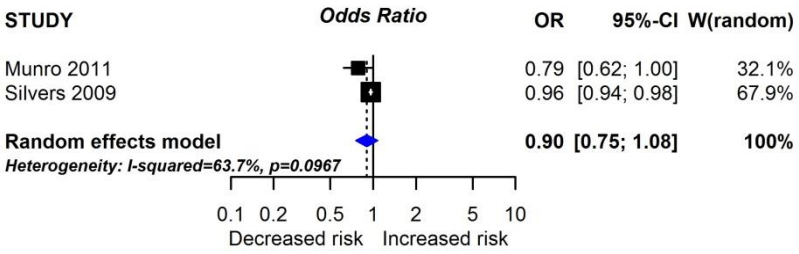


1.4 Total Breastfeeding per month and Wheeze

1.4.1 Age at outcome measurement 5-14

Two studies reported data for TBF exposure per month and risk of wheeze at age 5-14, and are shown in Figure 25. They show no significant association, with high statistical heterogeneity. Both studies are prospective cohort studies in a normal risk population, with the study of Silvers having a low risk of bias in all domains, whilst the study of Munro carried an unclear risk due to unclear selection bias, which may contribute to explain the high heterogeneity between studies.

Figure 25 Total breastfeeding per month and risk of wheeze in children aged 5-14 years



1.5 Total Breastfeeding and Recurrent Wheeze

1.5.1 Age at outcome measurement 0-4

1.5.1.1 Ever vs. never

Eleven observational studies had data that could be used to calculate combined OR of risk of recurrent wheeze in children 0-4 years old who were exposed to ever vs. never TBF, showing a negative association between this exposure and risk of wheeze. There were 9 prospective cohorts and 2 case-control studies. The study of Businco had a high overall risk of bias due to lack of adjustment for relevant potential confounders. The two case-control studies had unclear risk of bias, three prospective cohorts had unclear risk of bias, and 5 had a low risk of overall bias. These differences in overall risk might partly explain the very high heterogeneity observed between studies (I^2=80.7%). For this reason data were not pooled in meta-analysis

(Figure 26). There was no visual or statistical evidence of publication bias as illustrated in Figure 27. The subgroup analysis showed no difference between the various groups compared, with extreme heterogeneity in most analyses (Table 5). Dose response analysis (Figure 28-Figure 30) showed some evidence of a dose response, although only a small proportion of studies could be included in dose response analysis due to available data.

Figure 26 Total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 0-4 years

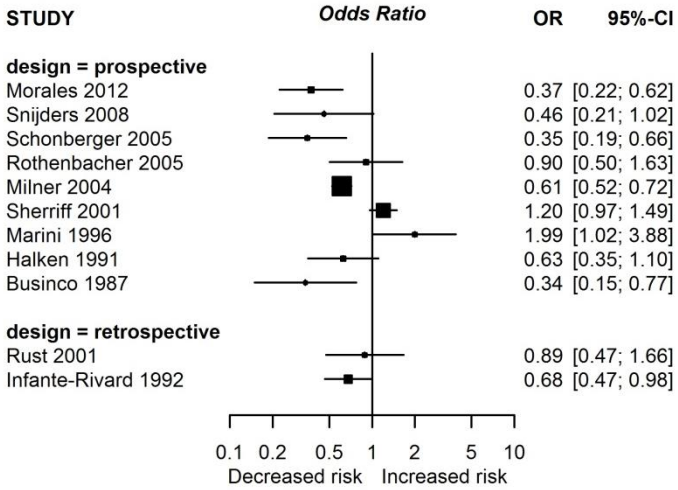
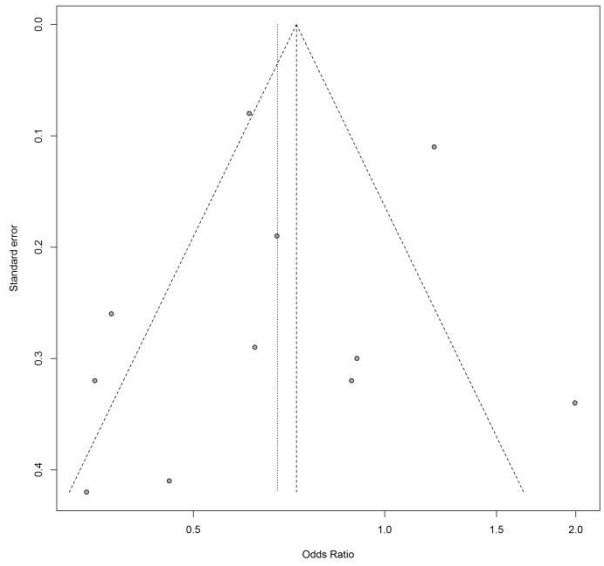


Figure 27 Risk of publication bias in studies investigating total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 0-4 years



Egger's test p-value = 0.663

Table 5 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ever vs. never (or ever) 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 value used)	11	0.68 [0.51; 0.91]	80.7	
Adjusted	7	0.78 [0.53; 1.15]	78.0	Not tested
Unadjusted	9	0.63 [0.50; 0.79]	77.1	
Study Design – Prospective	9	0.66 [0.46; 0.94]	84.4	0.68
Study Design – Retrospective	2	0.73 [0.53; 1.00]	0.0	
Risk of disease – High	3	0.62 [0.19; 2.03]	88.2	0.86
Risk of disease – Normal	8	0.69 [0.52; 0.94]	79.6	
Risk of bias – Low	5	0.68 [0.41; 1.12]	79.4	0.96
Risk of bias – High/Unclear	6	0.67 [0.47; 0.96]	73.9	

Figure 28 Total breastfeeding short vs. never term and risk of recurrent wheeze in children aged 0-4 years

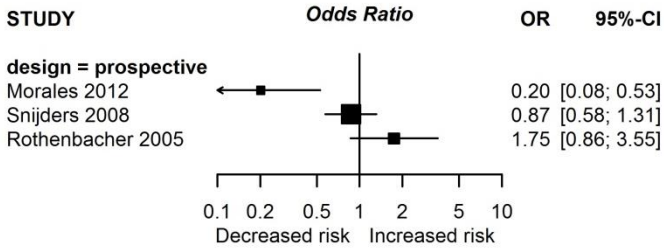


Figure 29 Total breastfeeding medium vs. never term and risk of recurrent wheeze in children aged 0-4 years

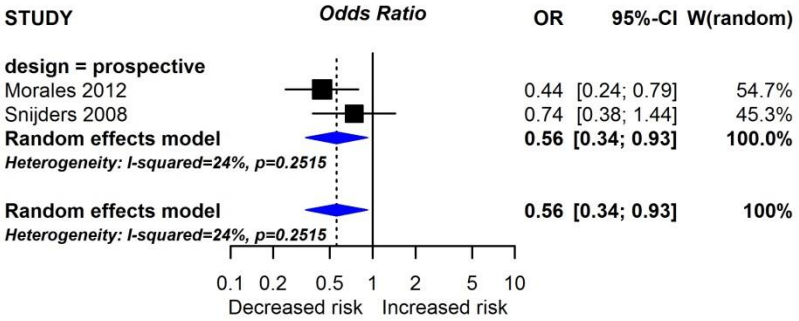
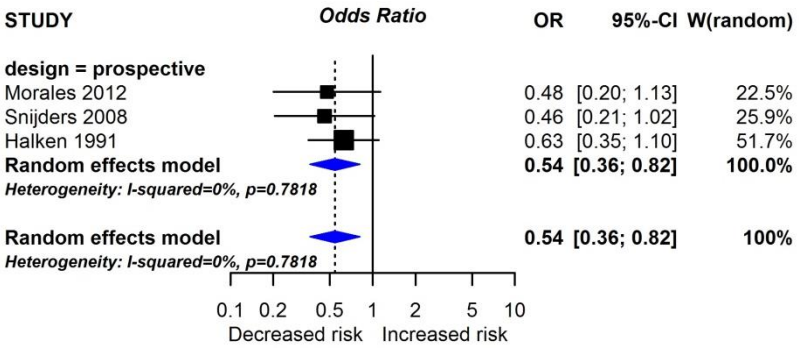


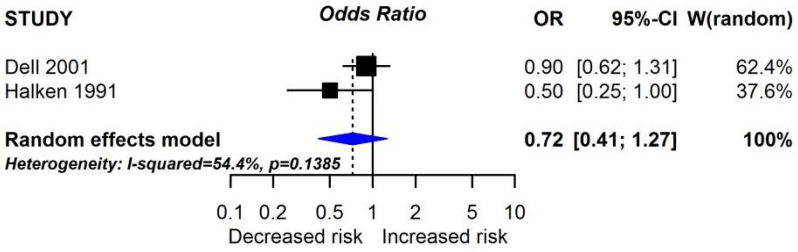
Figure 30Total breastfeeding long vs. never term and risk of recurrent wheeze in children aged 0-4 years



1.5.1.2 1-2 Months

Two prospective cohort studies had outcome data suitable for meta-analysis, showing no evidence of association between TBF for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 0-4 years. The study of Halken had an overall low risk of bias whilst the study of Dell had an unclear overall risk bias. There was evidence of high heterogeneity between the studies (I^2=54.4%)

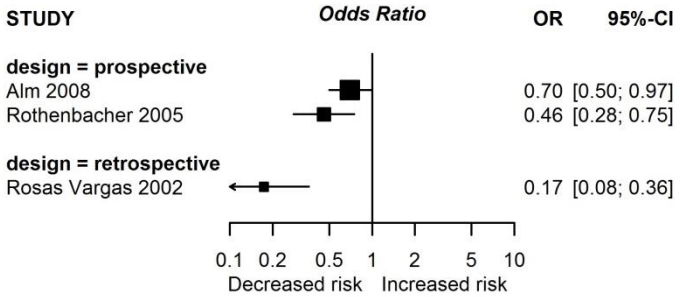
Figure 31 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 0-4 years



1.5.1.3 3-4 Months

Three observational studies had data eligible for meta-analysis, however they could not be pooled due to extreme heterogeneity (Figure 32). The studies of Alm and Rothenbacher were prospective cohorts and one (Rosas-Vargas) was a case-control study. The latter had a high risk of overall bias due to lack of adjustment for potential confounders. The other two studies had a low overall risk of bias.

Figure 32 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 0-4 years



1.5.1.4 5-7 Months

Three prospective cohort studies (Miyake, Kull, Gustaffson) and three case-control studies (Visser, Tanaka, Dell) reported data that could be pooled to calculate the OR for wheeze in children aged 0-4 years who were exposed to TBF for ≥5-7 months vs. <5-7 months. As shown in Figure 33, their combined effect suggests no difference in risk of wheeze (OR 0.79; 95% CI 0.61, 1.04), with moderate heterogeneity between studies (I^2=39.7%). In subgroup and stratified analyses (Table 6), there was evidence for a relationship between TBF ≥5-7 months and reduced risk of recurrent wheeze at age 0-4 in prospective studies, and studies reporting adjusted data and low risk of bias, but not in retrospective or unadjusted studies or studies at high/unclear risk of bias.

Figure 33 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of recurrent wheeze in children aged 0-4 years

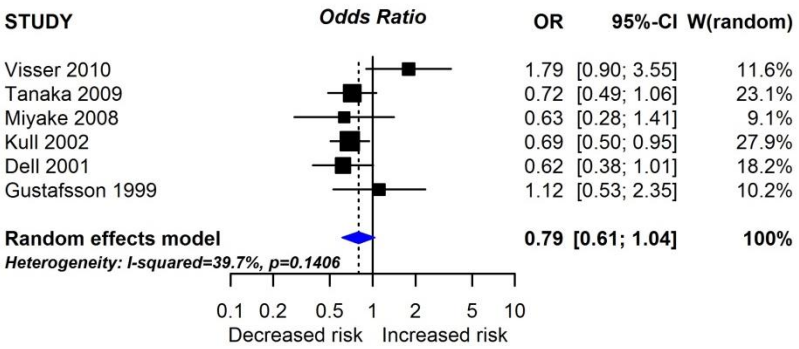


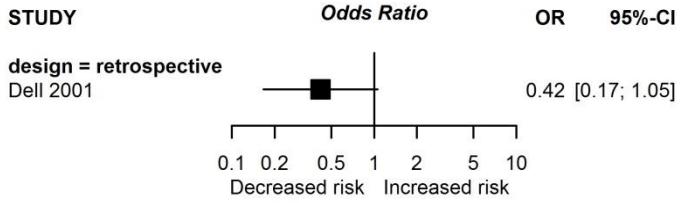
Table 6 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ≥5-7 months vs. <5-7 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.79 [0.61; 1.04]	39.7	
Adjusted	4	0.68 [0.55; 0.84]	0.0	Not tesed
Unadjusted	5	0.80 [0.56; 1.16]	60.6	
Study Design – Prospective	3	0.73 [0.56; 0.96]	0.0	0.56
Study Design – Retrospective	3	0.87 [0.51; 1.49]	69.7	
Risk of disease – High	-	-	-	-
Risk of disease – Normal	6	0.79 [0.61; 1.04]	39.7	
Risk of bias – Low	1	0.69 [0.51; 0.95]	--	0.39
Risk of bias – High/Unclear	5	0.85 [0.59; 1.23]	48.1	

1.5.1.5 8-12 Months

One case-control study reported risk of recurrent wheeze in children breastfeed ≥8-12 months vs. <8-12 months. The study had an overall unclear risk of bias and suggested no significant difference in OR of disease (Figure 34).

Figure 34 Total breastfeeding for ≥8-12 months vs. <8-12 months and risk of recurrent wheeze in children aged 0-4 years



Subgroup analyses to investigate differences in risk of recurrent wheeze and TBF ≥5-7 months vs. <5-7 months in children aged 0-4 years, showed no statistically significant differences (Table 7).

1.5.2 Age at outcome measurement 5-14

1.5.2.1 Risk of recurrent wheeze at age 5-14, in relation to TBF Ever vs. never

Twenty five observational studies reported the association between recurrent wheeze at age 5-14 and TBF ever vs. never. Most studies reported ORs below 1, with an overall effect size suggestive of a negative association between TBF and disease (OR 0.88; 95% CI 0.82, 0.94) and moderate heterogeneity across studies (I^2=36.5%) (Figure 35). Thirteen studies were prospective cohorts (9 of which had a low overall risk of bias, 3 had high risk, and 1 unclear), 1 retrospective cohort study (with a high overall risk of bias due to confounding not being accounted for in the analyses), 4 case-control studies (of which 3 had a high overall risk of bias and one had an unclear overall risk of bias), 1 nested case-control study (with high risk of bias due to selection bias), and six cross-sectional studies (of which 3 were considered to have a high overall risk of bias mainly due to selection or confounding bias, 2 had an unclear risk of bias and 1 study had a low risk of bias). A funnel plot was used to examine the likelihood of publication bias (Figure 36), which showed significant asymmetry, confirmed

by a statistically significant Egger's test P=0.01. Dose response analysis (Figure 37-Figure 39) suggests an association between increasing duration of TBF and greater protection against recurrent wheeze at age 5-14.

Figure 35 Total Breastfeeding ever vs. never and risk of recurrent wheeze in children aged 5-14 years

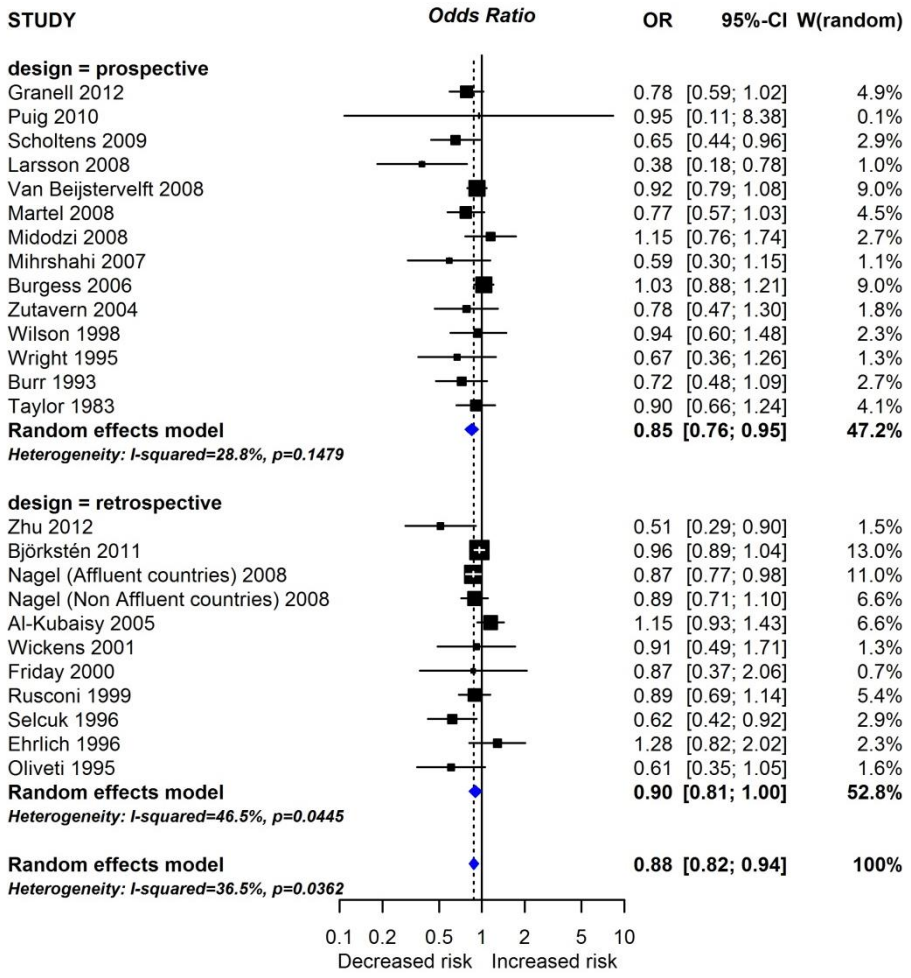
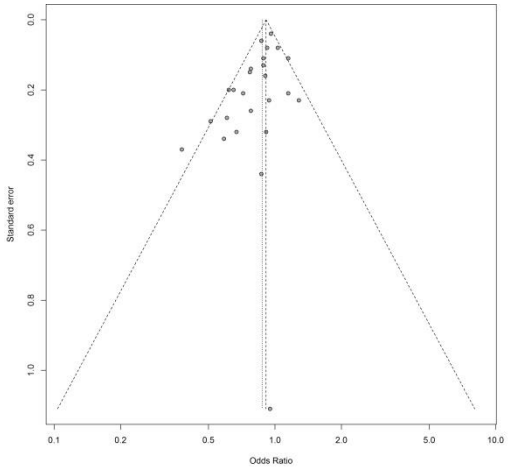


Figure 36 Risk of publication bias in studies investigating total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 5-14 years



Egger's test p-value = 0.012

Table 7 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ever vs. never months 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)	25	0.88 [0.82; 0.95]	36.5	
Adjusted	15	0.82 [0.74; 0.91]	44.9	Not tested
Unadjusted	22	0.83 [0.75; 0.91]	57.4	
Study Design – Prospective	14	0.85 [0.76; 0.95]	28.8	0.44
Study Design – Retrospective	11	0.90 [0.81; 1.00]	46.5	
Risk of disease – High	3	0.70 [0.51; 0.97]	0.0	0.18
Risk of disease – Normal	22	0.89 [0.82; 0.96]	39.7	
Risk of bias – Low	10	0.80 [0.68; 0.93]	55.9	0.16
Risk of bias – High/Unclear	15	0.90 [0.83; 0.98]	18.7	

