BREASTFEEDING, SOLID FOOD INTRODUCTION AND TYPE I DIABETES MELLITUS

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1. Total breastfeeding duration and risk of TIDM

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

Table 1 describes the main characteristics of the studies analysed in this report. A total of 65 observational studies, and no intervention studies, reported the association between duration of breastfeeding and risk of TIDM. Of these, 15 were prospective cohort studies, 7 nested case-controls, 1 cross-sectional study and 42 case-control studies. Over half of the studies (n=39) are from Europe – others are from North America (n=9), South America (n=4), Asia (n=8), the Middle East (n=4) and Africa (n=1). Overall, valid data on total breastfeeding duration in the first year of life (TBF) and TIDM risk were available from almost 50,000 subjects including over 12,000 with TIDM. Information on TIDM was obtained mainly from serology (Islet auto-antibodies) in 15 prospective studies and via medical diagnosis in 50 (mainly case control) studies. With regards to time of outcome diagnosis, 12 studies explored the association between exposure to breastfeeding and TIDM in the first 5 years of life, 2 didn't report the age at outcome assessment, and others evaluated TIDM in older children or young adults. 58 studies used interview or questionnaire to assess the exposure (TBF), 7 studies assessed medical records only.

Risk of bias was assessed using the NICE Methodological checklists for cohort and case-control studies. Figure 1 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of studies had a high risk of bias, most commonly due to lack of adjustment for confounding bias i.e. no adjusted data presented. Over a quarter of studies had an 'unclear' overall risk of bias, most commonly due to insufficient information to evaluate assessment bias. We undertook subgroup/stratified analyses for meta-analyses with >5 studies, and Funnel plots and Egger's test where there were ≥10 studies in a meta-analysis.

Five levels of comparison were used to assess the risk of TIDM according to total breastfeeding 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

Across all cut-offs for TBF duration, there was evidence of a lower risk of TIDM with longer duration of breastfeeding, however meta-analyses showed moderate to high statistical heterogeneity across studies. Stratified and subgroup analyses showed some evidence of risk

difference when specific risk groups and study design characteristics were analysed. Prospective studies, which often used autoantibodies at a young age as a surrogate for TIDM, and sometimes reported HR rather than OR, tended to not show a significant association between TBF and TIDM risk. In contrast, retrospective studies using clinical TIDM as an outcome tended to report an association between longer TBF and reduced TIDM risk, sometimes with low statistical heterogeneity. It is possible that the difference observed between these two groups of study design lies in the type of outcome used to measure TIDM. In general adjusted and unadjusted analyses showed similar findings. We were not able to clearly confirm the relationship between TBF and TIDM in dose-response analysis, although data were limited for this analysis - and only a small number of the 24 studies (~1/3 of TIDM cases) which could not be included in any meta-analysis found the same association between TBF and reduced TIDM risk. Thus our data must be interpreted as VERY LOW certainty evidence (GRADE -1 inconsistency) that longer duration of TBF is associated with reduced TIDM risk.

Table 1 Description of observational studies on total breastfeeding duration and Risk of TIDM

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Couper, 1999 (1)	317/70	PC	Australia	D/Q	Islet autoantibodies	2	First degree relatives of diabetic children
Couper, 2009 (2)	548/~30	PC	Australia	D/I	Islet autoantibodies	2	First degree relatives of diabetic children
Fronczak, 2003 (3)	222/~16	PC	USA	Q	Islet autoantibodies	4	Newborn screening, or Colorado register
Holmberg, 2007 (4)	3788/~51	PC	Sweden	Q	Islet autoantibodies	6	General population
Hummel, 2000 (5)	568	PC	Germany	Q	Islet autoantibodies	2	Offspring of diabetic parents
Karlen, 2012 (6)	1409	PC	Sweden	Q	Islet autoantibodies	1	General population
Lamb 2008 (7)	642	PC	Australia	I	Islet autoantibodies	13	St. Joseph's Hospital in Denver, Colorado
Lamb, 2013 (8)	260	PC	America	I	Islet autoantibodies	Not reported	not reported
Ludvigsson, 2003 (9)	205	PC	Sweden	Q	Islet autoantibodies	2	Relatives of diabetics
Norris, 2003 (10)	1183/~733	PC	USA	I	Islet autoantibodies	4	St Joseph's Hospital, Colorado
Viner, 2008 (11)	11211/61	PC	UK	Q	Medical diagnosis	>10	not reported
Virtanen, 1998 (12)	697/43	PC	Finland	Q	Medical diagnosis, Islet autoantibodies	<25	Siblings of diabetic children
Virtanen, 2011 (13)	~4000/~160	PC	Finland	Q	Medical diagnosis or islet autoantibodies	5	Odu and Tampere University Hospitals
Wahlberg, 2006 (14)	8715/31	PC	Sweden	Q	Islet autoantibodies	2	General population

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Ziegler, 2003 (15)	1460/~68	PC	Germany	Q	Islet autoantibodies	5	Newborn children
Jones, 1998 (16)	518/60	NCC	UK	R	Medical diagnosis	5.0-9	Hospital admission
Kimpimaki, 2001 (17)	455/65	NCC	Finland	Q	Medical diagnosis	<4	Turku, Oulu and Tampere Hospital births
Kyvik, 1992 (18)	228/76	NCC	Denmark	R	Medical diagnosis	<20	National Service Conscript records
Norris, 1996 (19)	171/18	NCC	USA	Q/R	Islet autoantibodies	<7	Siblings or offspring of Barbara Davies Centre Diabetics
Robertson, 2010 (20)	1444/361	NCC	UK	R	Medical diagnosis	<15	AMND and SSG register, hospital births
Savilahti, 2009 (21)	6209/45	NCC	Finland	R	Medical diagnosis	12	NHI database
Virtanen, 2000 (22)	287/33	NCC – nested in Virtanen, 1998 (12)	Finland	Q	Medical diagnosis	7	Siblings of previously diagnosed diabetic child
Glatthaar, 1988 (23)	946/~200	CS	Australia	Q	Medical diagnosis	<18	School register
Ahadi, 2011 (24)	202/101	CC	Iran	Q/I	Medical diagnosis	7	Hospital admission
Alves, 2012 (25)	246/123	CC	Brazil	I	Medical diagnosis	7	Siblings
Ashraf, 2010 (26)	195/128	CC	USA	Q	Medical diagnosis	<10	Children's hospital
Baruah, 2011 (27)	86/43	CC	India	I	Medical diagnosis	<18	Endocrinology ward
Bener, 2009 (28)	340	CC	Qatar	I	Medical diagnosis	<16	Endocrinology clinic and community

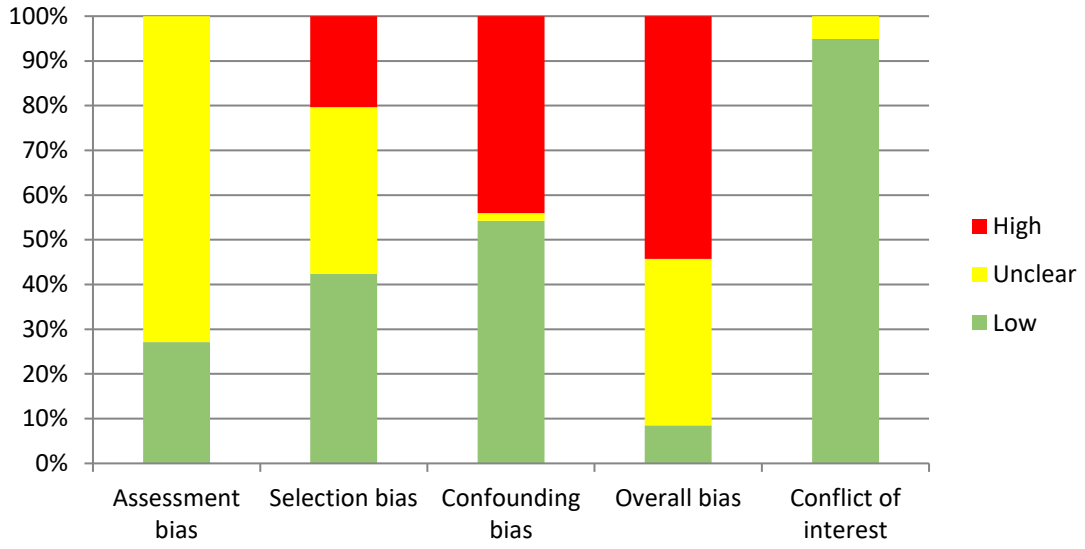
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Blom, 1989 (29)	867/339	CC	Sweden	Q	Medical diagnosis	7	Paediatric referral and population register
Bodington, 1994 (30)	393/209	CC	UK	Q	Medical diagnosis	<15	Independent sources and population register
Borras, 2011 (31)	1530/306	CC	Spain	R	Medical diagnosis	not reported	Diabetes register and Catalonia birth register
Esfarjani, 2001 (32)	104/52	CC	Iran	Q	Medical diagnosis	<14	Endocrine clinic and paediatric OPD attendance
Dahlquist, 2002 (33)	2226/610	CC	Austria, Latvia, Lithuania, Luxembourg and UK	Q/I	Medical diagnosis	<15	Diabetes register and population register
Gimeno, 1997 (34)	626/313	CC	Brazil	Q	Medical diagnosis	<18	Juvenile Diabetes Association or hospital records
Hathout, 2006 (35)	402/102	CC	USA	Q/I	Medical diagnosis	7	Diabetes hospital care and Hospital Well Child clinics
Hypponen, 1999 (36)	821/435	CC	Finland	Q	Medical diagnosis	8	Finnish Population Registry
Kostraba, 1992 (37)	264/132-white 108/54-black	CC	USA	Q/I	Medical diagnosis	10	Alleghany Hospital diabetes register
Kostraba, 1993 (38)	306/142	CC	USA	Q	Medical diagnosis	<18	Colorado IDDM Registry and otor vehicle driver register
Majeed, 2011 (39)	310/96	CC	Iraq	Q	Medical diagnosis	<17	Hospital admission or OPD
Malcova, 2006 (40)	2334/868	CC	Czech Republic	Q	Medical diagnosis	<15	Czech Childhood Diabetes Register and diabetes clinic
Marshall, 2004 (41)	577/196	CC	UK	I	Medical diagnosis	<16	Paediatric clinic and Local Health Authority Register