Figure 37 Total breastfeeding (dose response) short vs. never term and risk of recurrent wheeze in children aged 5-14 years

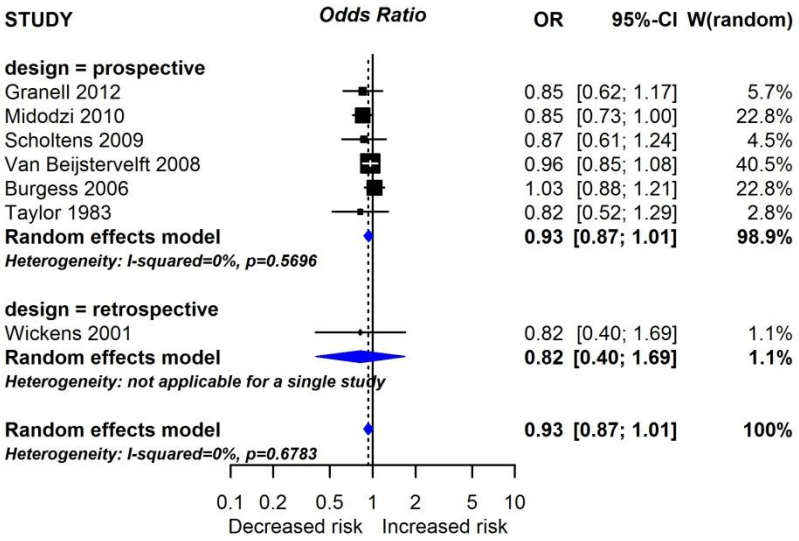


Figure 38 Total breastfeeding (dose response) medium vs. never term and risk of recurrent wheeze in children aged 5-14 years

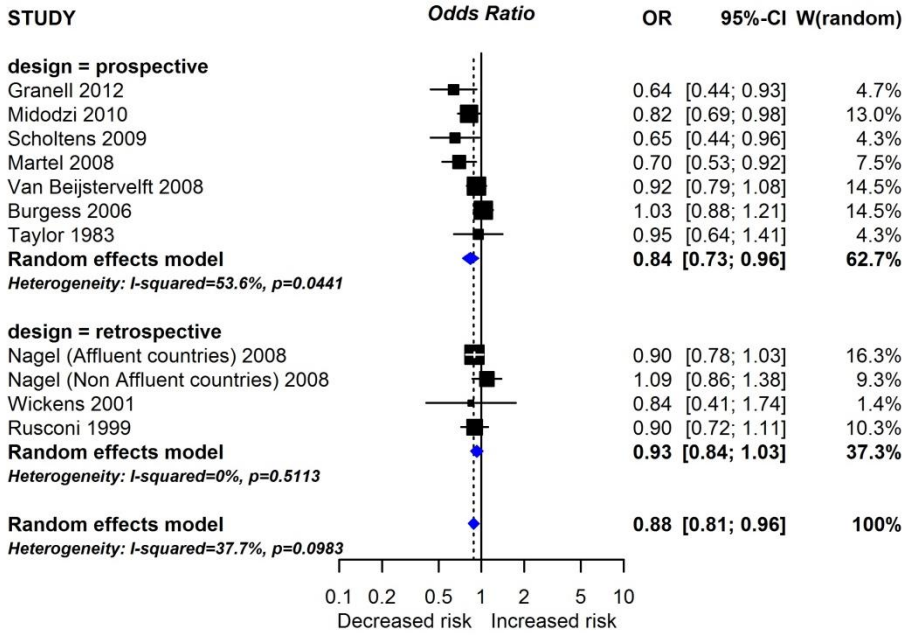
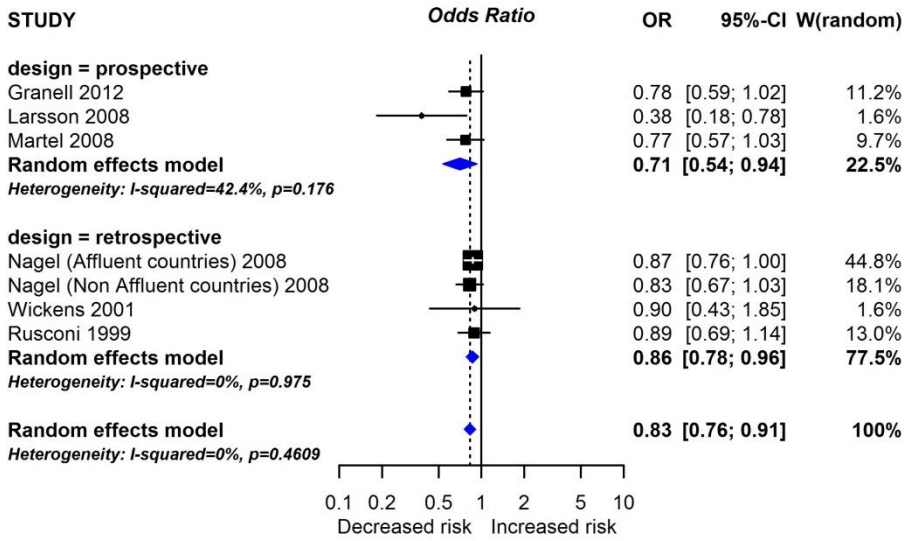


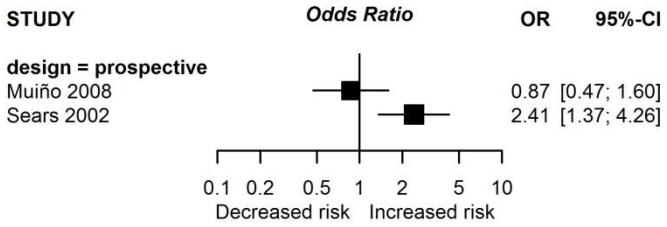
Figure 39 Total breastfeeding (dose response) long vs. never term and risk of recurrent wheeze in children aged 5-14 years



1.5.2.2 1-2 Months

Two observational studies reported risk of recurrent wheeze in infants with TBF for ≥1-2 months vs. <1-2 months, and could not be pooled due to extreme heterogeneity (I^2>80%). The study of Muino had an overall high risk of bias due to lack of adjustment for potential confounders, whilst the study of Sears reported adjusted data and had an unclear overall risk of bias (Figure 40).

Figure 40 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 5-14 years



1.5.2.3 3-4 Months

Figure 41 shows the pooled OR from ten observational studies that reported risk of recurrent wheeze at age 5-14 in infants who had TBF for ≥3-4 months vs. <3-4 months, showing a statistically significant association with reduced risk of wheeze (OR 0.76; 95% CI 0.67, 0.87), and moderate heterogeneity across studies (I^2=33.7%). Six studies were prospective cohorts (4 of which had a low overall risk of bias, 1 had a high risk of bias due to lack of adjustment for potential confounders, and 1 had an unclear overall risk of bias), 2 were retrospective cohorts (1 with a high risk of bias due to lack of adjustment for confounders and 1 was considered to carry a low overall risk of bias), 1 nested case-control study (with unclear overall risk of bias) and one cross-sectional (with unclear overall risk of bias). Egger's test showed that there was statistical evidence of publication bias (P=0.01) (

Figure 42). Subgroup and stratified analyses (Table 8) did not show important group differences, and findings were similar in adjusted and unadjusted analyses.

Figure 41 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years

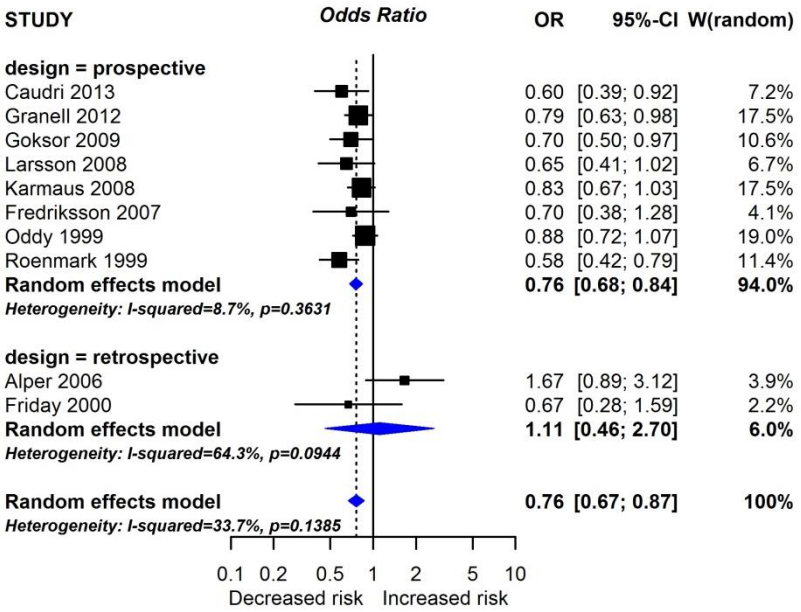
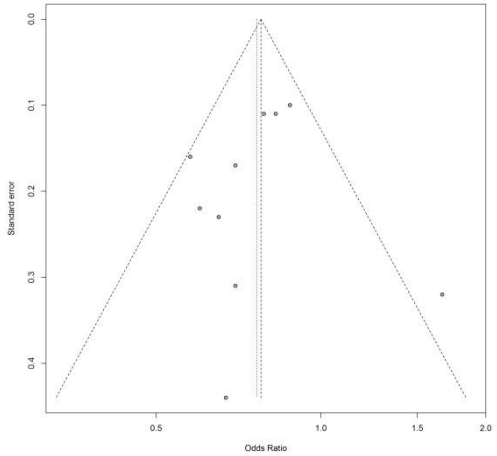


Figure 42 Risk of publication bias in studies investigating total breast feeding and recurrent wheeze ≥3-4 months vs. <3-4 months in children aged 5-14 years



Egger's test p-value = 0.012

Table 8 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ≥3-4 months vs. <3-4 months 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)	10	0.76 [0.67; 0.87]	33.7	
Adjusted	5	0.74 [0.56; 0.96]	48.0	Not tested
Unadjusted	7	0.67 [0.58; 0.77]	0.0	
Study Design – Prospective	8	0.76 [0.68; 0.84]	8.7	0.40
Study Design – Retrospective	2	1.11 [0.46; 2.70]	64.3	
Risk of disease – High	1	0.67 [0.28; 1.59]	--	0.77
Risk of disease – Normal	9	0.76 [0.67; 0.88]	40.5	
Risk of bias – Low	5	0.80 [0.72; 0.90]	0.0	0.74
Risk of bias – High/Unclear	5	0.76 [0.55; 1.05]	54.6	

1.5.2.4 5-7 Months

Nine observational studies reported the risk of recurrent wheeze in infants who had TBF for ≥5-7 months vs. <5-7 months that was eligible to calculate the overall OR (Figure 43), showing a reduced overall risk of disease (OR 0.76; 95% CI 0.62, 0.92). There was no evidence of heterogeneity across studies (I^2=0.0%). Four studies were prospective cohorts (of which 1 had a high overall risk of bias mainly due to selection bias, 1 had unclear risk of bias, and 2 had a low overall risk of bias), 1 retrospective cohort (carrying a high risk of overall bias due to lack of adjustment for potential confounders), 2 case-control (one of which lacked adjustment for potential confounders, therefore it carries a high risk of bias, and the other had unclear risk of bias) and 2 cross-sectional studies (both of which did not include adjustment for potential confounders, therefore carrying a high overall risk of bias). Funnel plot showed some asymmetry, but Egger's test did not confirm any clear evidence of publication bias (Figure 44). Subgroup and stratified analyses (Table 9) did not show important group differences, and findings were similar in adjusted and unadjusted analyses.

Figure 43 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of recurrent wheeze in children aged 5-14 years

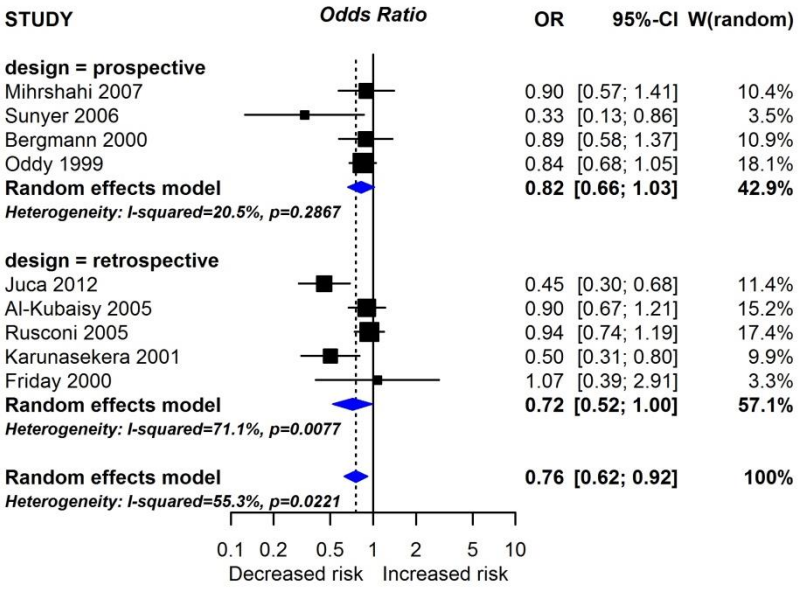
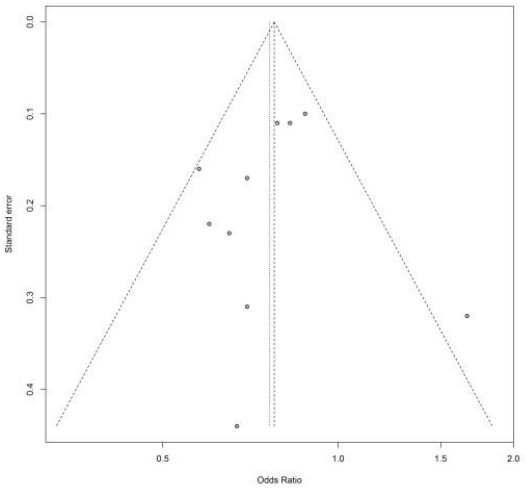


Figure 44 Risk of publication bias in studies investigating total breast feeding and recurrent wheeze ≥5-7 months vs. <5-7 months in children aged 5-14 years



Egger's test p-value = 0.637

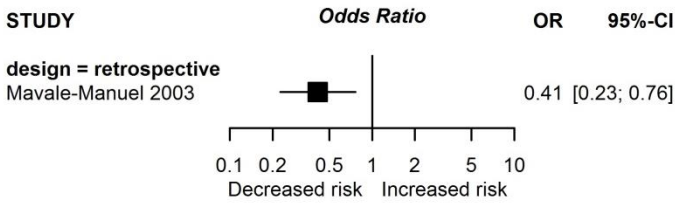
Table 9 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ≥5-7 months vs. <5-7 months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.76 [0.62; 0.92]	55.3	
Adjusted	5	0.74 [0.56; 0.96]	48.0	Not tested
Unadjusted	6	0.72 [0.54; 0.97]	71.1	
Study Design – Prospective	4	0.82 [0.66; 1.03]	20.5	0.50
Study Design – Retrospective	5	0.72 [0.52; 1.00]	71.1	
Risk of disease – High	2	0.92 [0.61; 1.39]	0.0	0.32
Risk of disease – Normal	7	0.73 [0.58; 0.91]	65.3	
Risk of bias – Low	3	0.78 [0.55; 1.10]	45.6	0.87
Risk of bias – High/Unclear	6	0.75 [0.57; 0.98]	64.6	

1.5.2.5 18+ Months

One case-control study reported the risk of recurrent wheeze in children aged 5-14 years old if they were exposed to TBF for ≥18+ months vs. <18+ months, showing no indication of effect (Figure 45). The study did not adjust for potential confounders and therefore carried an overall high risk of bias.

Figure 45 Total breastfeeding for ≥18+ months vs. <18+ months and risk of recurrent wheeze in children aged 5-14 years



1.5.3 Age at outcome measurement 15+

1.5.3.1 Ever vs. never

Six observational studies reported risk of recurrent wheeze in children over 15 years old if they were exposed to any TBF, showing no indication of an effect (OR 0.99; 95% CI 0.89, 1.11) (Figure 46). Three studies were prospective cohorts, all of which had an overall high risk of bias due to selection bias or lack of adjustment for relevant potential confounders. The other three studies were of cross-sectional design, one of which had a high risk of overall bias (due to selection bias), and the other two had a low or unclear overall risk of bias. The presence of high risk of bias in these studies might partly explain the high heterogeneity observed across studies (I^2=73.2%). Subgroup and stratified analyses (Table 10) did not show important group differences, and findings were similar in adjusted and unadjusted analyses. There were insufficient data for meaningful dose response analysis for this comparison.

Figure 46 Total breastfeeding ever vs. never and risk of recurrent wheeze in children aged 15+ years

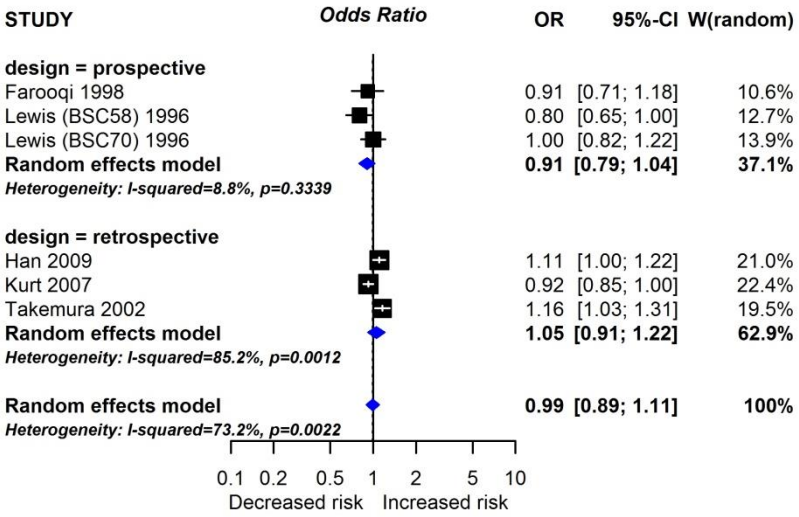


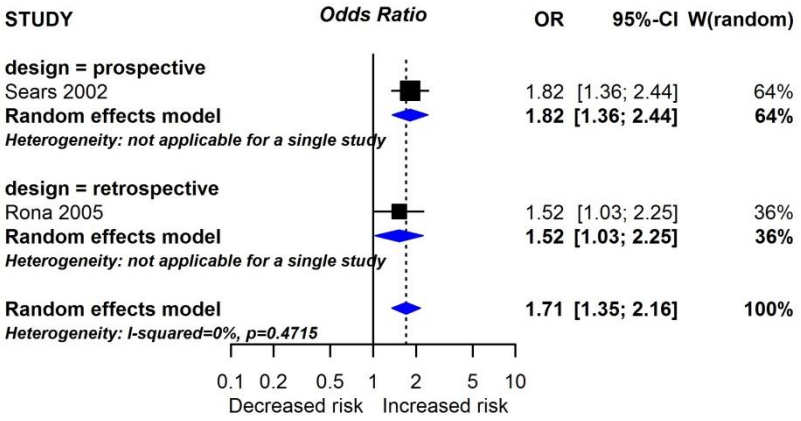
Table 10 Subgroup Analysis of risk of recurrent wheeze and total breastfeeding ever vs. never in children aged 15+ years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	1.00 [0.89; 1.11]	73.2	
Adjusted	2	1.01 [0.85; 1.20]	87.3	Not tested
Unadjusted	5	1.01 [0.90; 1.14]	62.1	
Study Design – Prospective	3	0.91 [0.79; 1.04]	8.8	0.14
Study Design – Retrospective	3	1.05 [0.91; 1.22]	85.2	
Risk of disease – High	-	-	-	-
Risk of disease – Normal	6	1.00 [0.89; 1.11]	73.2	
Risk of bias – Low	1	0.92 [0.85; 1.00]	--	0.18
Risk of bias – High/Unclear	5	1.02 [0.90; 1.15]	63.8	
Clear definition of breastfeeding duration	4	0.92 [0.86; 0.99]	0.0	0.14
Unclear definition of breastfeeding duration	2	1.05 [0.91; 1.18]	68.6	

1.5.3.2 1-2 Months

Two retrospective cohort reported the risk of recurrent wheeze in infants exposed to TBF for ≥1-2 months vs. <1-2 months. In both studies, the data were adjusted, and the studies had an unclear overall risk of bias. Both studies showed an increased risk of recurrent wheeze in children aged 15 or more who received TBF for≥1-2 months vs. <1-2 months, and this was confirmed in their combined effect estimate (OR 1.71; 95% CI 1.35, 2.16). There was no heterogeneity between studies (Figure 47).