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Mayer, 1988 (42)	747/268	CC	USA	Q/I	Medical diagnosis	<18	Colorado IDDM Registry or Barbara Davies Centre
McKinney, 1999 (43)	521/196	CC	UK	I	Medical diagnosis	<16	Yorkshire Childhood Diabetes Register and Family Health Service Authority Register
Meloni, 1997 (44)	200/100	CC	Italy	Q	Medical diagnosis	<17	Paediatric clinic or hospital admission
Patterson, 1994 (45)	1548/258	CC	UK	R	Medical diagnosis	<15	Diabetes register, hospital discharge, Health Service records
Perez-Bravo, 1996 (46)	165/80	CC	Chile	Q/I	Medical diagnosis	<15	Santiago de Chile registry
Perez-Bravo, 2003 (47)	250/143	CC	Chile	Q	Medical diagnosis	8	School volunteers
Rami, 1999 (48)	609/114	CC	Austria	Q	Medical diagnosis	<15	Austrian diabetes register
Rosenbauer, 2008 (49)	2631/760	CC	Germany	Q/I	Medical diagnosis	<5	Hospital based surveillance system ESPD and local registration office records
Sadauskaite-Kuehne, 2004 (50)	1944/803	CC	Sweden/Lithuania	Q	Medical diagnosis	7	Population register and outpatients
Samuelsson, 1993 (51)	1089/297	CC	Sweden	Q/R	Medical diagnosis	<15	Paediatric department and population register
Siemiatycki, 1989 (52)	482/161	CC	Canada	I	Medical diagnosis	<17	Hospital admission
Sipetic, 2005 (53)	315/105	CC	Serbia	I	Medical diagnosis	<16	Hospital admission
Skrodeniene, 2010 (54)	1099/286	CC	Lithuania	Q	Medical diagnosis	9	Population register and outpatients
Soltesz, 1994 (55)	305/130	CC	Hungary	Q	Medical diagnosis	<14	Incidence register
Strotmeyer, 2004 (56)	485/247	CC	China	Q	Medical diagnosis	10	Diabetes register and population register

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Tai, 1998 (57)	310/117	CC	Taiwan	I	Medical diagnosis	8	Taipei City
Telahun, 1994 (58)	129/55	CC	Ethiopia	Q	Medical diagnosis	<15	Ethio-Swedish Children's Hospital Diabetic Clinic
Tenconi, 2007 (59)	477/159	CC	Italy	R/I/Q	Medical diagnosis	16	Diabetes register or paediatric admissions
Thorsdottir, 2000 (60)	220/55	CC	Iceland	I	Medical diagnosis	12	Statistical Bureau of Iceland
Verge, 1994 (61)	475/217	CC	Australia	Q	Medical diagnosis	<15	New South Wales diabetes register and school records
Virtanen, 1992 (74) (46) (46)	852/426	CC	Finland	Q	Medical diagnosis	<14	Hospital admissions
Virtanen, 1993 (62)	1380/690	CC	Finland	Q	Medical diagnosis	14	Finnish National Population Registry
Visalli, 2003 (63)	900/150	CC	Italy	Q	Medical diagnosis	6-18	EURODIAB study register and school records
Wadsworth, 1997 (64)	639/276	CC	UK	Q	Medical diagnosis	<5	BPASU reporting system and District Health Authority Immunisation Register

Q: questionnaire, I: interview, R: medical records, PC: prospective cohort, NCC: nested case control, CS: Cross-sectional, CC: case control

Figure 1 Risk of bias in observational studies of total breastfeeding duration and TIDM



1.2. Outcomes from studies of total breastfeeding and TIDM

1.2.1. Ever vs. never breastfed

Figure 2 shows the combined effect of 32 eligible observational studies including over 6000 people with TIDM investigating the risk of TIDM according to whether infants were breastfed for any duration or never breastfed. Overall, there was a 22% (OR 0.78; 95% confidence interval [CI] 0.68, 0.89) reduction in the risk of having TIDM in infants who were ever breastfed, with high heterogeneity across studies (I^2=51.2%). Subgroup analyses are shown in Table 2. Adjusted and unadjusted analyses yielded similar findings, with high heterogeneity in each. In the small number of studies with prospective design (total 313 cases), in those which used TIDM associated antibodies rather than disease as an outcome (and recruited high risk populations; total 116 cases) and in studies with low risk of bias (total 86 cases), there was no evidence of an association between BF and TIDM. Risk of bias was commonly considered unclear, due to lack of information about blinding of outcome assessors to exposure data. We found no evidence of publication bias (Egger's test P-value=0.81) (Figure 3).

Figure 2 Breastfeeding ever vs. never and TIDM risk

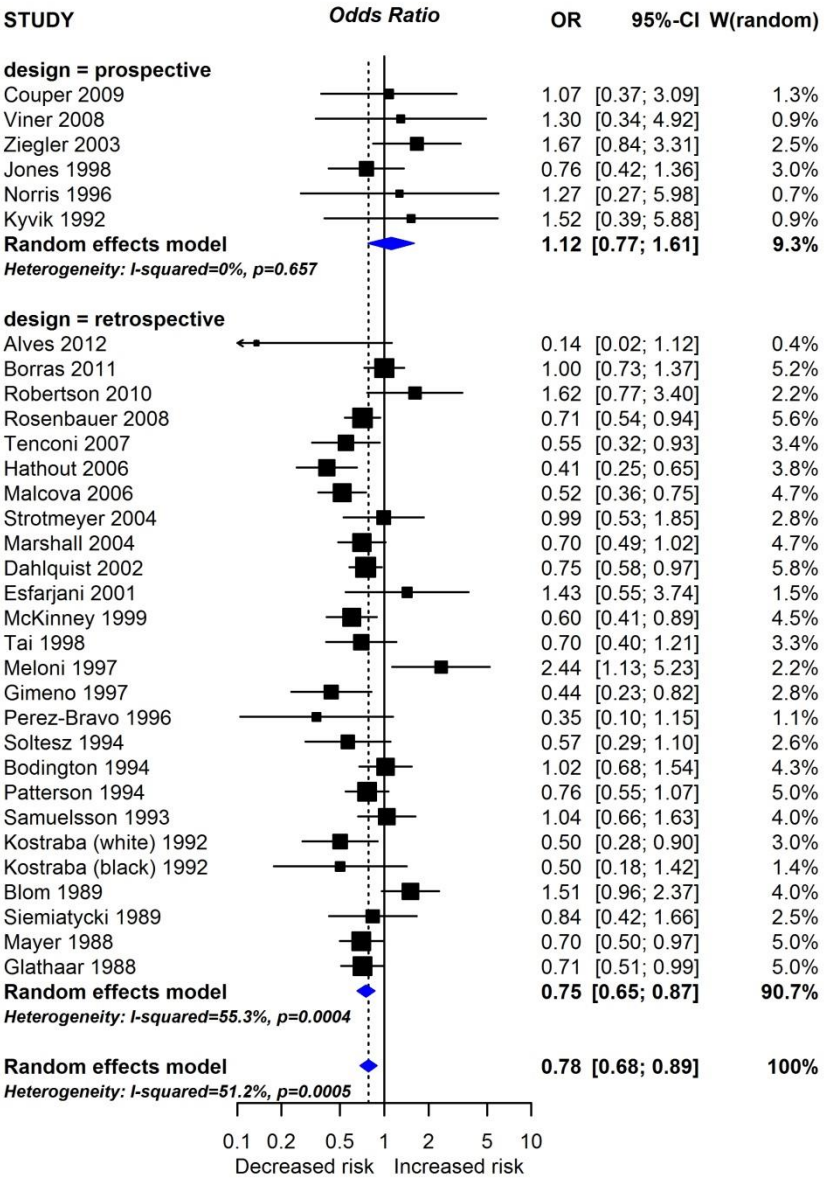
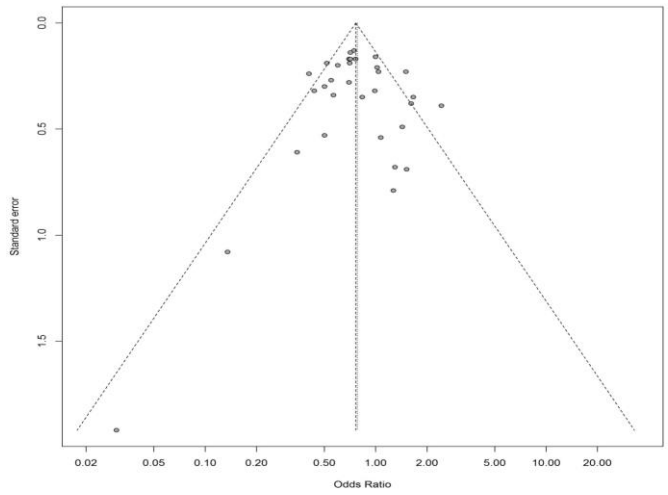


Table 2 Stratified and subgroup analyses of association between ever vs. never being breastfed and risk of TIDM

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	32	0.78 [0.68-0.89]	51.2	
Adjusted	15	0.76 [0.64-0.91]	51.8	Not tested
Unadjusted	29	0.81 [0.70-0.94]	54.0	
Risk of disease – High	3	1.44 [0.84-2.47]	0	**0.025**
Risk of disease – Normal	29	0.76 [0.67-0.87]	51.4	
Risk of bias – Low	2	1.59 [0.85-2.98]	0	**0.025**
Risk of bias – High/Unclear	30	0.76 [0.66-0.87]	50.1	
Study Design – Prospective	6	1.15 [0.77-1.61]	0	**0.049**
Study Design - Retrospective	26	0.75 [0.65-0.87]	55.3	
Method of diagnosis – clinical	29	0.76 [0.66-0.87]	51.4	**0.025**
Method of diagnosis – serological (single or combination of antibodies)	3	1.44 [0.84-2.47]	0	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

Figure 3 Risk of publication bias in observational studies investigating breastfed ever vs. never and TIDM risk

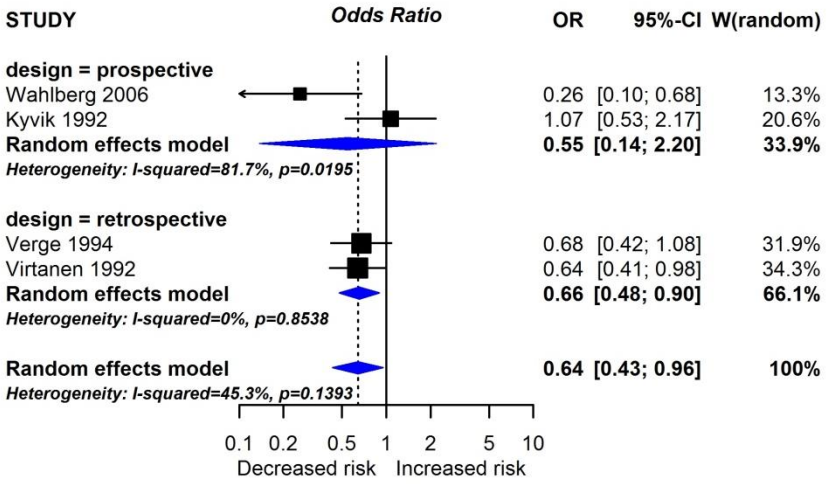


Egger's test p=0.81

1.2.2. Total breastfeeding ≥1-2 months vs. < 1-2 months

Four studies examined the risk of TIDM if infants were breastfed for over 1-2 months compared to less than this duration. Figure 4 shows that the combined risk of TIDM is 36% lower (Pooled OR 0.64; 95% CI 0.43, 0.96) if infants were breastfed for at least 1-2 months. There was moderate heterogeneity across studies (I^2=45.3%). Stratified and subgroup analyses was not performed due to the small number of studies included. The study of Kyvik presented unadjusted data from a nested case control study, considered at high risk of bias, comparing ≥5 months with 0-1 months TBF; Virtanen and Verge presented adjusted data from case control studies; Wahlberg unadjusted data from a prospective cohort study using autoantibodies as an outcome. The reason for the statistical heterogeneity is not clear, but may relate to use of autoantibodies at age 2 as an outcome in Wahlberg, and presentation of unadjusted data in Kyvik.

Figure 4 Breastfeeding for ≥1-2 months vs. < 1-2 months and TIDM risk



1.2.3. Total breastfeeding duration ≥3-4 months vs. <3-4 months

The association between breastfeeding for at least 3-4 months vs. less than this duration and risk of TIDM was examined in 10 studies. Meta-analysis showed reduced risk of TIDM (OR 0.55; 95% CI 0.39, 0.77) (Figure 5) although there was high heterogeneity across studies (I^2=61.2%). There was little evidence of different outcomes in subgroup or stratified analyses, other than a greater reduction in risk in individuals with high disease risk versus low/normal risk (Table 3). Ziegler, Fronczak and Couper presented HR from prospective studies using autoantibodies for TIDM diagnosis in young children. Holmberg also used autoantibodies in young children in a prospective study. In general heterogeneity was reduced in retrospective studies using clinical diagnosis of TIDM.

Figure 5 Breastfeeding for ≥3-4 months vs. <3-4 months and TIDM risk

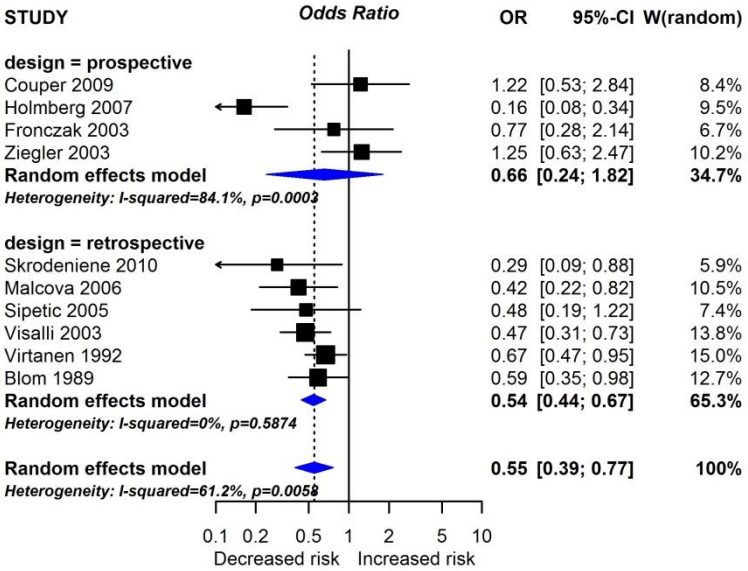
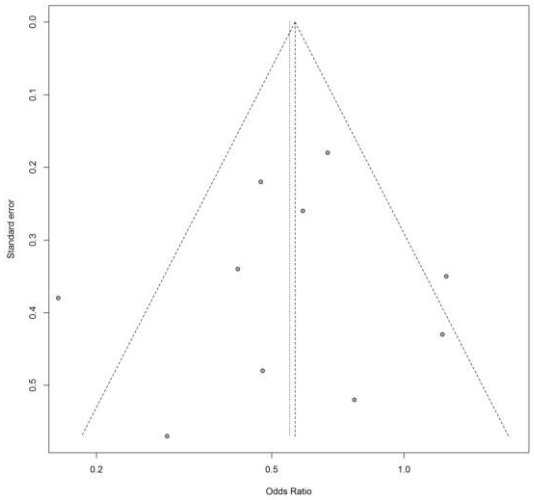


Table 3 Stratified and subgroup analyses of breastfeeding ≥3-4 months vs. <3-4 months and TIDM risk