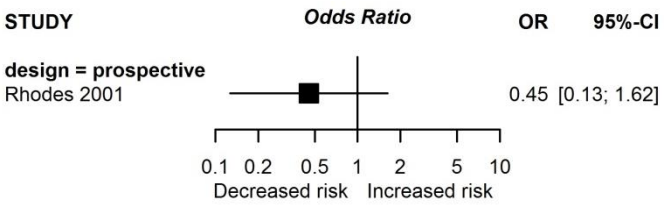
Figure 47 Total breastfeeding for ≥1-2 months vs. <1-2 months and risk of recurrent wheeze in children aged 15+ years



1.5.3.3 3-4 Months

One prospective cohort study reported OR for recurrent wheeze in infants breastfed for ≥3-4 months vs. <3-4 months, and is shown in Figure 48. The data are unadjusted and had a high risk of selection bias, and therefore carry a high overall risk of bias, and show no significant difference in OR for recurrent wheeze in relation to breastfeeding status.

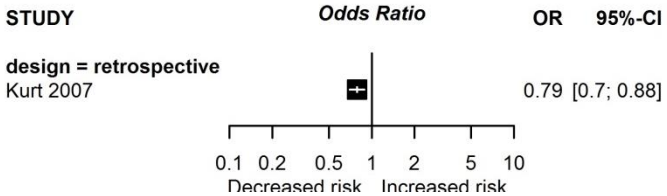
Figure 48 Total breastfeeding for ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 15+ years



1.5.3.4 5-7 Months

One cross-sectional study reported OR for recurrent wheeze in infants breastfed for ≥5-7 months vs. <5-7 months, and is shown in Figure 49. The data are adjusted, and carry a low overall risk of bias, and show a statistically significant difference in the OR for recurrent wheeze in relation to breastfeeding status (OR 0.79; 95% CI 0.70, 0.88).

Figure 49 Total breastfeeding for ≥5-7 months vs. <5-7 months and risk of recurrent wheeze in children aged 15+ years



1.5.3.5 Total breastfeeding and bronchial hyper-responsiveness (BHR)

1.5.3.6 Age at outcome 5-14 years

1.5.3.7 Ever vs. never

Five observational studies reported ORs that could be pooled to assess the overall risk of BHR in children aged 5-14 years old if they were exposed to ever vs. never TBF. There was no suggestion of an association with BHR in the exposed group (Figure 50). Three studies were prospective cohorts and carry low or unclear overall risk of bias, and there were two cross-sectional studies with selection bias, and therefore carried an overall high risk of bias. Dose response analysis shows no evidence that prolonged TBF is associated with altered BHR (Figure 51-Figure 54).

Figure 50 Total Breastfeeding any duration vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

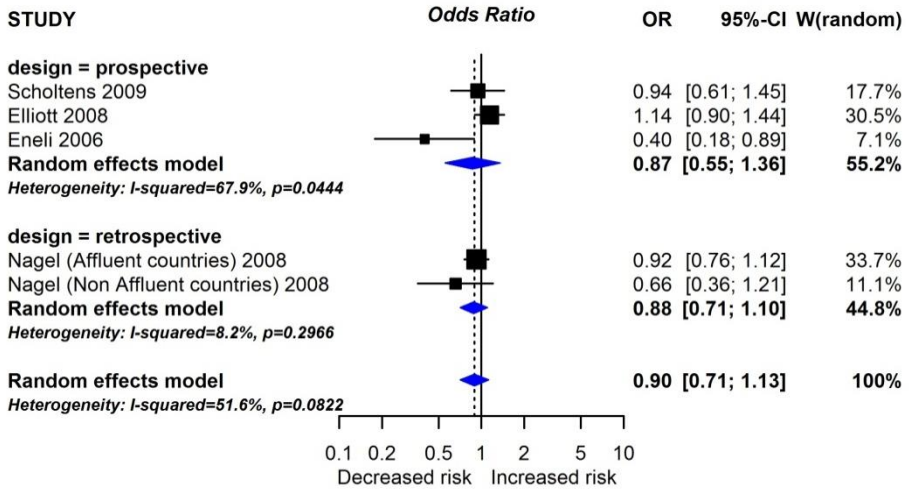


Figure 51 Total breastfeeding (dose response) never vs. ever and risk of bronchial hyper-responsiveness in children aged 5-14 years

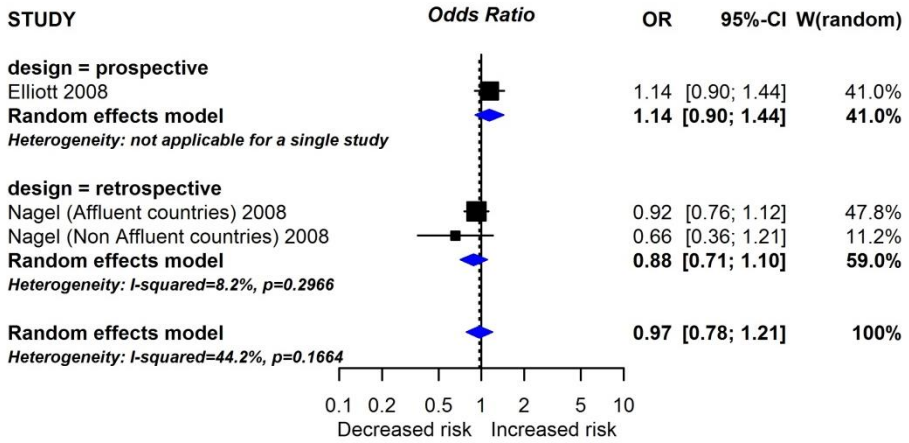


Figure 52 Total breastfeeding (dose response) short vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

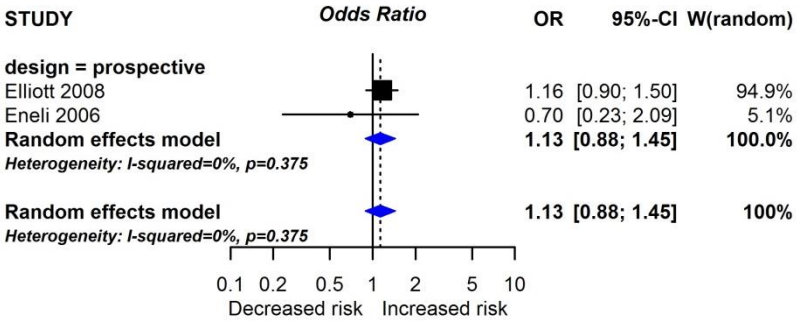


Figure 53 Total breastfeeding (dose response) medium vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

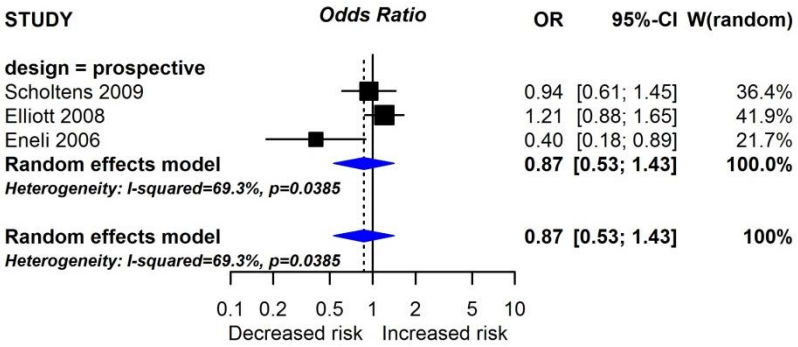
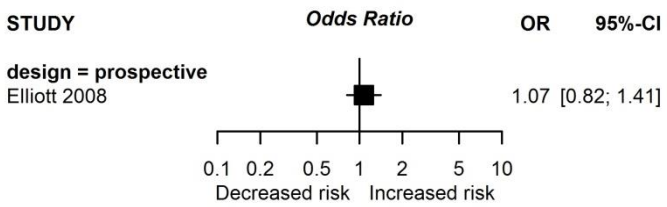


Figure 54 Total breastfeeding (dose response) long vs. never and risk of bronchial hyper-responsiveness in children aged 5-14 years

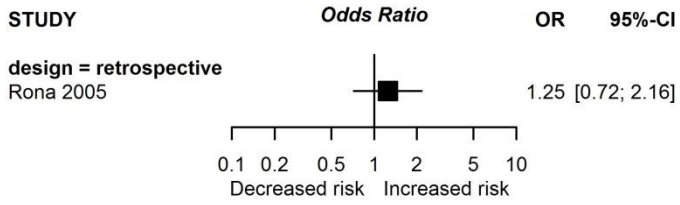


1.5.3.1 Age at outcome 15+ years

1.5.3.2 1-2 months

One retrospective cohort study reported risk of BHR in young adults according to their exposure to ≥1-2 months vs. <1-2 months of TBF (Figure 55). They show no suggestion of an association, and the study had unclear overall risk of bias.

Figure 55 Total Breastfeeding ≥1-2 months vs. <1-2 months and risk of bronchial hyper-responsiveness in children aged 15+ years

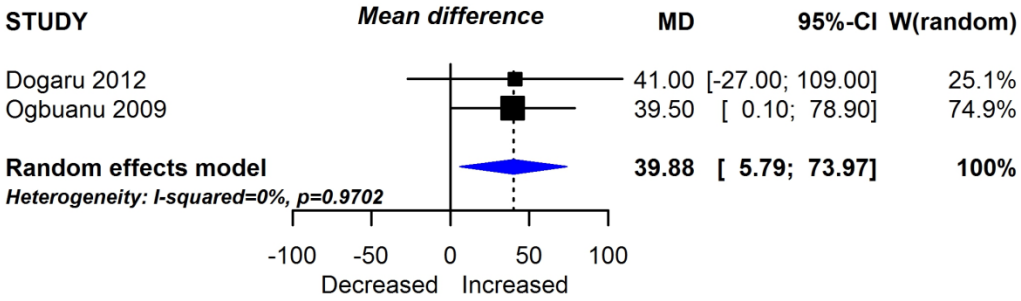


1.6 Data for TBF duration and lung function in children aged 5-14 years

1.6.1 Outcome: FEV1(ml)

Two prospective cohorts had results based on analysis with linear regression and adjusted mean differences: (1) Ogbuanu comparing breastfeeding never (reference) versus ≥ 4 months at 10 years of age; (2) Dogaru breastfeeding never (reference) versus ≥ 6 months at 12.2 years of age.

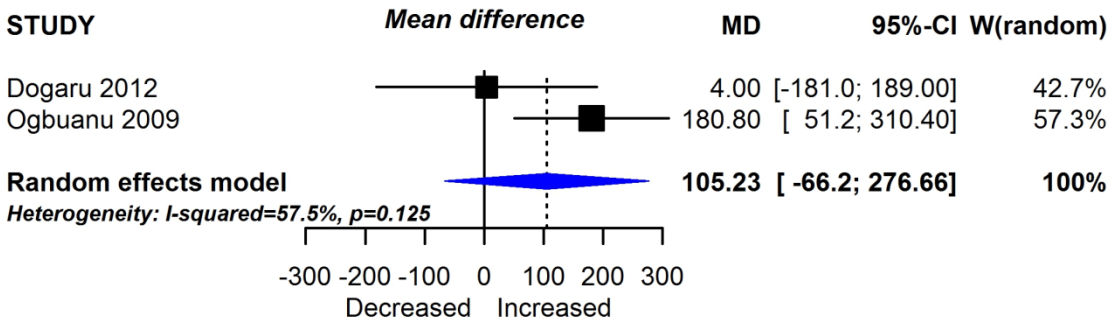
Figure 56 Total breastfeeding and FEV1 (ml) in children aged 5-14 years



1.6.2 Outcome: PEF (ml/sec)

Two prospective cohorts had results with adjusted mean differences based on linear regression: (1) Ogbuanu comparing breastfeeding never (reference) versus ≥ 4 months at 10 years of age; (2) Dogaru breastfeeding never (reference) versus ≥ 6 months at 12.2 years of age.

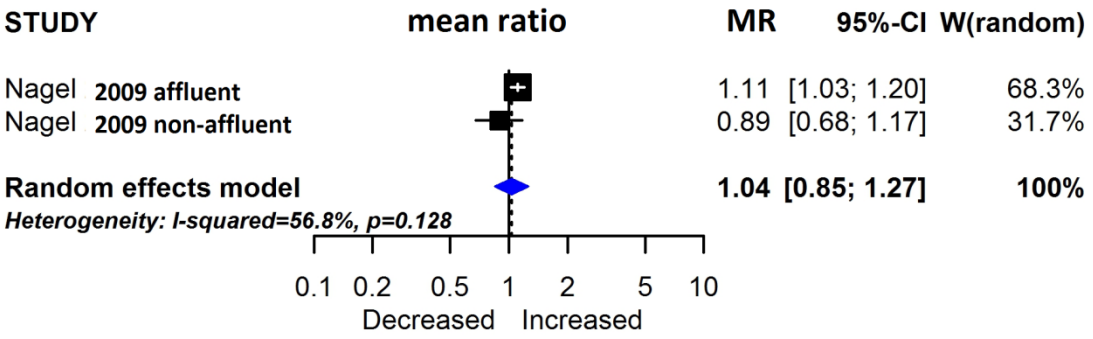
Figure 57 Total breastfeeding and PEF (ml/sec) in children aged 5-14 years



1.6.3 Outcome: FEV1% predicted

One large multicentre cross-sectional study, Nagel presented 2 adjusted estimates of mean ratio (MR) comparing breastfeeding never (reference) versus < 6 months, separately for affluent and non-affluent countries, based on ISAAC methodology, in children aged 8-12 years of age.

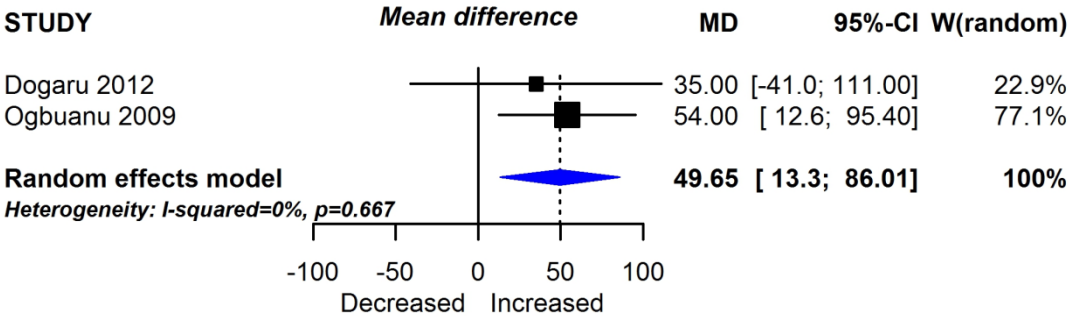
Figure 58 Total breastfeeding and FEV1% predicted in children aged 5-14 years



1.6.4 Outcome: FVC (ml)

Two prospective cohorts had results with adjusted mean differences based on linear regression: (1) Ogbuanu comparing breastfeeding never (reference) versus ≥ 4 months at 10 years of age; (2) Dogaru breastfeeding never (reference) versus ≥ 6 months at 12.2 years of age.

Figure 59 Total breastfeeding and FVC (ml) in children aged 5-14 years



1.6.5 Data for TBF duration and wheeze, BHR or lung function not included in meta-analysis

A total of 36 studies with data on wheeze and TBF exposure, not eligible for meta-analyses were identified (Table 11). Wheeze was measured between age 1 year and 36 years. There were 25 prospective cohorts, 1 retrospective cohort, 1 case-control, 1 a nested case-control, and 8 cross-sectional studies. 7 prospective cohort studies showed a negative association between wheeze (n=1) or recurrent wheeze (n=6) and TBF, whilst 2 cross-sectional studies showed a negative association between recurrent wheeze and TBF. Twenty one studies showed no evidence of an association between wheeze outcomes and TBF. Four studies showed a borderline association (P=0.05) and 2 studies had no data available to estimate size effect.

Data on the association between lung function outcomes and TBF from seven studies that could not be meta-analysed are summarised in Table 12. When P value was not reported in the paper, it was calculated (Altman, D. G. and J. M. Bland (2011). "How to obtain the P value from a confidence interval." BMJ **343**: d2304). Two studies were cross-sectional and five were prospective cohorts. Outcomes studied included forced expiratory volume in 1 second (FEV_1), forced expiratory mid flow (FEF_{50}), airflow obstruction ($FEV_1/FVC<0.80$), FEV_1/FVC as percentage of predicted value, FVC and BHR. Overall of 7 studies, 3 found a positive and statistically significant association between longer duration of TBF and at least one measure of lung function; however findings were not consistent between studies, and between meta-analyses and studies not included in meta-analysis.