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	10	0.55 [0.39-0.77]	61.2	
Adjusted	5	0.58 [0.40-0.85]	53.8	Not tested
Unadjusted	7	0.63 [0.38-1.04]	74.5	
Risk of disease – High	3	1.12 [0.70-1.79]	0	**0.002**
Risk of disease – Normal	7	0.45 [0.32-0.62]	53.6	
Risk of bias – Low	2	0.85 [0.47-1.53]	59.7	0.099
Risk of bias – High/Unclear	8	0.47 [0.32-0.69]	53.7	
Study Design – Prospective	4	0.66 [0.24-1.82]	84.1	0.719
Study Design - Retrospective	6	0.54 [0.44-0.67]	0	
Method of diagnosis – clinical	6	0.54 [0.44-0.67]	0	0.719
Method of diagnosis – serological (single or combination of antibodies)	4	0.66 [0.24-1.82]	84.1	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

Figure 6 Risk of publication bias in observational studies investigating TBF ≥3-4 months vs. <3-4 months and TIDM risk



Egger's test P=0.72

1.2.4. Total duration of breastfeeding ≥5-7 months vs. < 5-7 months

Six studies contributed data to meta-analysis of TBF ≥5-7 vs. <5-7 months and TIDM risk (Figure 7). There was reduced risk associated with prolonged TBF (OR 0.59; 95% CI 0.37, 0.92) but there was extreme heterogeneity across studies (I^2=76.6%). Table 4 shows subgroup and stratified analyses. There was reduced statistical heterogeneity in analysis of adjusted data. Studies of retrospective design and those with an unclear definition of breastfeeding showed a greater level of risk reduction for TIDM than prospective studies or those with clear TBF definition. Data from Majeed included in meta-analysis were unadjusted, and adjusted analysis in the same study was not statistically significant. Sensitivity analysis excluding the study by Majeed reduced heterogeneity (I^2=54.2%, OR 0.72, 95% CI 0.53, 0.98).

Figure 7 Breastfeeding for ≥5-7 months vs. <5-7 months and TIDM risk

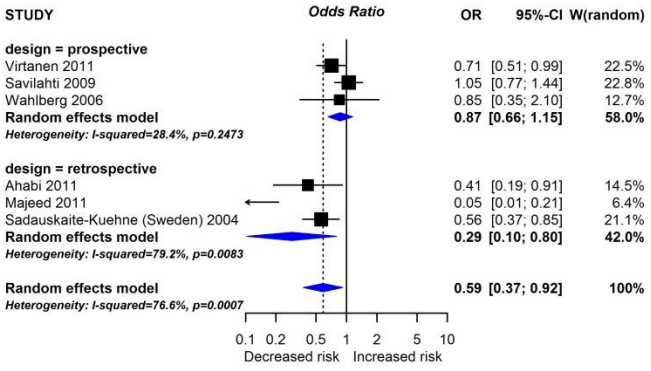


Table 4 Stratified and subgroup analyses of breastfeeding ≥5-7 months vs. <5-7 months and TIDM risk

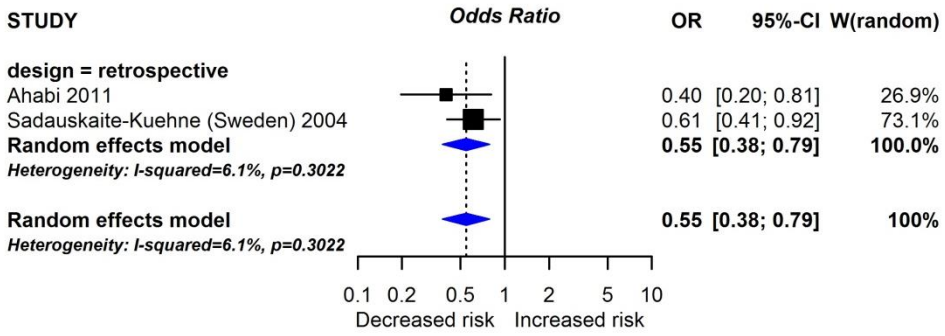
	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted value used)	6	0.59 [0.37-0.92]	76.6	
Adjusted	2	0.65 [0.50-0.84]	0	Not tested
Unadjusted	5	0.61 [0.35-1.06]	78.8	
Risk of disease – High	1	0.71[0.51-0.99]	-	0.377
Risk of disease – Normal	5	0.51 [0.27-0.97]	81.2	
Risk of bias – Low	1	0.71 [0.51-0.99]	-	0.377
Risk of bias – High/Unclear	5	0.51 [0.27-0.97]	81.2	
Study Design – Prospective	3	0.87 [0.66-1.15]	28.4	**0.042**
Study Design - Retrospective	3	0.29 [0.10-0.80]	79.2	
Method of diagnosis – clinical	4	0.45 [0.21-0.96]	85.9	0.244
Method of diagnosis – serological (single or combination of antibodies)	2	0.73 [0.53-0.99]	0	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

1.2.5. Total duration of breastfeeding ≥8-12 months vs. <8-12 months

Total breastfeeding duration for ≥8-12 months showed an overall reduced risk of TIDM compared to shorter TBF duration – 2 studies, pooled OR 0.55 (95% CI 0.38, 0.79) with no significant heterogeneity (I^2=6.1%) (Figure 8). Both studies are case control studies using medical diagnosis of TIDM, one reporting adjusted and one (Ahabi) unadjusted data.

Figure 8 Breastfeeding for ≥8-12 months vs. <8-12 months and TIDM risk



1.2.6. Dose response analysis of TBF and TIDM risk

We also analysed TBF duration by grouping studies according to the exposure rather than the reference group – short (≥1-3 months), medium (≥4-6 months) and long (≥7-12 months); all compared to a reference group of never BF. These analyses are shown in Figures 9, 10 and 11. The data showed no significant difference between any time frame analysed versus never. There was low heterogeneity in the short and medium versus never analyses (I^2=0 and I^2=11.7% respectively). There was extreme heterogeneity in the long versus never breastfeeding meta-analysis (I^2=84.3%) so pooled analysis was not reported; the reason for this heterogeneity is unclear. Sensitivity analysis excluding the study by Meloni reduced heterogeneity (I^2=33.7%, OR 0.40, 95% CI 0.19, 0.84), although there appeared to be no major difference in method between studies to explain the difference in results. All 3 studies reported adjusted data from case control studies using clinical diagnosis of TIDM.

We were unable to identify a clear explanation for why dose response analysis did not mirror the positive association seen in analyses using reference groups to define the cut off. Four individual studies were included in more than one dose response analysis - they did not show a clear trend, but in general there tended to be a stronger association between TBF and reduced TIDM for longer TBF exposure (11, 42, 49, 57).

Figure 9 Breastfeeding for short duration versus never

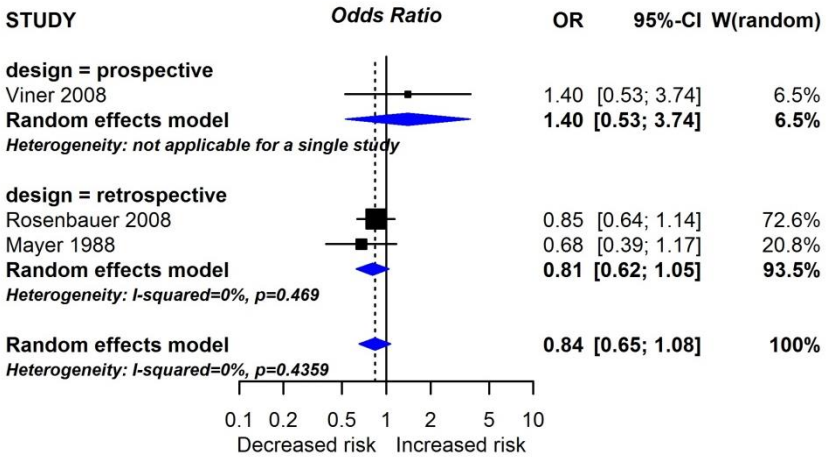


Figure 10 Breastfeeding for medium duration versus never

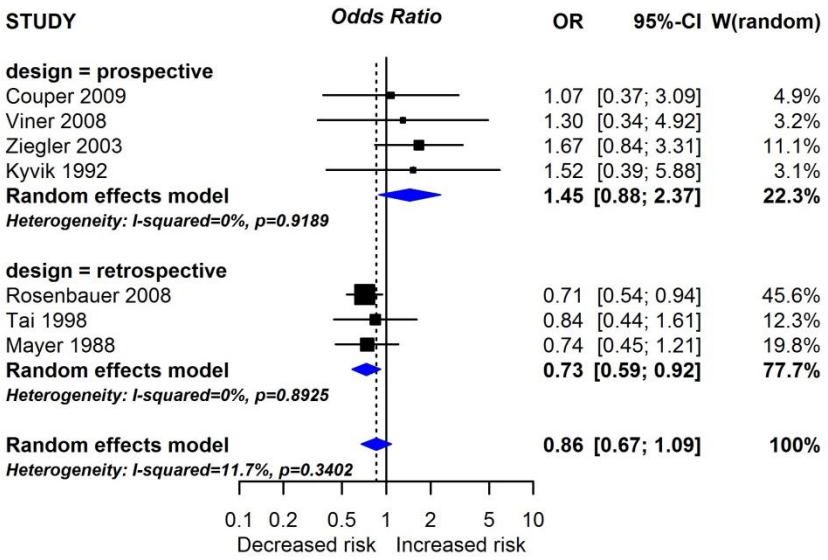
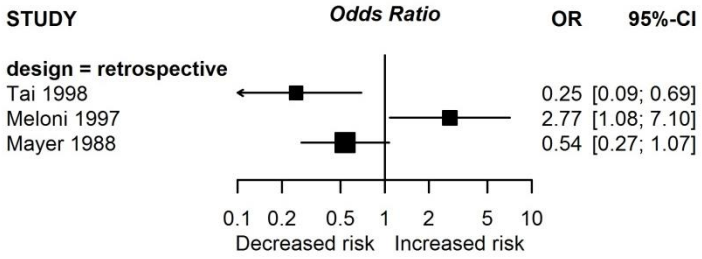


Figure 11 Breastfeeding for long duration versus never



1.2.7. Studies investigating TBF and TIDM as a continuous variable

Three studies reported OR of TIDM for each month increase in TBF duration. Meta-analysis of these data showed no significant association (pooled OR 1.01; 95 CI% 0.87, 1.18) but with extreme statistical heterogeneity (I^2=76.8%; Figure 12). Three additional studies comparing the mean duration of TBF between TIDM and unaffected subjects were meta-analysed (Figure 13). Data could not be pooled to extreme statistical heterogeneity (I^2=91.8%) which was present even when the study of Baruah (27) was excluded (I^2=92.8%). This extreme heterogeneity may be related to the non-Gaussian distribution of TBF duration in the population.

Figure 12 Risk of TIDM for each month increase in TBF duration

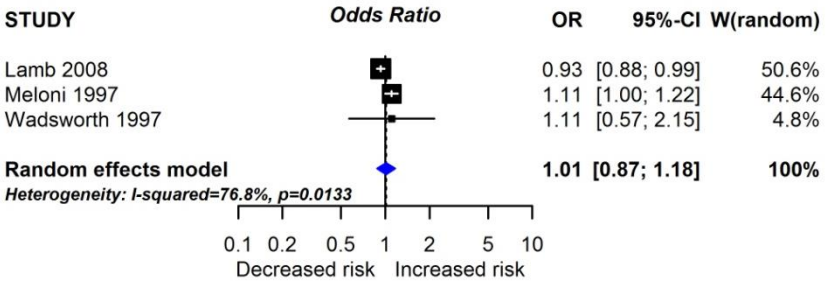
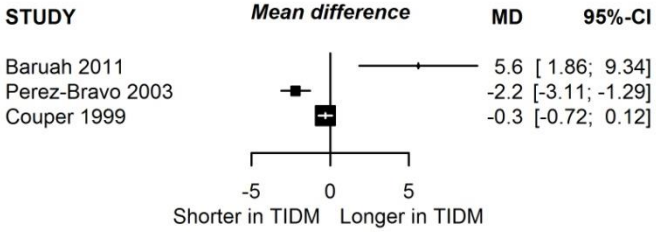


Figure 13 Difference in TBF in people with TIDM versus unaffected subjects



1.2.8 Data for TBF and TIDM which couldn't be meta-analysed

Meta-analyses included 7 cohort, 4 nested case control, 1 cross sectional and 29 case control studies in total, including at least 8221 participants with TIDM. A further 7 cohort, 3 nested case control and 14 case control studies reported relevant data which could not be included in meta-analysis, in relation to at least 3909 participants with TIDM. These studies are summarised in Table 5. Two of the case control studies (Ashraf (26), Perez-Bravo (47)) showed a significantly shorter TBF duration in TIDM compared to unaffected subjects. The other 22 studies showed no significant relationship, although TBF duration was shorter in people with TIDM in 9 of these 22 studies, longer in 4 and similar or unclear in 9. The study of Lamb 2008 (7) also reported adjusted HR 0.93 (95%CI 0.86, 0.99) for each additional month of breastfeeding.

Table 5 Other studies evaluating total breastfeeding and TIDM which couldn't be meta-analysed

First Author and Year of Publication	Design	N/n cases	Total BF duration	Units	Descriptive measure	Unaffected	TIDM	P value
Baruah, 2011 (27)	CC	86/43	continuous	Months	Mean	13	18.6	-
Kostraba, 1993 (38)	CC	306/142	continuous	Months	Mean	6.95	6.2	-
Marshall, 2004 (41)	CC	577/196	continuous	Months	Mean	4.6	3.9	-
Norris, 2003 (10)	PC	1183/~733	continuous	Months	Mean	6.1	5.9	-
Perez-Bravo, 2003 (47)	CC	250/143	continuous	Months	Mean	7.6	5.4	**<0.02**
Virtanen, 1993 (62)	CC	1380/690	continuous	Months	Mean	6.6	6.6	NS
Ashraf, 2010 (26)	CC	195/128	continuous	Months	Median(range)	3 (0-4)	1 (0-4)	**0.001**
Hummel, 2000 (mother with TIDM) (5)	PC	568	continuous	Months	Median	3	4	NS
Hummel, 2000 (father with TIDM)			continuous	Months	Median	4	2.50	0.41
Kimpimaki, 2001 (17)	NCC	455/65	continuous	Months	Median (IQR)	6.5 (3-10)	6.0 (2.9-10.5)	-
Norris, 1996 (19)	NCC	171/18	continuous	Months	Median (IQR)	8	10	-
Rami, 1999 (48)	CC	609/114	continuous	Months	Median (range)	2 (0-72)	2 (0-24)	0.54
Hypponen, 1999 (36)	CC	821/435	continuous	Months	Average			NS
Lamb, 2013 (8)	NCC	260	continuous	Months	Average			NS
Ludvigsson, 2003 (9)	PC	205	continuous	Months	Average			NS

Telahun, 1994 (58)	CC	129/55	continuous	Months	Average			NS
Lamb, 2008 (7)	PC	642	continuous	Months	aHR(95%CI)	0.93 (0.86, 0.99) per month TBF		-
Virtanen, 1998 (12)	PC	697/~43	categorical	>2 vs <2 months	aHR (95%CI)	0.53 (0.2-1.6)		-
Karlen, 2012 (6)	PC	1409	categorical	>7 vs 0-6 months	uOR (95% CI)	0.83 (0.52-1.32)		-
Wadsworth, 1997 (64)	CC	639/276	categorical	>2 vs <2 weeks	aOR (95% CI)	1.1 (0.56-2.16)		0.7
Bener, 2009 (28)	CC	340/170	categorical	Breastfed (yes)	%	97.2	95.1	-
Couper, 1999 (1)	PC	317/70	categorical	Breastfed (yes)	%	75	61	-
			continuous	Months	Mean	6.1	5.3	NS
Sadauskaite-Kuehne, 2004 (Lithuania) (50)	CC	813/286	categorical	Breastfed (yes)	%	91.6	95	NS
Strotmeyer, 2004 (56)	CC	485/247	categorical	Breastfed (yes)	%	91.1	91.0	-
Thorsdottir, 2000 (60)	CC	220/55	categorical	Breastfed (yes)	%			0.10

2. Exclusive breastfeeding duration and risk of TIDM

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

Table 6 describes the main characteristics of the studies analysed in this report. A total of 28 observational studies, and no intervention studies, reported the association between duration of exclusive breastfeeding (EBF) and risk of TIDM. Of these, 8 were prospective cohort studies, 2 nested case-control, and 18 case-control studies. Over half of the studies (n=16) are from Europe – others are from North America (n=4), South America (n=2), Asia/Pacific (n=4), and the Middle East (n=2). Overall, valid data on EBF duration and TIDM risk were available from almost 35,000 subjects and over 5300 people with TIDM. Information on TIDM was obtained mainly from Islet auto-antibodies in 8 prospective studies and via medical diagnosis in 20 (mainly case control) studies. With regards to time of outcome diagnosis, 6 studies explored the association between duration of EBF and TIDM in the first 5 years of life and 22 studies evaluated the outcome in older children or adolescents. 26 studies used interview or questionnaire to assess EBF duration, 1 study assessed medical records and 1 did not report the method of exposure assessment.