Table 11 Studies investigating the association between total breastfeeding and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Munro, 2011 (28)	PC	wheeze	1	700	continuous per week	OR (95%CI) average	0.94 (0.97, 1.00)	<0.05
Soto-Ramirez, 2013 (40)	PC	wheeze	1	2833	continuous	Adjusted RR average	1.26 (1.08, 1.47)	<0.05
Kerr, 1981 (85)	PC	wheeze	0.5	269	0+	average		NS
Hagendorens, 2005 (89)	PC	wheeze	1	693	0+			NS
Sunyer, 2001 (100)	PC	wheeze	4	596	0+			NS
Porro, 1993 (86)	CC	wheeze	<1.6	465/266	>1			NS
Wright, 1989 (105)	PC	wheeze	1	949	>1			NS

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Morgan, 2004 (66)	PC	wheeze, recurrent wheeze	1.5	?	>3			NS
Devereux, 2006 (23)	PC	wheeze	5	1704	0+	Adjusted OR		NS
McConnochie, 1986 (63)	RC	wheeze	8	223/29	0+	Adjusted OR	2.1	0.05
Mann, 1992 (67)	PC	wheeze	36	2139	0+			NS
da Costa Lima, 2003 (81)	PC	Recurrent wheeze	18	2247	0+, 3+, 6+, 9+, 12+	Adjusted PR (95%CI)	Increased recurrent wheeze with longer TBF	NS for 0+, 3+, 6+; P<0.05 for 9+, 12+
Burr, 1993 (13)	PC	wheeze-atopic	7	453	continuous			NS
Silvers, 2009 (76)	PC	recurrent wheeze	1, 5	987	continuous	Adjusted OR (95%CI)	0.93 (0.89-0.97)	<0.05
Silvers, 2012 (75)	PC	recurrent wheeze	5	984	continuous	Adjusted OR (95%CI) average	0.99 (0.96-1.0)	NS

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Hesselmar 2010 (5)	PC	recurrent wheeze	1.5	184	continuous	Median (IQR)		-
Oddy, 2004 (110)	NCC	recurrent wheeze	8	335/166	continuous	Adjusted OR average		NS
Klinnert, 2001 (55)	PC	recurrent wheeze	8	unclear	continuous	average		NS
Awasthi, 2004 (48)	CS	recurrent wheeze	7	2471	0+	Adjusted OR		NS
McConnochie, 1986 (63)	RC	recurrent wheeze	8	223/15	0+	RR	2.6	0.05
Midodzi, 2010 (18)	PC	recurrent wheeze	5	8499/888	0+	Adjusted HR (95%CI)	0.8 (0.7-0.97)	<0.05
Saarinen, 1995 (97)	PC	recurrent wheeze	5, 17	unclear	>1	OR	<1	<0.05
Nwaru, 2013 (24)	PC	recurrent wheeze	5	3142	>5	Adjusted HR (95%CI)	1.9 (1.2-3.0)	<0.05

First Author and year of publication	Design	Outcome	Age	N/n	TBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Nwaru, 2013 (24)	PC	atopic wheeze	5	3675	>5, >9	Adjusted HR		NS
Evenhouse, 2005 (71)	CS	recurrent wheeze	12-18	16903	0+, continuous	Adjusted OR		NS
Karino, 2008 (51)	CS	recurrent wheeze	18	9615	0+, >1, >3, >6			NS

Table 12 Studies investigating the association between total breastfeeding and lung function which were not eligible for meta-analysis

First Author and year of publication	Outcome	Exposure variable	Comparison (reference)	Age at outcome	Statistics and results		
					Analysis	Result 95% C.I.	P value
Soto-Ramırez 2012 (114)	FEV1(ml)	continuous	ml/week	10-18	linear mixed model, adjusted	1.21 (0.07; 2.35)	0.03
Tennant 2008 (116)	FEV1(ml)	categorical	<4mo (ref.) vs ≥ 4mo	50	linear regression, adjusted	-148 (-269; -027)[2]	0.02
Tennant 2010 (119)	FEV1(ml)	categorical	<1mo (ref.) vs ≥1mo	14	linear regression, adjusted	115 (13; 218)	0.03
Ogbuanu 2009 (113)	FEV1/FVC%	categorical	0 (ref) vs ≥4mo	10	linear regression, adjusted	-0.4 (-1.44; 0.64)	0.45
Soto-Ramırez 2012 (114)	FEV1/FVC%	continuous	% increase per week	10-18	linear mixed model, adjusted	-0.001 (-0.02; 0.02)	0.92
Dogaru 2012 (115)	FEF50 (L/s)	categorical	0 (ref) vs ≤3mo	12.2	linear regression, adjusted	0.04 (0.06; 0.14)	**0.05***
Dogaru 2012 (115)	FEF50 (L/s)	categorical	0 (ref) vs 4-6mo	12.2	linear regression, adjusted	0.13 (0.01; 0.26)	**0.05**
Dogaru 2012 (115)	FEF50 (L/s)	categorical	0 (ref) vs >6mo	12.2	linear regression, adjusted	0.12 (0.01; 0.22)	**0.03**
Suwanpromma 2012 (117)	FEV1/FCV<0.8	categorical	<3mo (ref) vs ≥3mo	6-18	Odds ratio, model, adjusted	**0.87 (0.59; 2.24)**	**<0.05**
Soto-Ramırez 2012 (114)	FVC (ml)	continuous	mL/week	10-18	linear mixed model, adjusted	1.48 (0.30; 2.66)	0.01
Guilbert 2007 (176)	FVC (ml)	categorical	<1mo (ref) vs >4mo	11-16	random-effects model, adjusted	103 (24.6; 181.4)[8]	**0.01**
Rona 2005 (90)	Bronchial hyper-responsiveness	categorical	≥1-2mo vs <1-2mo	≥15	polytomous logistic regression, adjusted	1.25 (0.72-2.16)	**0.43**

*Note that there may be a data entry error in this paper, since the mean is not within the 95% confidence interval. It is possible that the correct finding is 0.04 (-0.06, 0.14) which is not statistically significant.

1.6.6 Conclusion on association between TBF duration and lung function and bronchial hyper-responsiveness

The majority of the studies (~70%) reported at least one result indicating improvement in lung function, and the majority of these study estimates (around 70%) were statistically significant. However, findings were not consistent between studies or across closely related measures of lung function. Therefore we assessed the body of evidence as being inconclusive.

2 Exclusive breastfeeding and wheeze

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

Table 13 describes the main characteristics of the studies that assessed exclusive breastfeeding duration (EBF) in relation to wheeze risk. 2 systematic reviews reported combined risk of exposure to EBF and risk of wheeze. A total of 62 observational studies reported the association between EBF and wheeze. Of the observational studies, 42 were prospective cohort studies, 5 case-control studies, 3 nested case-control studies and 12 cross-sectional studies. The majority of studies (n=27) are from Europe – others are from the Asia-Pacific region (n=14) and North America (n=8), 7 from South America, 2 from South Asia and 2 from the Middle East. There are also 2 studies, which included multiple countries.

Overall, valid data on EBF duration in the first 2 years of life and wheeze risk were available from over 220,000 subjects. Information on wheeze was obtained solely from parental or self-reported in 13 studies, through Dr-diagnosis in 12 studies, and from the ISAAC questionnaire in 14 studies. One other study used spirometry alone. Another 18 studies used a combination of self /parental report, Doctor diagnosis, and/ or objective measures (e.g. bronchial hyper-responsiveness (BHR)). One study used the Canadian Asthma Consensus Guidelines. Three studies used an unclear method for defining wheeze.

With regards to time of outcome diagnosis, 25 studies explored the association between EBF duration and wheeze at age 0-4 years, 18 at age 5-14 years, and 2 at age 15 years or beyond. A further 15 studies investigated the association between EBF duration and wheeze at various time points between the ages of 1 and 22 years. Two studies examined children at a range of ages (8-18, 6-15). To ascertain exposure to EBF, 31 studies used a questionnaire method, 14 used an interview and 1 used a diary. A further 11 studies used a combination of 2 or more of these methods, whilst 5 studies had no information available on the method used.

Risk of bias in the intervention trials was low in the study of Kramer, and unclear due to unclear selection bias in the study of Kajosaari. Risk of bias in observational studies was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 56 illustrates the distribution of bias across the five main methodological areas of the

observational studies. Nearly 40% of studies were considered to have an overall high risk of bias, mainly due to lack of controlling for potential confounders and selection bias issues. 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 wheeze according to TBF duration, namely 'ever vs. never', '≥0-2 months vs. <0-2 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 children aged 0-4 years we found no consistent evidence for an association between EBF duration and risk of wheeze or recurrent wheeze. EBF ≥0-2 months was associated with reduced wheeze at age 0-4, but not recurrent wheeze. There was high heterogeneity in the analysis of wheeze, and subgroup analysis found a significant association in studies at low risk of bias, with no heterogeneity. EBF ≥3-4 months was not associated with wheeze or recurrent wheeze at age 0-4, but there was significant statistical heterogeneity in both analyses. EBF ≥5 months was associated with reduced wheeze in one prospective study, but not in one retrospective study, and there was no association with recurrent wheeze.

In children aged 5-14 we found no consistent evidence for an association between EBF duration and risk of wheeze or recurrent wheeze. EBF ≥0-2 months was associated with reduced wheeze in meta-analysis of two prospective studies, but not in two retrospective studies; and there was no association with recurrent wheeze. EBF ≥3-4 months was not associated with wheeze or recurrent wheeze, and there was extreme statistical heterogeneity and publication bias in the analysis of recurrent wheeze. EBF ≥5 months was associated with reduced wheeze in one prospective study and one retrospective study, but with borderline statistical significance; and there was extreme heterogeneity in the analysis of EBF ≥5 months and recurrent wheeze.

In people aged 15 years and over we found no evidence for an association between EBF and wheeze or recurrent wheeze.

When EBF was analysed as a 'per month' exposure, a significantly lower risk of wheeze was observed in children aged 0-4 years old, albeit with high statistical heterogeneity; and there

was significantly lower risk of recurrent wheeze at both 0-4 years and 5-14 years, with low heterogeneity.

We found no consistent evidence for a relationship between EBF and atopic wheeze, with one study reporting reduced atopic wheeze at age 0-4 with EBF ≥0-2 months, but no relationship with EBF ≥3-4 months; no evidence for a relationship between EBF ≥0-2 months and atopic wheeze at age 5-14 years; and one study reporting reduced risk of atopic wheeze at age 5-14 years with EBF ≥3-4 months.

Two studies reported decreased FEV1/FVC% associated with EBF ≥1 month, and meta-analysis was statistically significant with no heterogeneity. Other studies which could not be included in meta-analysis showed no consistent evidence for an association between EBF and measures of lung function.

Overall 18 studies reported data which could not be included in meta-analysis - 16 prospective cohort studies and 2 cross-sectional studies. These studies reported no consistent evidence for an association between EBF and wheeze.

Conclusion

We found no consistent evidence for an association between EBF and risk of wheeze, recurrent wheeze, atopic wheeze, BHR or measures of lung function.

Table 13 Characteristics of included studies evaluating exclusive breastfeeding and wheeze

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Brew, 2011 (122)	SR/PC/ CC/C-S	417,880	Q	'Current wheezing illness', defined in various ways, but usually including wheezing in last 12 months	5-18		31 studies included in the SR (180 – 168,330) participants and EBF for 3-4 months vs. less than 3-4 months
Kramer, 2012 (123)	SR /PC nested in RCTs	3,993 with wheeze data	Q	Self-reported symptoms, objective markers	5-7		Lactating mothers and their healthy, term, singleton infants exclusively or predominantly breast fed for at least 3 months
Kajosaari, 1991[1]	PC	135	-	DD asthma	1, 5	Finland	Solid food introduction at 6 months versus 3 months, in exclusively breastfed infants
de Vries, 2010 (124)	PC	4860	Q	Parent reported wheeze	0.5	Netherlands	ABCD study. Population based study of babies born between 2003 and 2004
Garcia-Marcos, 2010 (125)	CS	28687	Q	ISAAC ; >= 3 episodes of wheeze in the first 2 years	1	Spain, Netherlands and Latin America	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Hesselmar, 2010 (5)	PC	184	I	DD asthma : >=3 episodes of wheeze	1.5	Sweden	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Elliott, 2008 (6)	PC	8191	Q	Current wheeze; Wheeze ever; BHR: metacholine PC20	3, 7.5	UK	ALSPAC study. Population based cohort of children born 1991-1992.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kull, 2002; Kull, 2004; Kull, 2010 (9, 126, 127)	PC	3825	Q	>=4 episodes of wheeze OR inhaled corticosteroids (+/- sIgE); >=3 episodes of wheeze OR inhaled corticosteroids (+/- sIgE); Self reported wheeze; >=3 episodes of wheeze OR inhaled corticosteroids; >=3 episodes of wheeze PLUS inhaled glucocorticoids or cough/wheeze at excitement/stress; Spirometry	2, 4, 8	Sweden	BAMSE study. Population based cohort of children born between 1994-1996
Besednjak-Kocijancic, 2010 (128)	PC	408	NA	Unclear	1, 5	Slovenia	Infants with a positive history of parental allergy
Bacopoulou, 2009 (129)	PC	6643	Q	DD	7	Greece	Population based sample of neonates born in 1983
Cano Garcinuno, 2003 (130)	CS? Or PC	234	Q	DD	3	Spain	Children born in 1998-2002 attending primary health center
Salam, 2003 (131)	NCC	691	I	DD PLUS current wheeze; DD	8-18	USA	Cases and controls selected within the CHS study, a population based study of children recruited from public school classrooms from grades 4, 7, and 10 in 12 communities in southern California.

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Mihrshahi, 2007 (20)	PC	516	I	DD PLUS current wheeze	5	Australia	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Simon, 2008 (21)	PC	372	R/I	Transient wheezing: wheezing in the last 12 months at ages of 1,2 and/or 4 years but not at age of 6 years. vs never wheeze	6	USA	CAS study. Middle class mother-infant pairs enrolled in a health maintenance organisation in 1987-89
Fergusson, 1983; Horwood, 1995 (132, 133)	PC	1110	R/I	DD asthma (>=2 episodes of wheeze)	4, 6	New Zealand	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Giwercman, 2010 (134)	PC	313	I	Parent reported wheeze	2	Denmark	COPSAC study. Infants of mothers with a history of doctor-diagnosed asthma, recruited from August 1998 to December 2001.
Linneberg, 2006 (135)	PC	34793	Q/I	Parent reported wheeze	1.5	Denmark	DNBC. Population based birth cohort of children born between 1997-2002
Erkkola, 2012; Nwaru, 2013 (24, 136)	PC	3675	D	DD plus ISAAC (+/-) sIgE	5	Finland	DIPP study. Infants at high risk (HLA) for TIDM born between 1996-2004 invited to the allergy study between 1998 and 2000
Wilson, 1998 (25)	PC	545	Q	Self-reported wheeze; DD	7	UK	Dundee infant feeding study. Population based cohort of infants born between 1983-1986

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Mandhane, 2007; Sears, 2002 (137) (138)	PC	1037	R/I	DD PLUS current wheeze; Current wheeze PLUS airway hyperresponsiveness; Spirometry; BHR: metacholine PC20	9, 26	New Zealand	Dunedin Multidisciplinary Health and Development Research Study. Population based cohort of infants born between 1972-1973
Hetzner, 2009 (139)	PC	7900	I	DD	2	USA	Early Child Longitudinal Study Birth Cohort. Nationally representative sample of children born in the United States during 2001
Castro-Rodriguez, 2010 (140)	CS	1409	Q	ISAAC	1.4	Spain	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Chong Neto, 2007 (141)	CS	3003	Q	Parent reported wheeze ever	1	Brazil	EISL study. One-year old infants from urban and rural primary care health clinics born in 2004-2006
Munro, 2011 (28)	PC	700	Q	Parent reported wheeze	1, 2	UK	EuroPrevall-UK. Population based birth cohort of infants born in 2008
Tanaka, 2009 (32)	CS	1957	Q	ISAAC	3	Japan	Fukuoka Child Health Study. All 3-year old children who had the examination at public public health centers in Fukuoka city
van der Voort, 2012 (33)	PC	5368	Q	ISAAC	1, 4	Netherlands	Generation R study. Population-based multicultural birth cohort of infants born between 2002 and 2009

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Ehlayel, 2008 (142)	CS	1278	Q	ISAAC; Parent reported recurrent wheezing/asthma	5	Qatar	Children 0-5 years old attending primary healthcare centers for routine immunisation
Huang, 2013 (143)	PC	684	Q	ISAAC	2	China	Mother-infant pairs registered in Putuo District, Changzheng Town Community Health Service Center Child Health Clinic within the period from January to December, 2008
Nagel, 2009 (46)	CS	31579	Q	Parent reported current wheeze/asthma; Parent reported current wheeze (+/-SPT)	12	International - Affluent countries (China, Germany, Greece, Iceland, Italy, Netherlands, New Zealand, Norway, Spain); International - Nonaffluent countries (Albania, Brazil, China, Ecuador, Georgia, Ghana, India, Latvia, West Bank, Turkey)	ISAAC Phase 2. Schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries
Arshad, 1992; Kurukulaaratchy, 2004;	PC	1167	D/Q	DD asthma (>=3 episodes of wheeze); Parent reported wheeze; >=2 episodes of wheeze between age <4 and 10	1, 10	UK	Isle of Wight Prevention Study. Population based birth cohort of infants born in semi-rural areas between 1989 and 1990

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Kurukulaaratchy, 2006 (144-146)				years			
Juca (147)	CC	590	Q	ISAAC	14	Brazil	
Kemeny, 1991 (54)	PC	180	NA	>=2 episodes of wheeze	1	UK	Population based birth cohort of infants born at Dulwich and King's College Hospitals in London
Liu, 2012 (148)	CS	8733	Q	ISAAC; ATS guideline	8	China	Sample of children from kindergarden and elementary schools in Shenyang
Mai, 2007 (149)	NCC	723	Q	Canadian Asthma Consensus Guidelines: symptoms plus variable airway obstruction	10	Canada	Cases and controls selected from records of the Manitoba Health Services Insurance Plan and all were born 1995
Majeed, 2008 (150)	CC	398	Q/I	>=3 episodes of wheeze in past year	3	Pakistan	Cases are 1-12 years old children with wheeze/asthma admitted to paediatrics wards. Controls are age matched children and adolescents attending immediately after selection of the index case
Marini, 1996 (59)	PC	Unclear	Q	>=3 episodes of wheeze	1	Italy	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Midwinter, 1987 (151)	PC	453	NA	DD asthma	5	UK	Children born to parents with a family history of atopy in 1979-1981
Miyake, 2003 (65)	CS	6845	Q	ISAAC	15	Japan	12-15 years old children from all public junior high schools in Suita, Japan.
Silvers, 2009; Silvers, 2012 (75, 76)	PC	987	Q	DD PLUS current wheeze; Parent reported wheeze	1, 5	New Zealand	New Zealand Asthma and Allergy Cohort Study. Population based birth cohort of infants born between 1997 and 2001
Nielsen, 2013 (152)	PC	5429	Q	Unclear	0.5	Denmark	Population based birth cohort of infants born in 1995
Miyake, 2008 (79)	PC	763	Q	ISAAC	2	Japan	OMCHS study. Population based birth cohort of infants born in 2002-2003
da Costa Lima, 2003(81)	PC	2247	I	ISAAC	18	Brazil	Pelotas Birth Cohort. Population based birth cohort of infants born in 1982 in the city of Pelotas
Pesonen, 2006 (153)	PC	164	I	DD OR >=2 episodes of wheezing	5, 20	Finland	Population based birth cohort of infants born in 1981
van Merode, 2007 (154)	PC	222	Q	ISAAC	1	Holland	PREVASC study: cohort born in 2005 with family history of asthma (high risk of disease)