Risk of bias was assessed using the NICE Methodological checklist for cohort and case-control studies. Figure 14 illustrates the distribution of bias across the five main methodological areas of the studies. Over half of the studies had a high risk, most commonly due to lack of adjustment for confounding bias i.e., no adjusted data presented. A third of the studies had an 'unclear' overall risk of bias, most commonly due to insufficient information to assess selection and assessment bias.

Three levels of comparison were used to meta-analyse binary data for TIDM risk and EBF duration, based on the distribution of data reported in included studies: EBF duration with a cut-off in the first 2 months ('≥0-2 months vs. <0-2 months'); EBF duration '≥3-4 months vs. <3-4 months'; EBF duration '≥5-9 months vs. <5-9 months'.

Main Findings

Across all three EBF duration cut-offs there was some evidence of reduced TIDM risk with increased EBF duration. Stratified and subgroup analyses by specific risk groups and study

characteristics showed little evidence of difference. Adjusted and unadjusted analyses gave similar findings. The evidence for an association between EBF and TIDM from the 14 studies (1588 TIDM cases) which could not be included in meta-analysis was weaker as only three studies showed statistically significant associations between increased EBF duration and reduced TIDM risk and the others were inconclusive. All but one study used mean or median to present results which prevented the use of the data in the meta-analysis, and one study used a definition of breastfeeding duration that was not possible to combine with the other studies (Table 9). Overall the data suggest there is LOW certainty evidence that longer duration of EBF is associated with reduced TIDM risk, with relatively low statistical heterogeneity within individual meta-analyses, and reasonable consistency between meta-analyses.

Table 6 Characteristics of Included Studies for analysis of Exclusive Breast Feeding duration and TIDM Risk

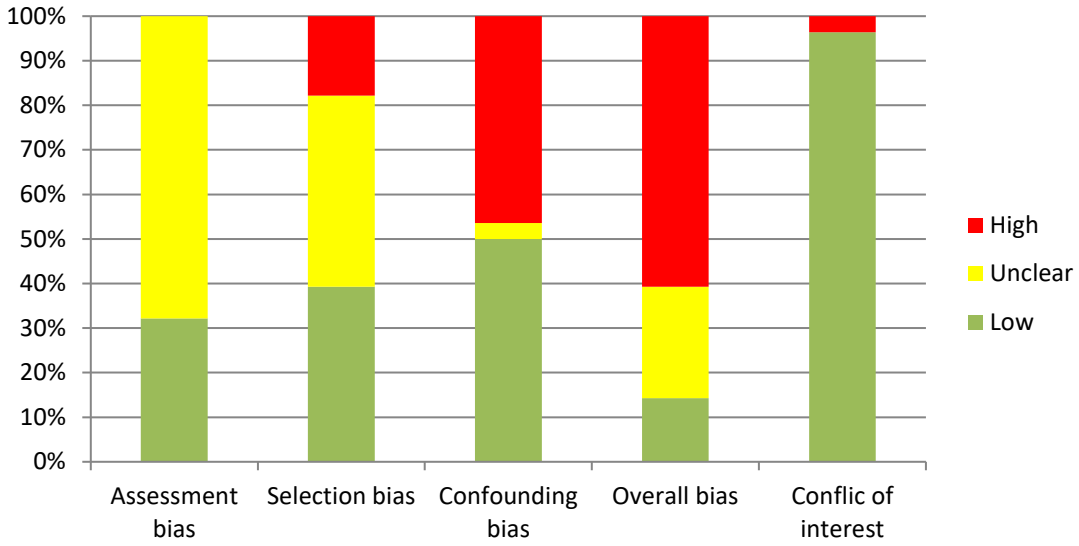
First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Couper, 1999 (1)	317/70	PC	Australia	D/Q	Islet autoantibodies	2	First degree relatives of diabetic children
Couper, 2009 (65)	548/~30	PC	Australia	D/I	Islet autoantibodies	2	First degree relatives of diabetic children
Frederikson, 2012 (abstract) (66)	1698	PC	USA	-	Medical diagnosis	<7	High risk children via HLA screening
Holmberg, 2007 (67)	3788/~51	PC	Sweden	Q	Islet autoantibodies	6	General population
Hummel, 2000 (5)	568	PC	Germany	Q	Islet autoantibodies	2	Offspring of diabetic parents
Virtanen, 2011 (13)	~4000/~160	PC	Finland	Q	Medical diagnosis or islet autoantibodies	<18	Odu and Tampere University Hospitals
Wahlberg, 2006 (15)	8715/31	PC	Sweden	Q	Islet autoantibodies	2	General population
Ziegler, 2003 (14)	1460/~68	PC	Germany	Q	Islet autoantibodies	5	Children of a mother/father withT1DM
Kimpimaki, 2001 (17)	455/65	NCC	Finland	I	Islet autoantibodies	<4	Turku, Oulu and Tampere Hospital births
Lamb, 2013 (8)	260	NCC	USA	I	Islet autoantibodies	<7	High risk children via HLA screening

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Alves, 2012 (25)	246/123	CC	Brazil	I	Medical diagnosis	7	Endocrine clinic attendance
Baruah, 2011 (27)	86/43	CC	India	I	Medical diagnosis	<18	Endocrinology ward
Esfarjani, 2001 (32)	104/52	CC	Iran	Q	Medical diagnosis	<14	Endocrine clinic attendance
Gimeno, 1997 (45)	626/313	CC	Brazil	Q	Medical diagnosis	<18	Juvenile Diabetes Association or hospital records
Kostraba, 1992 (38)	264/132-white 108/54-Black	CC	USA	Q/I	Medical diagnosis	10	Alleghany Hospital diabetes register
Liese, 2012 (68)	709/505	CC	USA	I	Medical diagnosis	<20	SEARCH surveillance (Colorado and South Carolina research centres)
Patterson, 1994 (34)	1548/258	CC	UK	R	Medical diagnosis	<16	Diabetes register, hospital discharge, Health Service records
Rabiei 2011 (69)	300/100	CC	Iran	Q	Medical diagnosis	11	Diabetes register
Rami, 1999 (48)	609/114	CC	Austria	Q	Medical diagnosis	<15	Austrian diabetes register
Sadauskaite-Kuehne, 2004 (50)	1944/803	CC	Sweden/Lithuania	Q	Medical diagnosis	7	Hospital admissions
Samuelsson, 1993 (51)	1026/297	CC	Sweden	R/Q	Medical diagnosis	<17	Paediatric department
Soltesz, 1994 (55)	305/130	CC	Hungary	Q	Medical diagnosis	<14	Incidence register

First Author & Publication Year	N/n cases	Design	Country	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Stene, 2000 (70)	1156/85	CC	Norway	Q	Medical diagnosis	<15	National Childhood Diabetes register
Stene, 2003 (71)	2213/545	CC	Norway	Q	Medical diagnosis	9	Diabetes register
Thorsdottir, 2000 (60)	220/55	CC	Iceland	I	Medical diagnosis	12	General population
Verge, 1994 (61)	475/217	CC	Australia	Q	Medical diagnosis	9	New South Wales diabetes register
Virtanen, 1992 (74)	852/426	CC	Finland	Q	Medical diagnosis	<14	Hospital admissions
Virtanen, 1993 (62)	1380/690	CC	Finland	Q	Medical diagnosis	<14	Finnish National Population Registry

PC = prospective cohort, NCC = nested case control, CC = case control, D = diary, I = interview, Q = questionnaire, R = medical records

Figure 14 Risk of bias in observational studies of exclusive breastfeeding and TIDM



1.3. Outcomes from studies of exclusive breastfeeding and TIDM

2.2.1 Exclusive breastfeeding for ≥0-2 months vs. <0-2 months

Nine studies reported the association between EBF for a duration of at least 0-2 months, compared to less than this (17, 34, 45, 50, 62). Meta-analysis showed significantly reduced TIDM risk with longer EBF duration (OR 0.74; 95% CI 0.63, 0.88) with low statistical heterogeneity (I^2=10.2%; Figure 15). There was no evidence of differences in strength of association in the stratified or subgroup analyses (Table 7). Adjusted analyses and unadjusted analyses showed similar findings, but heterogeneity was lower in the retrospective case control studies reporting clinical TIDM as an outcome, than in the prospective studies reporting autoantibodies as an outcome.

Figure 15 Exclusive breastfeeding for ≥0-2 months vs. < 0-2 months and TIDM risk

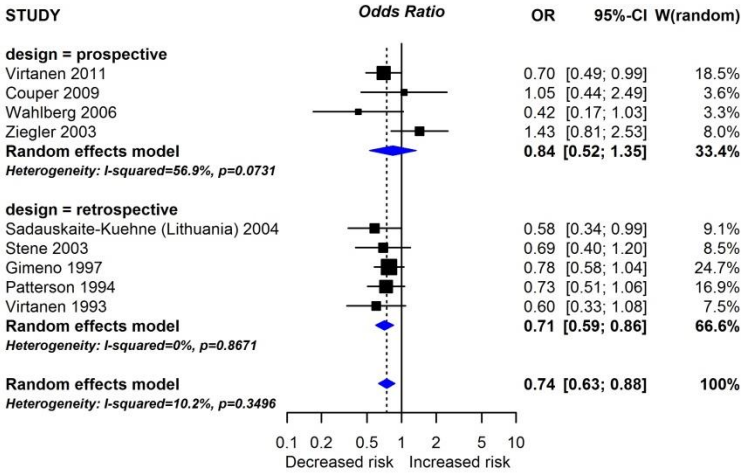


Table 7 Stratified and subgroup analyses of EBF duration ≥0-2 months vs. <0-2 months and TIDM risk

	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	9	0.74 [0.63-0.88]	10.2	
Adjusted	6	0.76 [0.63-0.92]	18.8	Not tested
Unadjusted	7	0.77 [0.59-1.00]	45.8	
Risk of disease – High	3	0.97 [0.59-1.59]	57	0.221
Risk of disease – Normal/Low	6	0.70 [0.58-0.84]	0	
Overall risk of bias – Low	2	0.96 [0.48-1.95]	77.5	0.402
Overall risk of bias – High/Unclear	7	0.71 [0.59-0.84]	0	
Study Design – Prospective	4	0.84 [0.52-1.35]	56.9	0.519
Study Design – Retrospective	5	0.71 [0.59-0.86]	0	
Method of diagnosis – clinical	5	0.71 [0.59-0.86]	0	0.519
Method of diagnosis – serological	4	0.84 [0.52-1.35]	56.9	
Clear definition of exclusive breastfeeding	4	0.78 [0.54-1.13]	55.3	0.703
Unclear definition of exclusive breastfeeding	5	0.72 [0.59-0.89]	0	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

2.2.2 Exclusive breastfeeding for ≥3-4 months vs < 3-4 months

Nine studies reported data which could be meta-analysed, for risk of TIDM in relation to EBF for more or less than 3-4 months (Figure 16). Pooled data showed significantly reduced risk of TIDM with longer EBF duration (OR 0.68; 95% CI 0.55, 0.83), with moderate statistical heterogeneity (I^2 =28.6%). There was no evidence of differences in strength of association in the stratified or subgroup analyses (Table 8). Adjusted analyses and unadjusted analyses showed similar findings.

Figure 16 Exclusive BF for ≥ 3-4 months vs. < 3-4 months and TIDM risk

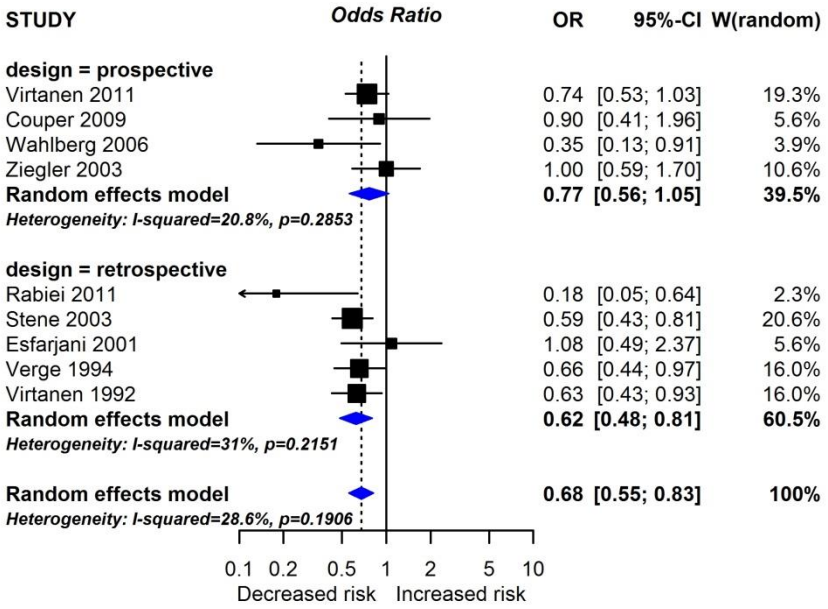


Table 8 Stratified and subgroup analyses of EBF duration ≥3-4 months vs. <3-4 months and TIDM risk

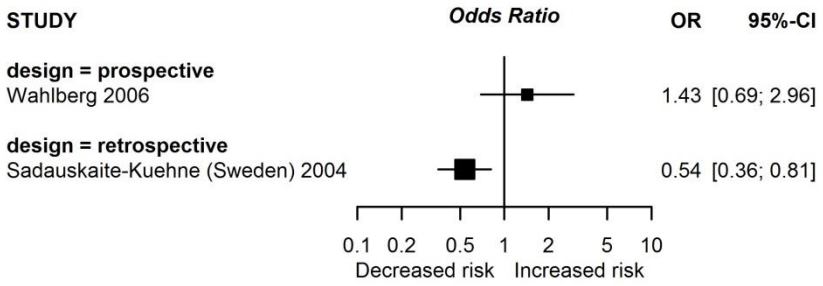
	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	9	0.68 [0.55-0.83]	28.6	
Adjusted	6	0.66 [0.54-0.82]	32.6	Not tested
Unadjusted	8	0.71 [0.60-0.84]	14.8	
Risk of disease – High	3	0.82 [0.63-1.06]	0	0.104
Risk of disease – Normal/Low	6	0.60 [0.47-0.78]	30.2	
Risk of bias – Low	3	0.74 [0.59-0.93]	0	0.348
Risk of bias – High/Unclear	6	0.62 [0.45-0.85]	37.8	
Study Design – Prospective	4	0.77 [0.56-1.05]	20.8	0.326
Study Design - Retrospective	5	0.62 [0.48-0.81]	31.0	
Method of diagnosis – clinical	5	0.62 [0.48-0.81]	31.0	0.326
Method of diagnosis – serological	4	0.77 [0.56-1.05]	20.8	
Clear definition of exclusive breastfeeding	4	0.71 [0.54-0.93]	27.9	0.705
Unclear definition of exclusive breastfeeding	5	0.65 [0.47-0.90]	39.1	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios

2.2.3 Exclusive breastfeeding for ≥5-9 months vs. <5-9 months

Two studies reported the association between risk of TIDM and exposure to exclusive breastfeeding for ≥5-9 months. There was extreme statistical heterogeneity between studies (I^2=81.2%). The study of Wahlberg reported unadjusted OR for diabetes associated antibodies in preschool children. The study of Sadauskaite-Kuehne reported adjusted OR for clinical TIDM in 7 year old children in a case-control study. These differences in study design and outcome assessment may explain the extreme heterogeneity. One study suggested a protective effect, and one study suggested no evidence of protection (Figure 17).

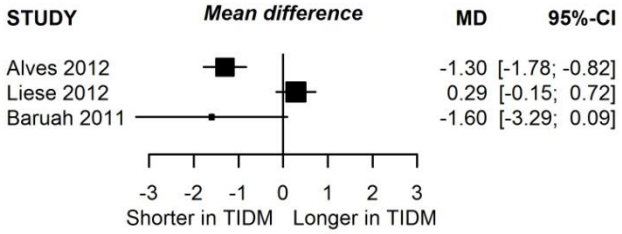
Figure 17 Exclusive breastfeeding for ≥5-9 months vs. < 5-9 months and TIDM risk



2.2.4 Studies investigating EBF as a continuous variable and risk of TIDM

Three studies reported the unadjusted relationship between EBF duration and TIDM risk, comparing the mean duration of EBF in TIDM versus unaffected subjects. There was extreme statistical heterogeneity (I^2=92%) attributable to the study of Liese, so data were not pooled (Figure 18). There was also heterogeneity *within* the study of Liese, with shorter duration of EBF in controls than TIDM in South Carolina, but longer EBF in controls in Colorado. It is not clear that EBF is normally distributed in general, so one reason for the extreme heterogeneity may be inappropriate analysis of EBF duration as arithmetic mean (sd) in these studies.

Figure 18 Difference in EBF in people with T1DM versus unaffected subjects



2.2.5 Other studies evaluating EBF and TIDM which couldn't be meta-analysed

Meta-analyses included 4 cohort and 9 case control studies in total, including at least 3733 participants with TIDM. A further 4 cohort, 2 nested case control and 8 case control studies reported relevant data which could not be included in meta-analysis, in relation to at least 1588 participants with TIDM. All but one study used mean or median to present results which prevented the use of the data in the meta-analysis, and one study used a definition of breastfeeding duration that was not possible to combine with the other studies (Table 9). Two of the case control studies (Alves (25), Baruah (27)) and one prospective cohort study (Holmberg (67)) showed a significantly shorter EBF duration in TIDM compared to unaffected subjects. The other 11 studies showed no significant relationship, although EBF duration was shorter in people with TIDM in 2 of these 11 studies, longer in 2 and similar or unclear in 7.