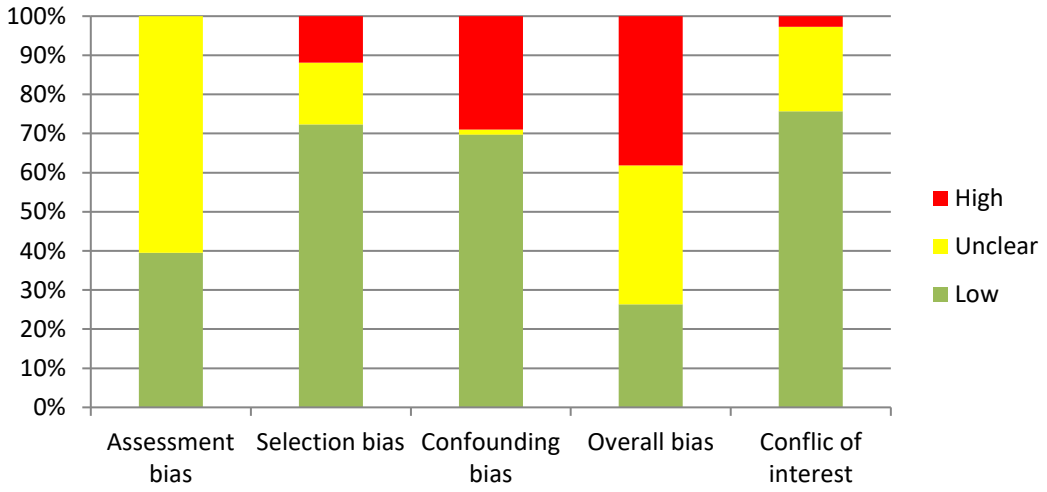
First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Prietsch, 2006 (155)	CS	685	Q	Unclear	13	Brazil	Population representative sample of infants aged 12-15 months (normal risk of disease)
Kramer, 2003; 2009; 2009 (b) (156-158)	PC	2951	I	ISAAC	1, 6.5	Belarus	PROBIT study: recruited in hospitals, born 1996-1997 (normal risk of disease)
Ratageri, 2000 (159)	CC	180	NA	DD asthma using International Paediatric Consensus Group criteria	9	India	Hospital-based study (normal risk of disease)
Rothenbacher, 2005 (94)	PC	803	Q/I	DD	2	Germany	Recruited from university service, born in 2000-2001 (normal risk of disease)
Rullo, 2007; Rullo, 2009; Rullo, 2009 (b); Rullo, 2010 (160-163)	PC	101	Q/I	>=3 episodes of wheeze in past year; Persistent wheeze: ever wheezing treated with inhaled corticosteroids and beta-2 agonists in the past year	1.5, 2.5, 4, 5	Brazil	Recruited from hospital (high risk of asthma)
Rylander, 1993 (164)	CC	550	I	Physician assessment	4	Sweden	Cases from a health service and control from population (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Siltanen,2003 (165)	PC	285	Q	DD PLUS current wheeze; >=3 episodes of wheezing;	4	Finland	Infants recruited from maternal hospital born in 1994-1995 (normal risk of disease)
Salem, 2002 (166)	CS	424	Q	Wheeze ever	5	Iraq	Population representative sample of children aged 0.16-2 years old (normal risk of disease)
Silva, 2005 (167)	PC	73	Q	Physician assessment (>=3 episodes of wheeze)	4	Brazil	Recruited from health services in urban area, born in 1998 (high risk of disease)
Strassburger, 2010 (168)	PC	343	I	ISAAC	3.5	Brazil	Recruited from hospital, born 2001-2002 (normal risk of disease)
Mai, 2008 (169)	NCC	723	Q	Physician assessment	10	Canada	Study of Asthma, Genes and the Environment (SAGE) project: population-based study with children born in 1995 (normal risk of disease)
Matheson, 2007 (170)	PC	5729	Q	Self-reported current asthma	7, 32	Tasmania	Tasmanian ASTHMA Study: population based born in 1961 (high risk/low risk of disease)
Takemura, 2001 (102)	CS	23828	Q	>=2 episodes of wheeze PLUS DD asthma	6-15	Japan	The Tokorozawa Childhood Asthma and Pollinosis Study: Representative sample of children in public elementary schools (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Wright, 2001 (171)	PC	1043	Q/I	DD PLUS wheeze >=2 times between 6 and 13 years	13	USA	Tuscon Children's Respiratory Study: Recruited from local health maintenance organisation born in 1980-1984 (normal risk of disease)
Van Asperen, 1983 (172)	PC	79	I	Parent reported wheeze	1	Australia	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of disease)
Watson,2013 (173)	PC	369	Q/I	ISAAC	1.5	New Zealand	Recruited from Polynesian women, non-random sample (high risk of disease)
Oddy, 1999; Oddy, 2002; Oddy, 2003; Oddy, 2004 (109, 111, 174, 175)	PC	2456	D/I	DD PLUS wheeze in the past 12 months; Parent reported current wheeze; DD asthma PLUS >=3 episodes of wheeze	1, 6	Australia	Western Australia Pregnancy Cohort: Recruited from antenatal clinics born in 1989-1992 (high risk/low risk of disease)
Whu, 2007 (176)	CC	261	I	DD PLUS asthma medication	4	USA	Hospital-based study cases born in 2000 (normal risk of disease)
Zutavern 2004 (114)	PC	606	I	Parent reported current wheeze	2, 5.5	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Poysa, 1992 (177)	PC	68	NA	BHR: metacholine PC20	10	Finland	High risk of disease, born 1979-1980
Guilbert, 2007 (178)	PC	679	I	Spirometry	13	USA	Tuscon Children's Respiratory Study: A population-based cohort of healthy infants born in 1980-1984 (normal risk of disease)

Figure 60 Risk of bias in studies of exclusive breastfeeding and wheeze



2.2 Exclusive Breastfeeding and Wheeze

2.2.1 Systematic reviews

Two systematic reviews investigated overall association between exclusive breastfeeding and wheeze. Brew and colleague found no evidence that EBF for more than 3-4 months vs. less was associated with wheeze (OR 0.96 [0.86, 1.06]) (I^2=54.2%). Kramer reported no association between EBF for 6 or more months' vs 3-4 months and having at least 2 episodes of wheezing in the first 12 months RR 0.79 (0.49, 1.28; I^2=0%). No intervention trials were identified, other than the cluster RCT of Kramer which is included in the 'TBF' section of this report.

2.2.2 Age at outcome measurement 0-4

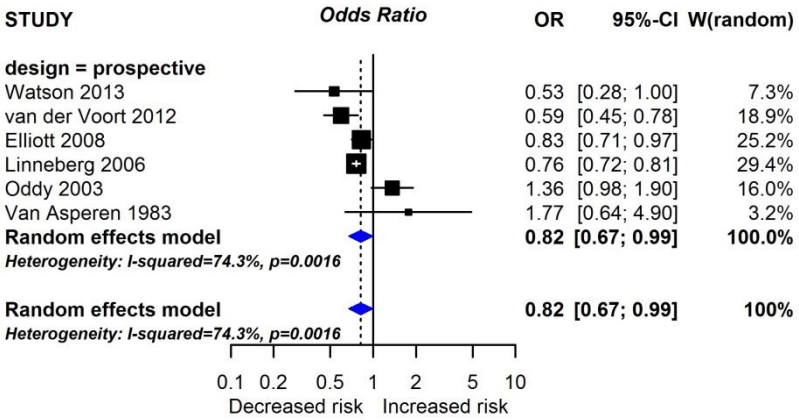
2.2.2.1 0-2 months

Six prospective cohort studies reported data on risk of wheeze that could be pooled to estimate the effect of exposure to EBF for ≥0-2 months vs. <0-2 months in children aged 0-4 years, suggesting a protective effect of EBF on wheeze in the exposed group (OR 0.82; 95% CI 0.67, 0.99) (Subgroup analyses for EBF for ≥0-2 months vs. <0-2 months and risk of wheeze showed a statistically significant difference between studies at low risk of overall bias and high/unknown risk (P=0.01) (Table 14).

Figure 61). There was very high heterogeneity between studies (I^2=74.3%). Two of the studies had a low overall risk of bias, whilst three had an unclear overall risk, and the study of Van Asperen lacked controlling for potential confounders, so carries an overall high risk of bias.

Subgroup analyses for EBF for ≥0-2 months vs. <0-2 months and risk of wheeze showed a statistically significant difference between studies at low risk of overall bias and high/unknown risk (P=0.01) (Table 14).

Figure 61 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of wheeze in children aged 0-4 years



2.2.2.2 3-4 months

Nine observational studies reported data on risk of wheeze that could be pooled to estimate the effect of exposure to EBF for ≥3-4 months vs. <3-4 months in children aged 0-4 years, suggesting no evidence of an effect of EBF on wheeze in the exposed group (

Figure 62). There was very high heterogeneity between studies (I^2=73.2%). Six studies were prospective cohorts (of which 2 had an overall high risk of bias due to not accounting for potential confounders), two were cross sectional (both carry a high risk of overall bias due to selection bias), and one is a case-control study (which did not account for confounding and therefore carries an overall high risk of bias). A Funnel plot was used to investigate publication bias, showing a slight asymmetry but no statistical evidence of such a bias (Figure 63).

Prolonged exposure to EBF for ≥3-4 months vs. <3-4 months showed no difference in the subgroup analyses (Table 15).

Figure 62 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years

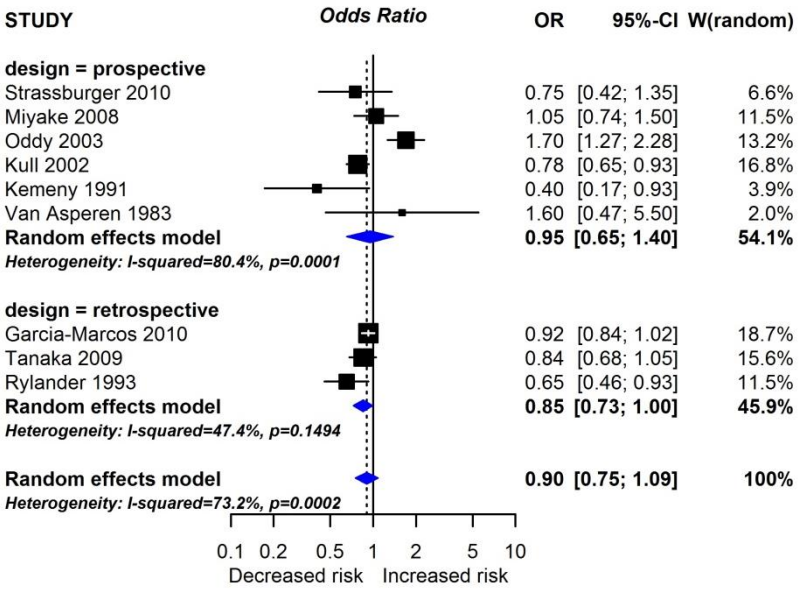
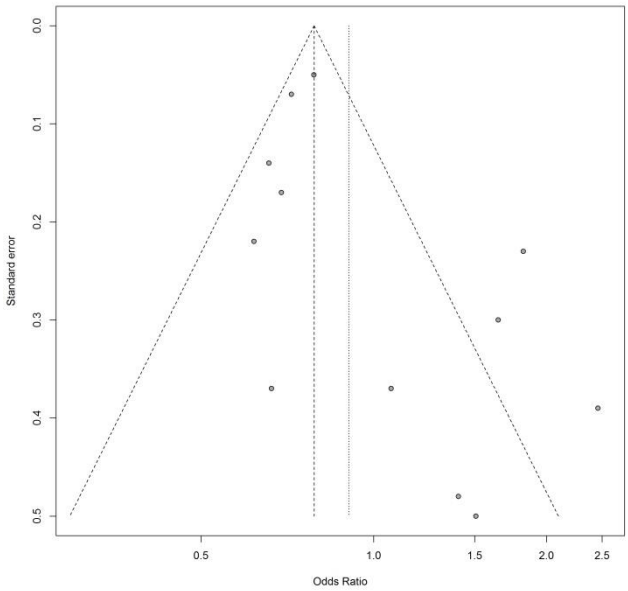


Figure 63 Risk of publication bias in studies of exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years



Egger's test p-value = 0.141

2.2.2.3 5+ months

Two observational studies, a prospective cohort and a cross-sectional study reported data on risk of wheeze that could be pooled to estimate the effect of exposure to EBF for ≥5 months vs. <5 months in children aged 0-4 years (Figure 64). There was extremely high heterogeneity between the two studies (I^2=86.6%), possibly explained by the overall high risk of bias of the retrospective Salem study (mainly due to lack of adjustment for potential confounders) and the unclear overall risk of bias in the prospective Oddy study.

Figure 64 Exclusive breast feeding ≥5 months vs. <5 months and risk of wheeze in children aged 0-4 years

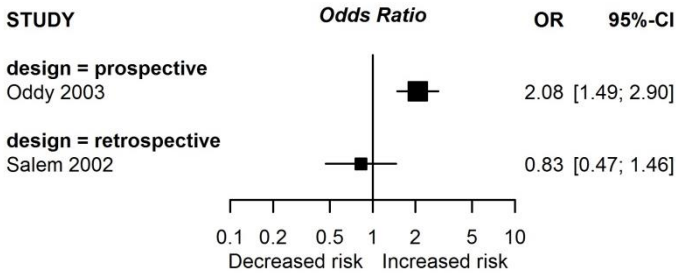


Table 14 Subgroup Analyses of risk of wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.82 [0.67; 0.99]	74.3	
Adjusted	4	0.85 [0.69; 1.05]	77.4	Not tested
Unadjusted	5	0.88 [0.52; 1.48]	93.6	
Study Design – Prospective	6	0.82 [0.67; 0.99]	74.3	--
Study Design – Retrospective	--	--	--	
Risk of disease – High	2	0.91 [0.28; 2.91]	74.1	0.87
Risk of disease – Normal	4	0.82 [0.67; 1.00]	80.7	
Risk of bias – Low	2	0.58 [0.45; 0.75]	0.0	0.01
Risk of bias – High/Unclear	4	0.92 [0.74; 1.16]	79.0	
Clear definition of breastfeeding duration	4	0.73 [0.54; 0.99]	62.8	0.34
Unclear definition of breastfeeding duration	2	1.00 [0.57; 1.76]	91.1	

Table 15 Subgroup Analyses of risk of wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 0-4 years

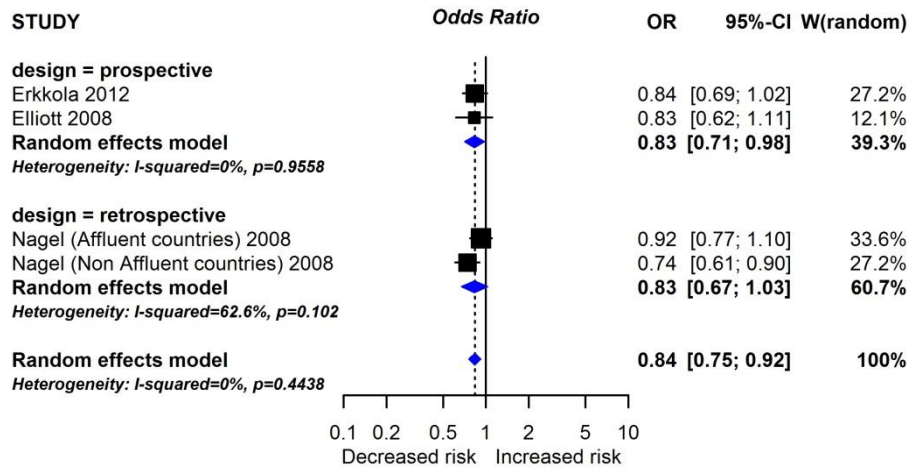
	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.90 [0.75; 1.09]	73.2	0.28
Adjusted	6	0.97 [0.80; 1.17]	77.1	
Unadjusted	8	0.89 [0.65; 1.2157]	84.5	
Study Design – Prospective	9	0.95 [0.65; 1.40]	80.4	0.60
Study Design – Retrospective	3	0.85 [0.73; 1.00]	47.4	
Risk of disease – High	1	1.6000 [0.4654; 5.5002]		0.36
Risk of disease – Normal	8	0.8917 [0.7380; 1.0773]	75.9	
Risk of bias – Low	4	0.8468 [0.7022; 1.0213]	12.5	0.74
Risk of bias – High/Unclear	5	0.8980 [0.6724; 1.1993]	83.8	

2.2.3 Age at outcome measurement 5-14

2.2.3.1 0-2 months

Four observational studies reported data that could be pooled to estimate risk of wheeze with duration of EBF ≥0-2 months vs. <0-2 months, suggesting a reduced risk of disease (OR 0.84; 95% CI 0.75, 0.92; [Figure 65]). The analysis showed no statistical heterogeneity between studies (I^2=0.0%). Two studies were prospective cohorts, the study of Erkkola had an overall high risk of bias, mainly due to lack of adjustment for potential confounders, and the study of Elliot had an unclear risk of bias. The other two studies were of cross-sectional design and used the ISAAC questionnaire. Both had an overall high risk of bias, due to selection bias.

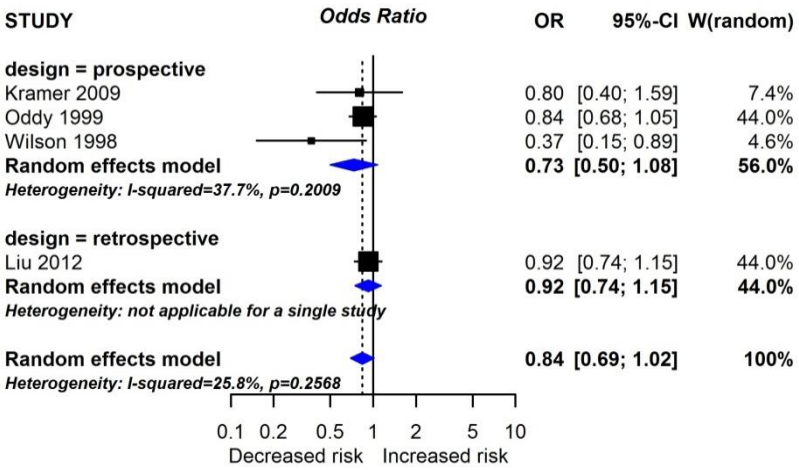
Figure 65 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of wheeze in children aged 5-14 years



2.2.3.2 3-4 months

Four observational studies reported data that could be pooled to estimate risk of wheeze with exposure to EBF ≥3-4 months vs. <3-4 months. Although all studies showed an OR below 1.0, there was no evidence of an association in the meta-analysis (Figure 66). Three of the studies were prospective cohorts (one of which had a high risk of bias due to confounding), and one was cross-sectional (with high risk of overall bias due to confounding).

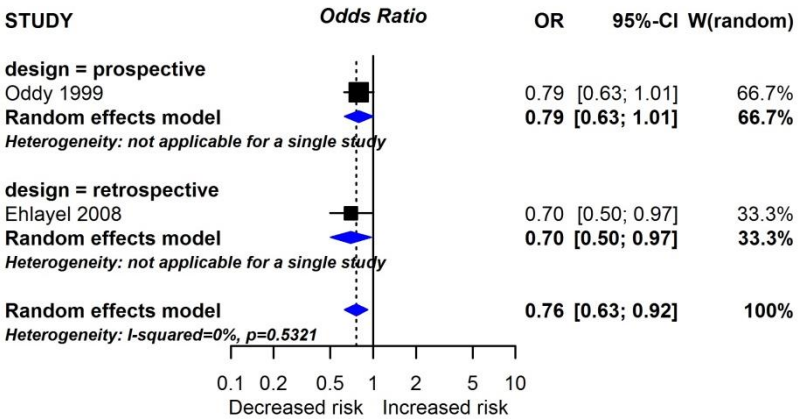
Figure 66 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 5-14 years



2.2.3.3 5+ months

Data were available from one cross-sectional study and one prospective study to examine the pooled effect of EBF for ≥5 months vs. <5 months and risk of wheeze in children aged 5-14 years old, showing a reduced risk of disease in the exposed group (OR 0.76; 95% CI 0.63, 0.92). The studies had no heterogeneity (I^2=0.0%) (Figure 67).

Figure 67 Exclusive breast feeding ≥5 months vs. <5 months and risk of wheeze in children aged5-14 years

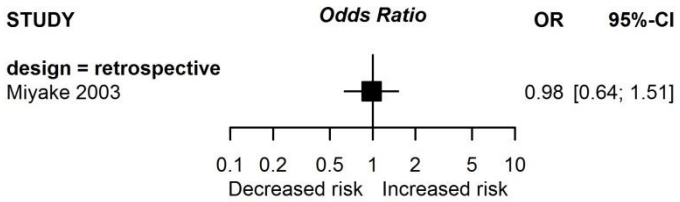


2.2.4 Age at outcome measurement 15+

2.2.4.1 0-2 months

One cross-sectional study reported risk of wheeze in children aged over 15 years old who were exposed to EBF for ≥0-2 months vs. <0-2 months (Figure 68). The study had high risk of bias due to lack of adjustment for potential confounders, and showed no association between exposure and disease.

Figure 68 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of wheeze in children aged 15+ years

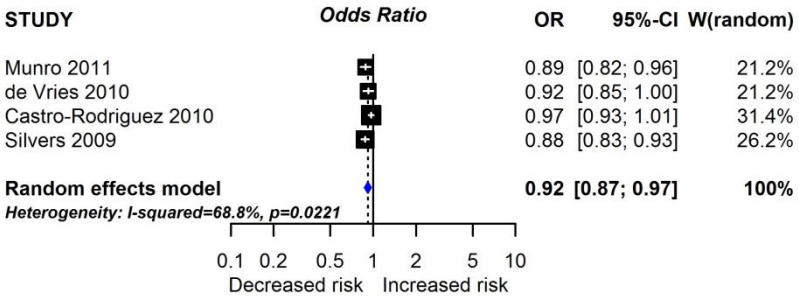


2.3 Exclusive Breastfeeding per month and Wheeze

2.3.1 Age at outcome measurement 0-4

Four observational studies reported associations between EBF per month and risk of wheeze in children aged 0-4 (Figure 69). The overall combined effect suggests a lower risk of disease in the exposed group (OR 0.92; 95% CI 0.87, 0.97). The analysis showed high statistical heterogeneity across studies (I^2=68.8%).

Figure 69 Exclusive breastfeeding per month and risk of wheeze in children aged 0-4 years



2.4 Exclusive Breastfeeding and Recurrent Wheeze

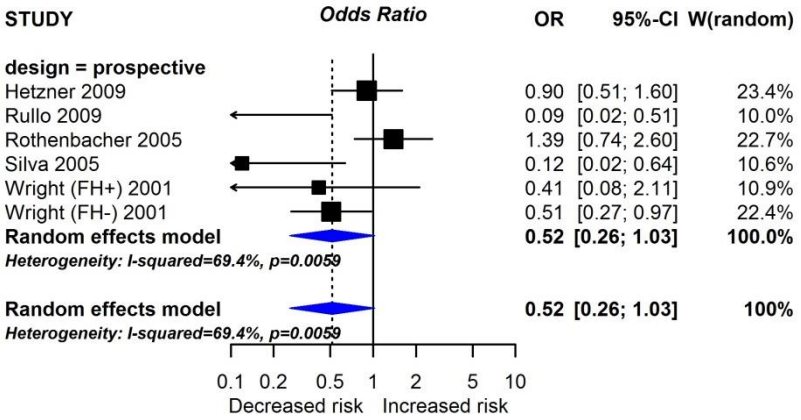
2.4.1 Age at outcome measurement 0-4

2.4.1.1 0-2 months

Five observational studies (six analyses) reported risk of recurrent wheeze with exposure to EBF for ≥0-2 months vs. <0-2 months in children aged 0-4 years old (Figure 70). There was no clear evidence of a significant effect and there was very high heterogeneity between studies (I^2=69.4%).

Subgroup analyses of risk of recurrent wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 0-4 years, showed statistically significant differences between children at high and low risk of disease (P<0.01) and between risk of bias (P=0.01) (Table 16). Studies at low risk of bias found no association between EBF and recurrent wheeze, with no statistical heterogeneity.

Figure 70 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of recurrent wheeze in children aged 0-4 years



2.4.1.2 3-4 months

Thirteen observational studies reported data eligible to calculate combined OR of wheeze in children aged 0-4 comparing EBF ≥3-4 months vs. <3-4 months. There was no evidence of an overall effect (Figure 71) and the heterogeneity was very high (I^2=68.7%), which might have been partly influenced by the different outcome measurements used across studies. Nine

studies were prospective cohorts (six of which had high risk of overall bias, mainly due to confounding or selection bias), 2 were cross-sectional studies (both of which had a high risk of overall bias) and one was a case-control study (which also had a high risk of overall bias, due to lack of adjustment for potential confounders). There was no evidence of publication bias (

Figure 72).

Subgroup analyses of risk of recurrent wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 0-4 years showed no statistically significant differences between groups (Table 17).

Figure 71 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 0-4 years

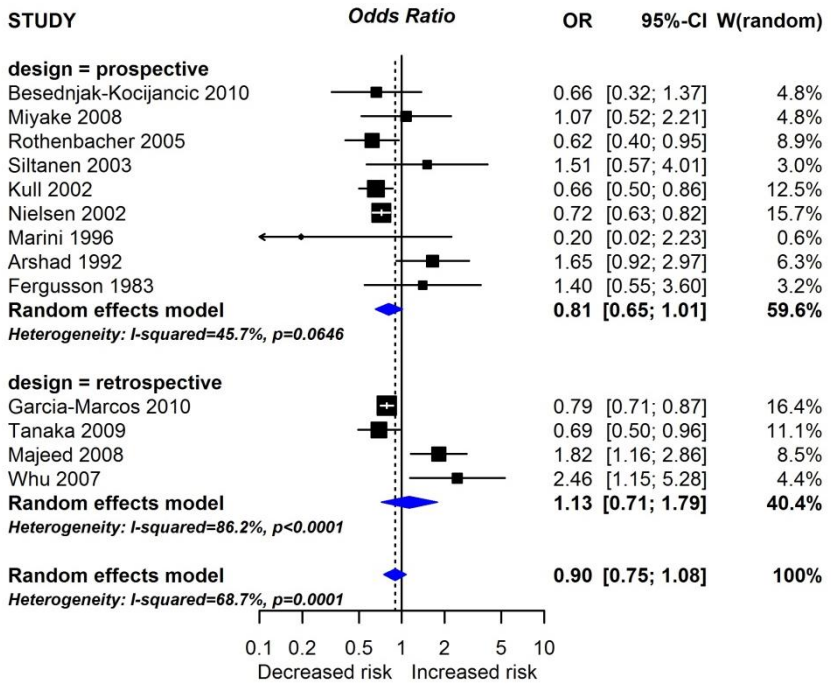
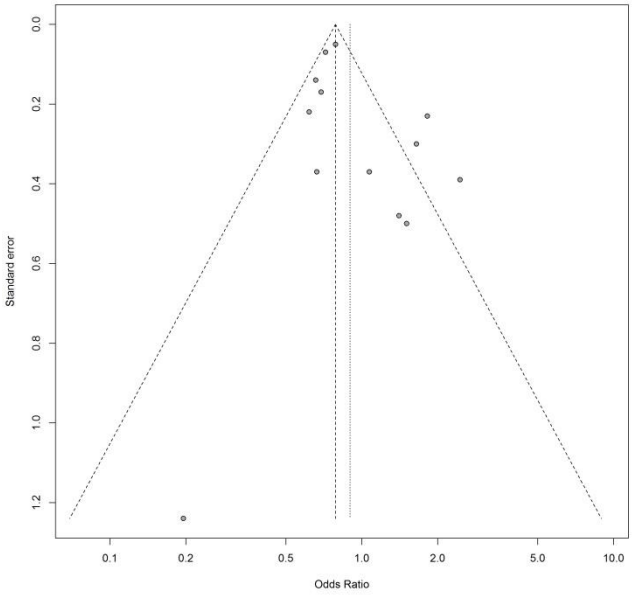


Figure 72 Risk of publication bias in studies of exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years



Egger's test p-value = 0.159

2.4.1.3 5+ months

Three observational studies reported data on risk recurrent wheeze with EBF ≥5 months vs. <5 months in children aged 0-4 years old. There was no evidence of an effect in the combined analysis (Figure 73), and the studies had high heterogeneity across studies (I^2=61.7%).

Figure 73 Exclusive breast feeding ≥5 months vs. <5 months and risk of recurrent wheeze in children aged 0-4 years

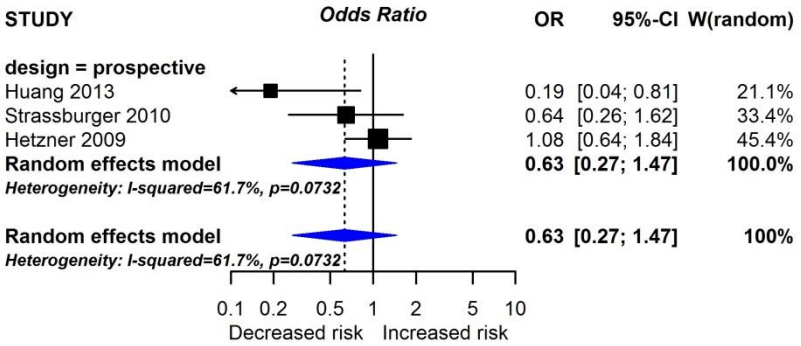


Table 16 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 0-4 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.52 [0.26; 1.03]	69.4	
Adjusted	3	0.25 [0.05; 1.37]	80.3	Not tested
Unadjusted	5	0.43 [0.18; 1.00]	73.7	
Risk of disease – High	3	0.17 [0.07; 0.45]	0.0	<0.01
Risk of disease – Normal	3	0.87 [0.50 1.50]	58.8	
Risk of bias – Low	2	1.10 [0.72; 1.67]	0.0	0.01
Risk of bias – High/Unclear	4	0.28 [0.12; 0.66]	42.3	

Table 17 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥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 value used)	13	0.90 [0.75; 1.08]	68.7	
Adjusted	9	0.79 [0.69; 0.92]	63.0	Not tested
Unadjusted	12	0.85 [0.67; 1.08]	69.2	
Study Design – Prospective	9	0.81 [0.65; 1.01]	45.7	0.20
Study Design – Retrospective	4	1.13 [0.71; 1.79]	86.2	
Risk of disease – High	2	0.60 [0.30; 1.20]	0.0	0.24
Risk of disease – Normal	11	0.92 [0.76; 1.12]	72.9	
Risk of bias – Low	3	0.83 [0.50; 1.37]	76.5	0.65
Risk of bias – High/Unclear	10	0.94 [0.76; 1.17]	69.4	

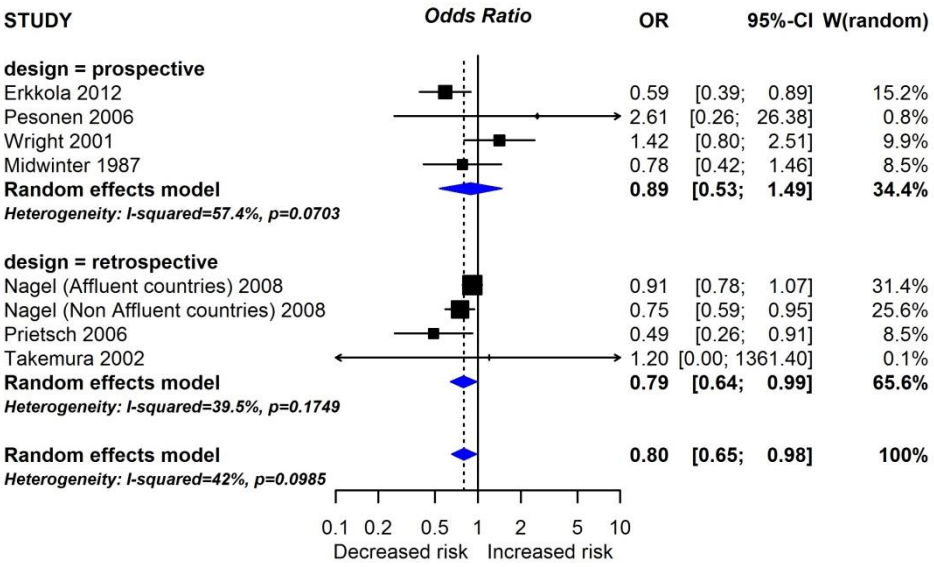
2.4.2 Age at outcome measurement 5-14

2.4.2.1 0-2 months

Eight observational studies reported data that could be pooled to assess the overall risk of recurrent wheeze in children aged 5-14 if with EBF ≥0-2 months vs. <0-2 months, and showed no evidence of an association with disease, but high heterogeneity between prospective studies was observed (I^2=57.4%) (Figure 74).

Subgroup analyses of risk of recurrent wheeze and EBF for ≥0-2 months vs. <0-2 months (Table 18) in children aged 5-14 years, showed no evidence of statistically significant differences between groups.

Figure 74 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of recurrent wheeze in children aged 5-14 years



2.4.2.2 3-4 months

Fifteen observational studies reported data eligible to calculated pooled effect of EBF ≥3-4 months vs. <3-4 months on recurrent wheeze in children aged 5-14 years. Data could not be pooled due to extreme statistical heterogeneity (Figure 75). Ten of them were prospective cohorts, two were nested case-control studies, 1 was a case-control study and 2 were cross-sectional studies. Most studies had low or unclear risk of bias, with the exceptions of three studies in which confounding was not accounted for and therefore they carry an overall high risk of bias. A funnel plot was used to explore publication bias (Figure 75). There was asymmetry across studies indicating risk of publication bias, which was confirmed by the Egger's test (P=0.01).

Subgroup analyses of risk of recurrent wheeze and EBF for ≥3-4 months vs. <3-4 months (Table 19) showed no evidence of statistically significant differences between groups.

Figure 75 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years

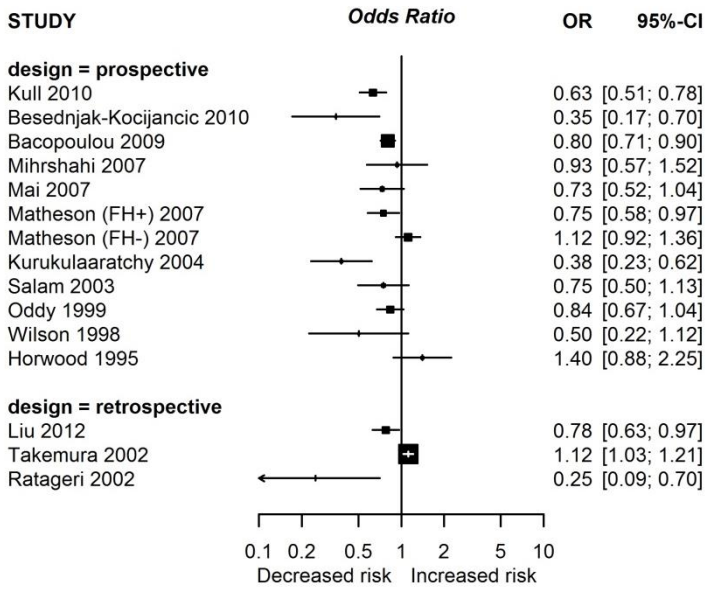
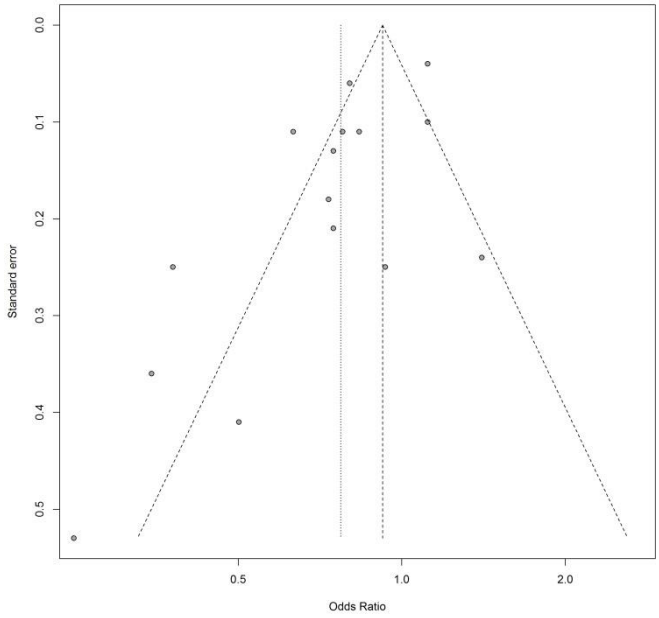


Figure 76 Risk of publication bias of studies investigating exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years



Egger's test p-value = 0.01

2.4.2.3 5+ months

Four observational studies reported data that was eligible to calculate pooled estimates of risk of recurrent wheeze in children aged 5-14 years old and exposure to EBF for 5 or more months, showing no evidence of an association (Figure 77) and an extremely high heterogeneity between studies (I^2=86.9%).

Figure 77 Exclusive breastfeeding ≥5 months vs. <5 months and risk of recurrent wheeze in children aged 5-14 years

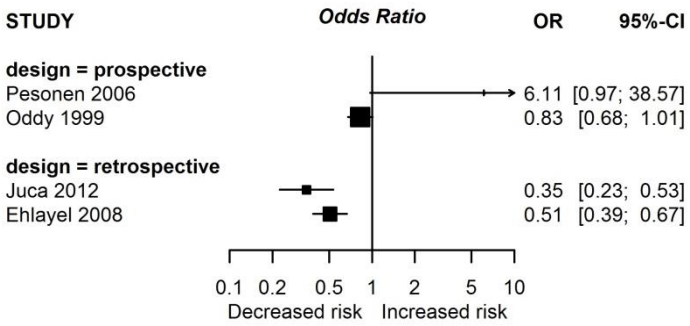


Table 18 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥0-2 months vs. <0-2 months in children aged 5-14 years

	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	9	0.91 [0.69; 1.19]	67.9	
Adjusted	5	0.93 [0.64; 1.35]	77.2	Not tested
Unadjusted	9	0.96 [0.75; 1.23]	81.9	
Study Design – Prospective	5	1.16 [0.63; 2.16]	78.1	0.26
Study Design – Retrospective	4	0.79 [0.64; 0.99]	39.5	
Risk of disease – High	1	0.78 [0.42; 1.46]	--	0.63
Risk of disease – Normal	8	0.93 [0.68; 1.25]	71.8	
Risk of bias – Low	1	2.61 [0.26; 26.38]	--	0.37
Risk of bias – High/Unclear	8	0.89 [0.68; 1.18]	70.9	

Table 19 Subgroup Analyses of risk of recurrent wheeze and exclusive breastfeeding ≥3-4 months vs. <3-4 months in children aged 5-14 years

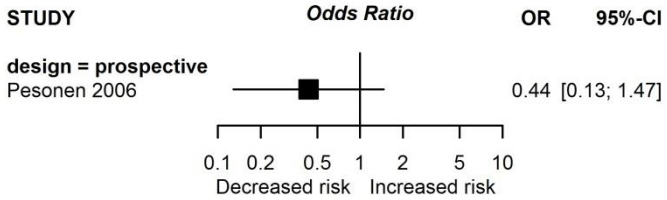
	Number of studies	OR [95% CI]	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	15	0.77 [0.66; 0.91]	83.2	
Adjusted	9	0.79 [0.69; 0.92]	63.0	Not tested
Unadjusted	11	0.77 [0.63; 0.95]	83.5	
Study Design – Prospective	12	0.76 [0.65; 0.90]	71.0	0.83
Study Design – Retrospective	3	0.80 [0.53; 1.22]	88.2	
Risk of disease – High	3	0.68 [0.44; 1.04]	62.1	0.51
Risk of disease – Normal	12	0.79 [0.66; 0.94]	85.0	
Risk of bias – Low	5	0.76 [0.55; 1.05]	78.3	0.87
Risk of bias – High/Unclear	10	0.79 [0.65; 0.95]	83.1	

2.4.3 Age at outcome measurement 15+

2.4.3.1 0-2 months

One prospective cohort study reported data for risk of recurrent wheeze in children aged 15+ and feeding ≥0-2 months vs. <0-2 months, showing no evidence of an association (Figure 78).

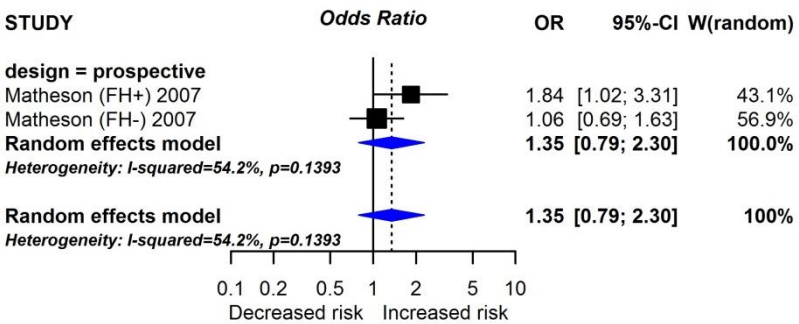
Figure 78 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of recurrent wheeze in children aged 15+ years



2.4.3.2 3-4 months

The prospective cohort study of Matheson reported ORs that were eligible to calculate pooled ORs or recurrent wheeze, showing no evidence of an association with the disease in the exposed group. The study had an overall low risk of bias (Figure 79).

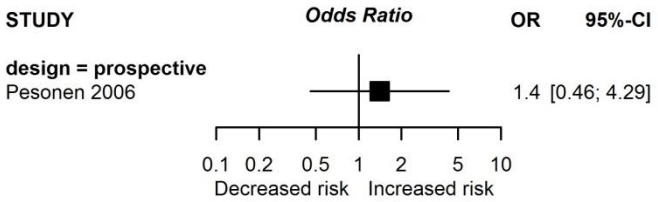
Figure 79 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 15+ years



2.4.3.3 5+ months

The study of Pesonen had reported data on risk of recurrent wheeze in children aged 15+ who were exposed to EBF for ≥5 months vs. <5 months, showing no indication of an effect (Figure 80).

Figure 80 Exclusive breast feeding ≥5 months vs. <5 months and risk of recurrent wheeze in children aged15+ years



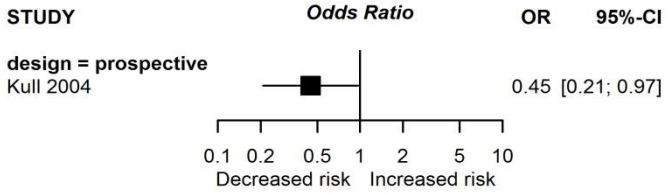
2.5 Exclusive Breastfeeding and Atopic Wheeze

2.5.1 Age at outcome measurement 0-4

2.5.1.1 0-2 months

The prospective cohort study of Kull (Figure 81) showed a lower risk of atopic wheeze in children aged 0-4 who were exposed to EBF for feeding ≥0-2 months vs. <0-2 months (OR 0.45; 95% CI 0.21, 0.97). The study carried a low risk of bias across all the domains studied.

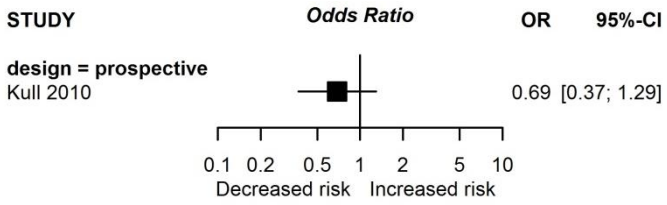
Figure 81 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of atopic wheeze in children aged 0-4 years



2.5.1.2 3-4 months

The prospective cohort study of Kull (Figure 82) showed no evidence of a protective effect of prolonged EBF for ≥3-4 months vs. <3-4 months on atopic wheeze in children aged 0-4. The study carried a low risk of bias across all the domains studied.

Figure 82 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of atopic wheeze in children aged 0-4 years

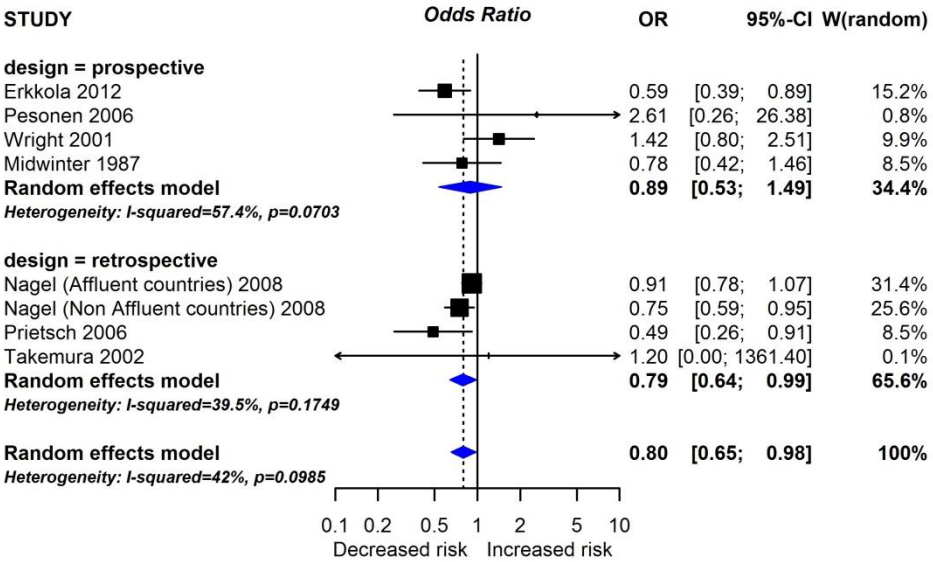


2.5.2 Age at outcome measurement 5-14

2.5.2.1 0-2 months

The cross-sectional study of Nagel investigated the risk of atopic wheeze at age 5-14 if EBF was ≥0-2 months vs. <0-2 months and reported no association with disease (Figure 83)

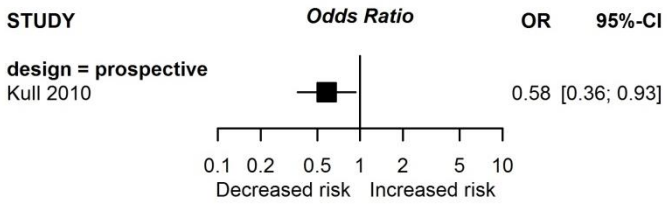
Figure 83 Exclusive breast feeding ≥0-2 months vs. <0-2 months and risk of atopic wheeze in children aged 5-14 years



2.5.2.2 3-4 months

The prospective cohort study of Kull (Figure 84) showed a reduced risk of atopic wheeze in children aged 5-14 years who were EBF for ≥3-4 months vs. <3-4 months (OR 0.58; 95% CO 0.36, 0.93). The study carried a low risk of bias across all the domains studied.

Figure 84 Exclusive breast feeding ≥3-4 months vs. <3-4 months and risk of atopic wheeze in children aged 5-14 years

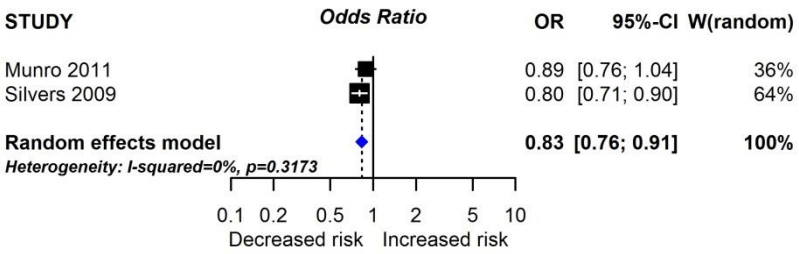


2.6 Exclusive Breastfeeding per month and recurrent wheeze

2.6.1 Age at outcome measurement 0-4

Two prospective cohort studies reported data eligible to calculate pooled effect estimates of risk of recurrent wheeze and exposure to EBF per month (Figure 85), suggesting a protective effect against disease in the exposed children between 0-4 years (OR 0.83; 0.76, 0.91). There was no evidence of heterogeneity between the two studies (I^2=0.0%). The study of Silvers had a low overall risk of bias, and the study of Munro had an unclear overall risk of bias.

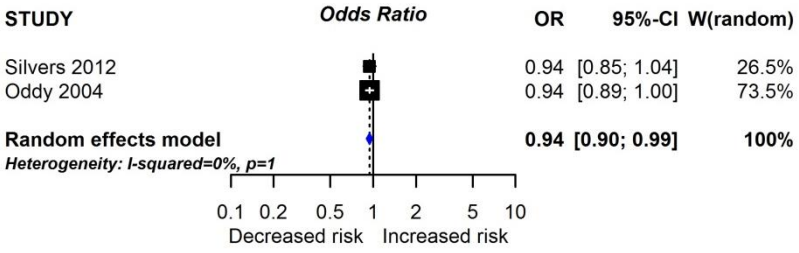
Figure 85 Exclusive breastfeeding per month and risk of recurrent wheeze in children aged 0-4 years



2.6.2 Age at outcome measurement 5-14

Two prospective cohort studies reported data eligible to calculate pooled effect estimates of risk of recurrent wheeze and exposure to EBF per month (Figure 86), suggesting a protective effect against disease in the exposed children between 5-14 years (OR 0.94; 0.90, 0.99). There was no evidence of heterogeneity between the two studies (I^2=0.0%). The study of Silvers had a low overall risk of bias, and the study of Oddy had an unclear overall risk of bias.

Figure 86 Exclusive breastfeeding per month and risk of recurrent wheeze in children aged 5-14 years



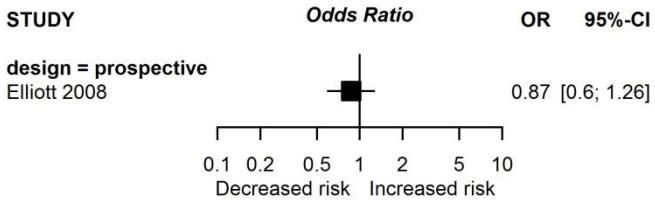
2.6.2.1 Exclusive breastfeeding and BHR

2.6.2.2 Age at outcome 5-14 years

2.6.2.3 0-2 Months

The prospective study of Elliot reported risk of BHR in children aged 5-14 who were exposed to EBF for ≥0-2 months vs. <0-2 months, showing no evidence of an association (Figure 87). The study had an unclear overall risk of bias, due to unclear risk of selection bias.

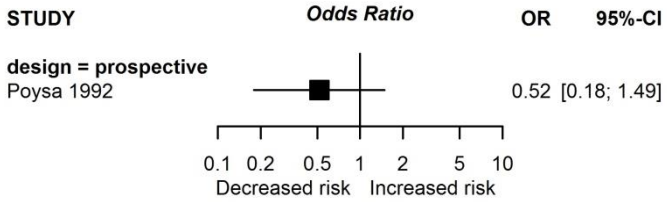
Figure 87 Exclusive breastfeeding ≥0-2 months vs. <0-2 months and risk of bronchial hyper-responsiveness in children aged 5-14 years



2.6.2.4 3-4 Months

The prospective study of Poysa reported risk of BHR in children aged 5-14 who were exposed to EBF for ≥3-4 months vs. <3-4 months, showing no evidence of an association (Figure 88). The study had a high overall risk of bias, due to risk of selection and confounding biases.

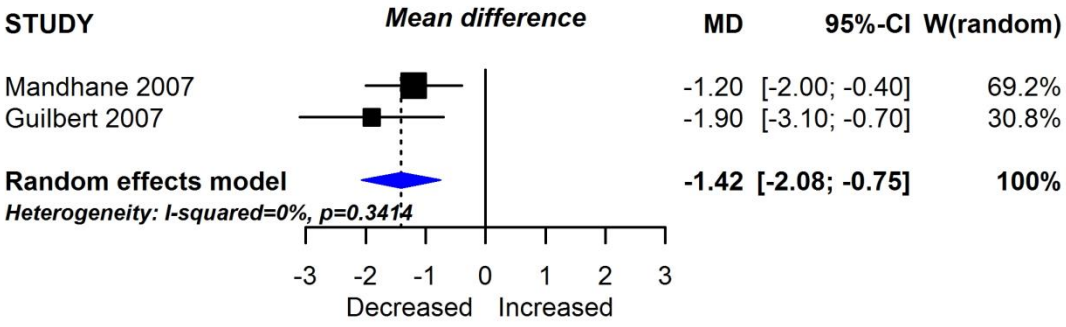
Figure 88 Exclusive breastfeeding ≥3-4 months vs. <3-4 months and risk of bronchial hyper-responsiveness in children aged 5-14 years



2.7 Data for EBF duration and lung function (FEV1/FVC%)

Two prospective cohorts had results with mean differences: (1) Mandhane, 2007, comparing breastfeeding < 1 month (reference) versus ≥ 1 months at 9 years of age, with unadjusted estimate; (2) Guilbert, 2007, breastfeeding < 1 month (reference) versus > 4 months between 11-16 years of age, with adjusted estimate.

Figure 89 Exclusive breastfeeding and FEV1/FVC% in children aged 5-14 years



2.8 Data for EBF duration and Wheeze, BHR or lung function that were not suitable for meta-analysis

Table 20 summarises the studies on wheeze, BHR or lung function for which data could not be meta-analysed. Meta-analysis was not possible due to the way the data were reported. In total there were 18 reports, of which 16 were prospective cohort studies and 2 cross-sectional studies.

From 9 studies reporting wheeze, and 10 reporting recurrent wheeze, just 2 reported a statistically significant association between increased EBF and reduced wheeze and 2 studies reported a significant association between increased EBF and increased wheeze.

There were 2 studies for BHR, both reporting no significant association between EBF and BHR. There were 14 measures reported from 3 prospective studies of lung function, in individuals aged 8-26 years old. Of these 14 measures, 2 were significantly associated with increased EBF, 2 with reduced EBF and 10 were not associated with EBF.

Table 20 Studies investigating the association between exclusive breastfeeding and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Giwercman, 2010 (134)	PC	wheeze	2	313	0+	Adjusted HR (95%CI)	0.67 (0.48-0.96)	<0.05
Zutavern 2004 (114)	PC	wheeze, recurrent wheeze	2, 5.5	606	>2	Adjusted OR		NS
Cano Garcinuno (130) (2003)	CS	wheeze	3	234	>3	Adjusted HR (95%CI)	0.83 (0.42-1.64)	0.60
Chong Neto, 2007 (141)	CS	wheeze	1	3003/1364	>4, >6	Adjusted PR		NS
Kramer, 2003 (156)	PC	wheeze	1	3483/8	>6	Adjusted OR (95%CI)	1.49 (0.66-3.36)	0.34
da Costa Lima, 2003 (81)	PC	wheeze	18	2247	0+	Adjusted PR (95%CI)	1.22 (1-1.5)	0.054
Kurukulaaratchy, 2006 (145)	PC	wheeze-atopic	10	unclear	>3	Adjusted OR (95%CI)	0.09 (0.01-0.93)	0.04

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Kurukulaaratchy, 2006 (145)	PC	wheeze-non atopic	10	492/178	>3	Adjusted OR		NS
Rullo, 2007 (163)	PC	recurrent wheeze	1.5, 5	101	>6	Adjusted OR		NS
Hesselmar 2010 (5)	PC	recurrent wheeze	1.5	184	continuous			NS
Nwaru, 2013 (24)	PC	recurrent wheeze	5	3675	0+, >3	Adjusted HR		NS
Mandhane, 2007 (138)	PC	recurrent wheeze	9	714/76	>1	Adjusted OR	1.22	0.04
Pesonen, 2006 (153)	PC	recurrent wheeze	5	160/1	>2	Prevalence	3.5% Vs 0%	-
Kramer, 2009 (157)	PC	recurrent wheeze	6.5	2951/44	>6	Adjusted OR (95%CI)	1.2 (0.6-2.4)	0.62

Table 21 Studies investigating the association between exclusive breastfeeding and BHR or lung function which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Elliot 2008 (4)	PC	Bronchial hyper-responsiveness	5-14	3295	≥0-2mo vs <0-2mo	logistic regression, adjusted	0.87 (0.60-1.26)	0.46
Poysa 1992 (175)	PC	Bronchial hyper-responsiveness	5-14	119	≥3-4mo vs <3-4mo	Compared proportions, unadjusted	0.52 (0.18-1.49)	0.12
Kull, 2010 (127)	PC	FEV1(ml)	8	1838	>4	Adjusted Mean difference (95%CI)	17.4 (-5.7, 40.5)	NS
		PEF(L)	8	2168	>4	Adjusted Mean difference (95%CI)	4.5 (0.68, 8.29)	0.02
Mandhane, 2007 (138)	PC	FEV1/FVC%	26	714	>1	Mean difference (95%CI), unadjusted	-0.1 (-0.93; 0.73)	0.83
			9	714	>1	Mean difference (95%CI), unadjusted	-1.2 (-2.00; -0.40)	0.004
Guilbert, 2007 (178)	PC	FEF25–75(ml/s)	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	-2.9 (-132.3-126.5)	0.9

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Guilbert, 2007 (176)	PC	FEF25–75(ml/s)	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	-124 (-267-19)	0.009
Guilbert, 2007 (176)	PC	FEF25–75/ FVC%	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	-2.7 (-6.8-1.5)	0.02
Guilbert, 2007 (176)	PC	FEF25–75/ FVC%	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	-7.6 (-12.1;-3.1)	0.001
Guilbert, 2007 (176)	PC	FEV1(ml)	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	27 (-33.8-87.8)	0.1
Guilbert, 2007 (176)	PC	FEV1(ml)	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	20 (-38 .8-78.8)	0.5
Guilbert, 2007 (176)	PC	FEV1/FVC%	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	-0.7 (-1.9, -0.5)	0.2
Guilbert, 2007 (176)	PC	FEV1/FVC%	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	-1.9 (-3.1; -0.7)	0.004
Guilbert, 2007 (176)	PC	FVC(ml)	13	679	2-4 vs >1	Adjusted Mean difference (95%CI)	43 (-84.4, 170.4)	0.2

First Author and year of publication	Design	Outcome	Age	N/n	EBF duration (continuous or categorical in months)	Measure of association	Effect	P-value
Guilbert, 2007 (176)	PC	FVC(ml)	13	679	>4 vs <1	Adjusted Mean difference (95%CI)	103 (24.6, 181.4)	0.01
Elliot 2008 (4)	PC	Bronchial hyper-responsiveness	5-14	3295	≥0-2mo vs <0-2mo	logistic regression, adjusted	0.87 (0.60-1.26)	0.46
Poysa 1992 (175)	PC	Bronchial hyper-responsiveness	5-14	119	≥3-4mo vs <3-4mo	Compared proportions, unadjusted	0.52 (0.18-1.49)	0.12

3 Solid Food Introduction and Wheeze

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

Table 21 describes the main characteristics of the studies that assessed solid food introduction (SFI) in relation to wheeze risk. A total of 15 observational studies, and no intervention studies, reported the association between SFI and wheeze. Of these, 13 were prospective cohort studies and 2 were case-control studies. The majority of studies (n=9) are from Europe – others are from the Asia-Pacific region (n=4), North America (n=1), 1 from South Asia.

Overall, valid data on SFI duration in the first 2 years of life and wheeze risk were available from over 14,000 subjects. Information on wheeze was obtained solely from parental or self-reported in 3 studies and through Dr-diagnosis in 7 studies. Another 4 studies used a combination of self /parental report, Doctor diagnosis, and/ or objective measures (e.g. bronchial hyper-responsiveness (BHR)). One study used an unclear method for defining wheeze.

With regards to time of outcome diagnosis, 8 studies explored the association between SFI duration and wheeze at age 0-4 years and 4 at age 5-14 years. No studies investigated outcomes at age 15 years or beyond. A further three studies investigated the association between SFI duration and wheeze at various time points between the ages of 1 and 10 years. To ascertain exposure to SFI, 4 studies used a questionnaire method, 6 used an interview and 1 used a food frequency questionnaire (FFQ). A further 4 studies used a combination of 2 or more of these methods.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 84 illustrates the distribution of bias across the five main methodological areas of the studies. Over 40% of the studies had a high risk of overall bias, mainly due to confounding bias. The majority of the studies were considered to have a low risk of conflict of interest bias. Overall, there was no suggestion of an effect of SFI on wheeze. None of the meta-analyses that could be carried out showed an effect of SFI on wheeze. There were additionally three studies that could not be meta-analysed and showed no association with wheeze.

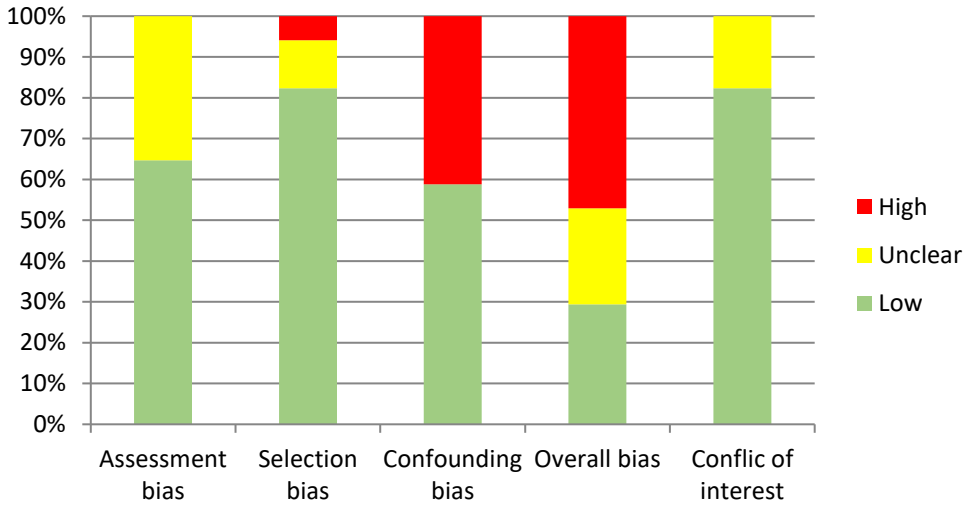
Table 22 Characteristics of included studies evaluating solid food introduction and wheeze

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Hesselmar, 2010 (5)	PC	184	I	DD asthma (>=3 episodes of wheeze)	1.5	Sweden	ALLERGYFLORA study. Population based study of babies selected from antenatal clinics between 1998 and 2003 - mainly high risk of allergic disease
Mihrshahi, 2007 (20)	PC	516	I	DD PLUS current wheeze	5	Australia	CAPS study. Infants born in 1997-1999 with family history of asthma or wheezing
Fergusson, 1983(132)	PC	1110	R/I	DD asthma (>=2 episodes of wheeze)	4	New Zealand	Christchurch Child Development Study. Population based cohort of infants born in 1977 in the Christchurch urban region
Larsson, 2008 (22)	PC	4779	Q	DD	9	Sweden	DBH study. Preschool children aged 1–6 years surveyed in 2000 and 2005.
Forsyth, 1993; Wilson, 1998 (25, 179)	PC	545	Q, D/I	Self-reported wheeze; DD; Physician assessment	2, 7.3	UK	Dundee infant feeding study. Population based cohort of infants born between 1983-1986
Karunasekera, 2001 (52)	CC	600	Q	Physician assessment	10	Sri Lanka	Hospital-based cases aged 1-10 years old with age matched controls from inpatient clinics
Snijders, 2008 (56)	PC	1894	Q	>=4 episodes of wheeze	2.0	Netherlands	KOALA study. Population based birth cohort of infants born between 2000-2002 (consisting of cohorts with conventional and alternative lifestyle)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Zutavern, 2008 (180)	PC	2073	FFQ	Parent reported current wheeze OR asthma medication; DD	6	Germany	LISA study. Population based birth cohort of infants born between November 1997 and January 1999 at selected maternity hospitals in 4 German cities
Majeed, 2008 (150)	CC	398	Q/I	DD asthma AND >=2 episodes of wheeze	3	Pakistan	Cases are 1-12 years old children with wheeze/asthma admitted to paediatrics wards. Controls are age matched children and adolescents attending immediately after selection of the index case
Marini, 1996 (59)	PC	Unclear	Q	Physician assessment (>=3 episodes of wheeze)	3	Italy	Infants with family history of allergy whose mother were proposed to participate in an allergy prevention program
Morgan, 2004 (66)	PC	144	I	DD	1.5	U.K.	Infants from five prospective randomised dietary trials conducted in the UK between 1993 and 1997. Two trials involved term appropriate for gestational age (AGA) infants, one trial involved term small for gestational age (SGA) infants (birth weight 10th centile for gestational age and sex), and two trials involved preterm infants (37 weeks gestation, birth weight 2000g).
Hide, 1981; Kurukulaaratchy, 2004 (101, 146)	PC	843	D/Q, Q	Parent reported wheeze; >=2 episodes of wheeze between age <4 and 10 years; Late onset wheeze: onset >4 years of age and still wheezed at 10 years	1, 10	UK	The Isle of Wight Prevention study: born in 1977-1978 (normal risk of disease)
Van Asperen, 1983 (172)	PC	79	I	Parent reported wheeze	1.3	Australia	Cohort recruited from medical service, born in 1980-1981 with family history of atopy (high risk of disease)

First Author & Publication Year	Design	N	Exposure assessment	Method of outcome assessment	Age at outcome (years)	Country	Population characteristics
Joseph, 2012 (181)	PC	594	I	Unclear	3	USA	WHEALS STUDY: Recruited from hospital prenatal care and born in 2005 (normal risk of disease)
Zutavern 2004 (114)	PC	606	I	Parent reported current wheeze	2, 5.5	UK	Cohort recruited from general practices and born in 1993-1995 (normal risk of disease)

Figure 90 Risk of bias in studies of solid food introduction and wheeze



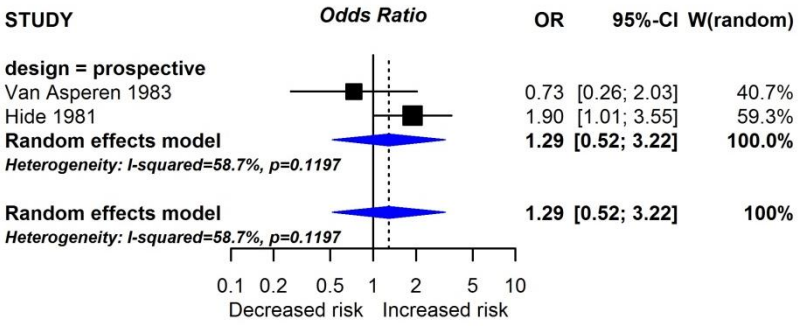
3.2 Solid Food Introduction and Wheeze

3.2.1 Age at outcome measurement 0-4

3.2.1.1 3-4 months

Two prospective cohort studies reported data that could be pooled to estimate the combined effect of SFI on wheeze at age 0-4 years, showing no suggestion of a protective effect (Figure 91). The study of Hide had a low overall risk of bias, whilst the study of Van Asperen had a high overall risk of bias (due to confounding bias), which might contribute to explain the high heterogeneity observed between studies (I^2=58.7%)

Figure 91 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 0-4 years

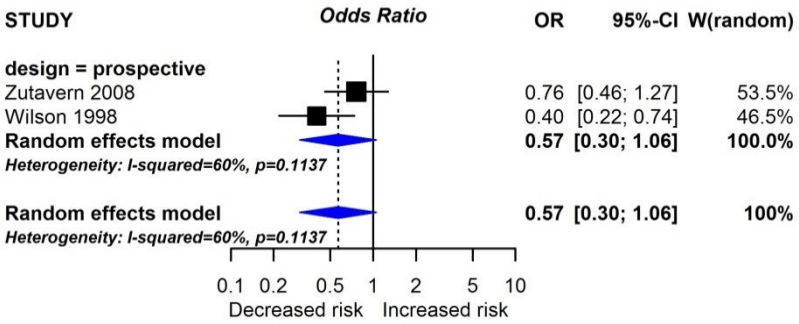


3.2.2 Age at outcome measurement 5-14

3.2.2.1 3-4 months

Two prospective cohort studies reported data that could be pooled to estimate the combined effect of SFI at ≥3-4 months vs. <3-4 months, on wheeze at age 5-14 years, showing no suggestion of a protective effect (Figure 92). The study of Zutavern had a low overall risk of bias, whilst the study of Wilson carried a had a high overall risk of bias (due to confounding bias), which might contribute to explain the high heterogeneity observed between studies (I^2=60.0%)

Figure 92 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of wheeze in children aged 5-14 years



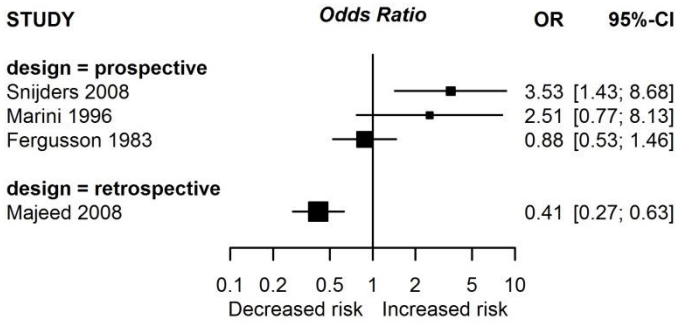
3.3 Solid Food Introduction and Recurrent Wheeze

3.3.1 Age at outcome measurement 0-4

3.3.1.1 3-4 months

Three prospective cohort studies and one case-control study reported data that could be pooled to estimate overall risk of recurrent wheeze at age 0-4 years comparing SFI at ≥3-4 months vs. <3-4 months. There was no evidence of an effect (Figure 93). Two studies (Majeed and Ferguson) had a high risk of overall bias (due to confounding bias), one had a low risk and one was unclear. These variations might explain the high heterogeneity observed between studies (I^2=87.3%)

Figure 93 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 0-4 years

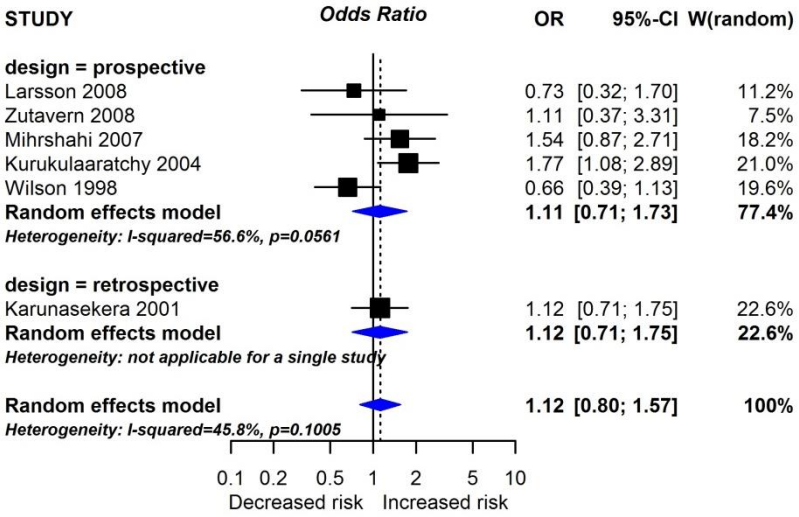


3.3.2 Age at outcome measurement 5-14

3.3.2.1 3-4 months

Five prospective cohort studies and one case-control study reported data that could be pooled to estimate overall risk of recurrent wheeze at age 5-14 years comparing SFI at ≥3-4 months vs. <3-4 months. There was no evidence of an effect (Figure 94). With the exception of the study of Wilson (which had a high risk of overall bias due to confounding bias), all prospective cohorts had a low risk of overall bias. The study of Karunasekera (case-control) had an unclear overall risk of bias. There was moderate heterogeneity observed between studies (I^2=45.8%)

Figure 94 Solid Food Introduction ≥3-4 months vs. <3-4 months and risk of recurrent wheeze in children aged 5-14 years



Subgroup analyses of risk of wheeze and solid food introduction ≥3-4 months vs. <3-4 months in children aged 5-14 years showed no indication of statistically significant differences between the various groups examined (Table 23). There were additionally three studies that could not be meta-analysed and showed no association with wheeze (Table 24).

Table 23 Subgroup Analyses of risk of wheeze and solid food introduction ≥3-4 months vs. <3-4 months 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)	6	1.12 [0.80; 1.57]	45.8	
Adjusted	2	1.43 [0.87; 2.38]	0.0	Not tested
Unadjusted	5	1.11 [0.77; 1.60]	54.7	
Study Design – Prospective	5	1.11 [0.72; 1.73]	56.6	0.99
Study Design – Retrospective	1	1.12 [0.71; 1.75]	--	
Risk of disease – High	1	1.54 [0.87; 2.71]	--	0.27
Risk of disease – Normal	5	1.04 [0.71; 1.54]	49.8	
Risk of bias – Low	3	1.20 [0.77; 1.86]	3.0	0.82
Risk of bias – High/Unclear	3	1.10 [0.67; 1.88]	71.8	
Clear definition of breastfeeding duration	5	1.11 [0.72; 1.73]	56.6	0.99
Unclear definition of breastfeeding duration	1	1.12 [0.71; 1.75]	--	

Table 24 Studies investigating the association between solid food introduction and wheeze which were not eligible for meta-analysis

First Author and year of publication	Design	Outcome	Age	N/n	Age at SF introduction (continuous or categorical in months)	Average age at SF introduction	SF introduction Unaffected		SF introduction in Affected		P-value
Hesselmar 2010 (5)	PC	recurrent wheeze	1.5	184	continuous	Median (IQR)	4	4	4.2	4	NS
Joseph 2012 (181)	PC	wheeze	3	594	>4						NS
Forsyth, 1993 (179)	PC	wheeze	2	455	>2						NS

4 Conclusion

This systematic review on breastfeeding and solid food introduction did not find strong evidence of a relationship between these exposures and the outcomes of wheeze, recurrent wheeze, atopic wheeze, BHR or lung function. There were asymmetrical Funnel plots with evidence of publication bias in several meta-analyses of observational studies for TBF and EBF and wheezing, with small negative studies potentially missing. For this reason the only consistent finding, that TBF is associated with reduced risk of recurrent wheeze at age 5-14 years, was downgraded to VERY LOW certainty evidence, due to risk of publication bias. These findings highlight the importance of rigorous assessment of bias, including publication bias in the synthesis of existing scientific literature in this area, since previous reviews have not identified publication bias as an issue with this body of literature. The single intervention trial in this area found reduced risk of recurrent wheezing at age 1 year in infants born in centres randomised to a breastfeeding promotion intervention, but the outcome was not statistically significant OR 0.70 (0.29, 1.70). In the same trial there was no evidence for a difference in recurrent wheeze ('asthma ever') at age 6.5 years OR 1.2 (0.7, 1.9). Thus the intervention trial neither excludes nor supports an effect on wheezing.

Overall, the data for TBF and other outcomes, and for EBF and SF timing and all outcomes, showed significant heterogeneity in findings and rarely excluded the possibility of biological relationships. Thus we cannot confidently exclude the possibility that breastfeeding and solid introduction are related to risk of wheeze; however the currently available data do not support a relationship, aside from the VERY LOW certainty evidence that longer TBF is associated with reduced risk of recurrent wheeze at age 5-14 years.

We did not identify recent systematic reviews that met our requirements for inclusion in the review (i.e. R-AMSTAR score ≥32). There are however 3 recent important systematic reviews in this area which are relevant to discuss. The study of Dick (182) did not undertake meta-analysis, and no firm conclusions were made regarding the relationship between breastfeeding duration and risk of asthma at age ≤ 9 years. The systematic review of Waidyatillake (183) assessed the relationship between breastfeeding duration and lung function. Consistent with our approach and findings, Waidyatillake et al did not undertake meta-analysis, but identified the same studies as we did, and found evidence that increased

duration of TBF and EBF is associated with increased measures of lung function – especially FVC but also FEV1. We found evidence for a positive relationship between breastfeeding duration and lung function on at least one measure reported, for 5 of 7 studies reporting TBF, and 2 of 3 studies reporting EBF, with strongest evidence for FVC but also positive findings for measures of airway obstruction. However, findings were not consistent, and for two studies of EBF we found significant associations between longer duration and poorer lung function. We additionally studied bronchial hyper-responsiveness (BHR) where we were able to undertake limited meta-analysis and found no evidence of a relationship between TBF or EBF duration and BHR. The third relevant systematic review is the study of Dogaru, whose authors reported a strong association between increased breastfeeding duration and reduced risk of asthma, especially at age 0-2 years (184). Their approach of combining all durations of breastfeeding and creating a single pooled estimate for 'more' versus 'less' could be criticised on the basis that the reference group in some studies has significant overlap with the exposure group in other studies within the same meta-analysis. This may also lead to an exaggeration of any biases inherent in the included dataset. Our new finding of probable publication bias in this area, which has not been reported before, weakens the evidence base that prolonged breastfeeding duration reduces wheeze or asthma risk.

In summary we have found VERY LOW evidence that longer total duration of breastfeeding may be associated with reduced risk of recurrent wheeze at age 5-14 years. We have not found evidence for associations between duration of breastfeeding, or timing of solid food introduction, and other wheeze or lung function outcomes. The finding of probable publication bias means that these findings need to be interpreted with caution. We have identified a need for further investigation in this area – especially the study of mechanisms through which human milk feeding might promote lung growth in the developing infant, since we did not find evidence for an association between these exposures and allergic sensitisation; so if the association found here is real, then other mechanisms must be explored (183). A number of hypotheses have been proposed through which breastfeeding might promote lung growth – including reduced respiratory tract infections, reduced weight gain, altered respiratory dynamics during breastfeeding, increased exposure to breast milk derived growth factors, and as a secondary consequence of reduced asthma prevalence. Further work is needed to establish whether breastfeeding influences lung function in the developing infant, and whether the association seen here with recurrent wheezing from age 5-14 years can be confirmed.

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