Table 9 Other studies evaluating exclusive breastfeeding and TIDM which couldn't be meta-analysed

First Author and Year of Publication	Design	N/n cases	Exclusive BF duration	Units	Descriptive measure	Unaffected	TIDM	P value
Alves, 2009 (25)	CC	246/123	Continuous	Months	Mean (SD)	4.6	3.3	**<0.001**
Baruah, 2011 (27)	CC	86/43	Continuous	Months	Mean (SD)	6.6	5	**<0.05**
Couper, 1999 (1)	PC	317/70	Continuous	Months	Mean (SD)	4.5	3.4	NS
Liese, 2012 (68)	CC	709/505	Continuous	Months	Mean (SD)	2.40	2.69	0.23
Samuelsson, 1993 (51) (<5y)	CC	1089/297	continuous	Months	Mean (SE)	3.0 (0.5)	4.5 (0.7)	0.17
Samuelsson, 1993 (51) (5-9y)			continuous	Months	Mean (SE)	3.6 (0.3)	3.2 (0.3)	0.34
Samuelsson, 1993 (51) (>10y)			continuous	Months	Mean (SE)	2.4 (0.1)	2.2 (0.2)	0.31
Hummel, 2000 (mother with TIDM) (4)	PC	568	continuous	Months	Median	1	2	NS
Hummel, 2000 (father with TIDM) (4)			continuous	Months	Median	3	1	0.31
Kimpimaki, 2001 (17)	NCC	455/65	continuous	Months	Median (IQR)	1.8 (0.5-3.9)	2 (1-4)	-
Rami, 1999 (48)	CC	609/114	continuous	Months	Median (range)	2 (0-18)	2 (0-7)	-
Soltesz, 1994 (55)	CC	305/130	continuous	Months	Median	2.5	2	NS
Frederikson, 2012 (66)	PC	548	continuous	Months	Average			NS

First Author and Year of Publication	Design	N/n cases	Exclusive BF duration	Units	Descriptive measure	Unaffected	TIDM	P value
Kostraba, 1992 (white) (38)	CC	302/132	continuous	Months	Average	3.3	4.5	0.40
Kostraba, 1992 (black)		106/54	continuous	Months	Average	6.8	3.3	0.16
Lamb, 2013 (8)	NCC	260	continuous	Months	Average			NS
Thorsdottir, 2000 (60)	CC	220/55	continuous	Months	Average			NS
Holmberg, 2007 (67)	PC	3788	categorical	>4 vs 1-3 months	aOR (95% CI)	0.50 (0.27-0.93)		**0.028**

3 Age at introduction of solid food and risk of TIDM

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

General characteristics of included studies are summarised in Table 10. No intervention trials were identified. Data were available from a total of 17 studies with over 4000 people with TIDM. There were 2 prospective cohort studies, 1 nested case-control studies, and 14 case-control studies evaluating timing of solid food introduction and TIDM risk. The studies were European (n=8), North American (n=3), Asia-Pacific (n=1), South American (n=2) and Middle Eastern (n=3). This analysis addresses the first introduction of non-milk feed in any form (here termed 'solid food') into the infant diet.

Two studies evaluated TIDM risk only in young children (age ≤5), and 15 studies only in older children (up to 20 years old). Other than one study which didn't describe the source of dietary exposure assessment, and another which used diary records, all studies obtained information on age of solid food introduction based on questionnaire or interview data.

Based on the distribution of data reported in included studies, meta-analysis of binary data compared TIDM risk and timing of solid food introduction ≥3-4 months vs. <3-4 months.

A summary of the risk of bias in included studies is shown in Figure 19. Just over half of studies had a high overall risk of bias, mainly due to reliance on unadjusted data, hence high risk of confounding bias. Meta-analyses showed extreme statistical heterogeneity, with no clear evidence that delaying introduction of solid food until after 3-4 months was associated with altered risk of TIDM. Studies which analysed EBF duration as a continuous variable, or could not be included in meta-analysis, also showed a mixed and unclear picture. We were not able to exclude a clinically important association, due to the small number of studies in meta-analysis and high statistical heterogeneity and confidence intervals.

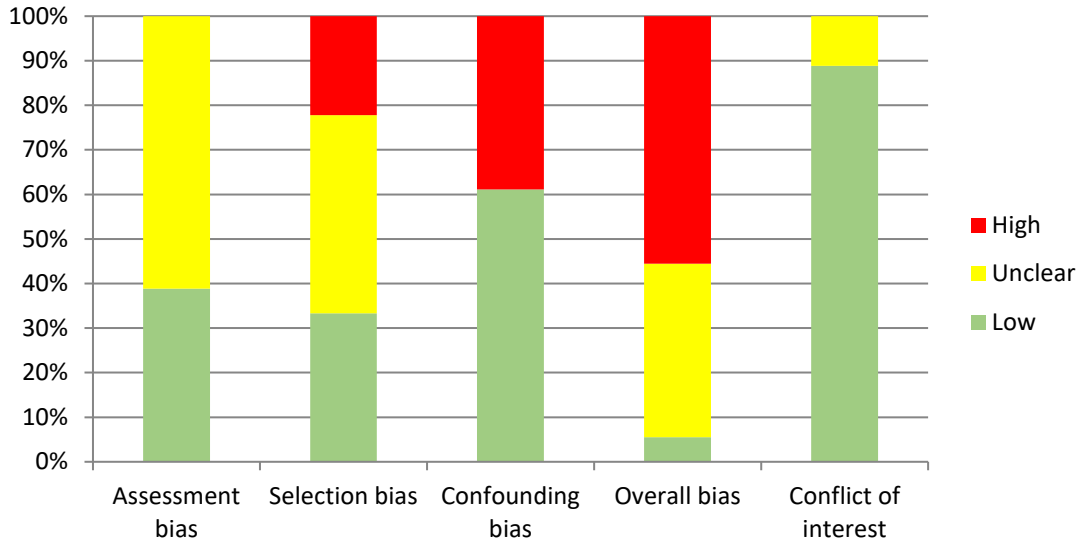
Table 10 Characteristics of studies reporting timing of solid food and TIDM risk

First Author & Publication Year	N/n cases	Country	Design	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Frederiksen, 2012 (66)	1698	USA	PC	-	Medical diagnosis	<7	High risk children via HLA screening
Ziegler, 2003 (15)	1460/~68	Germany	PC	Q	Islet autoantibodies	5	Newborn children
Savilahti, 2009 (72)	6209/45	Finland	NCC	D	Medical diagnosis	12	NHI database
Alves, 2012 (25)	246/123	Brazil	CC	I	Medical diagnosis	9	Endocrinology clinic
Dahlquist, 2002 (33)	2226/610	Austria, Latvia, Lithuania, Luxembourg and UK	CC	Q/I	Medical diagnosis	<15	Diabetes register
Esfarjani, 2001 (32)	104/52	Iran	CC	Q	Medical diagnosis	<14	Endocrine clinic attendance
Hypponen, 1999 (36)	821/435	Finland	CC	Q	Medical diagnosis	8	Hospital admissions
Kostraba, 1993 (38)	309/142	USA	CC	Q	Medical diagnosis	<18	Colorado IDDM Registry
Liese, 2012 (40, 68)	709/505	USA	CC	I	Medical diagnosis	<20	SEARCH surveillance (Colorado and South Carolina research centres)
Majeed, 2011 (39)	395/96	Iraq	CC	Q	Medical diagnosis	<18	Paediatric clinic
Meloni, 1997 (44)	200/100	Italy	CC	Q/I	Medical diagnosis	<15	Paediatric clinic

First Author & Publication Year	N/n cases	Country	Design	Exposure assessment	Specific outcome	Age at outcome (years)	Population characteristics
Perez-Bravo, 1996 (73)	165/80	Chile	CC	Q	Medical diagnosis	<15	Santiago de Chile registry
Rabiei, 2011 (69)	300/100	Iran	CC	Q	Medical diagnosis	<15	Diabetes register
Rosenbauer, 2008 (49)	2631/760	Germany	CC	Q	Medical diagnosis	<5	Hospital based surveillance system ESPD
Stene, 2003 (71)	2118/545	Norway	CC	Q	Medical diagnosis	9	Diabetes register
Strotmeyer, 2004 (56)	690/247	China	CC	Q	Medical diagnosis	10	Diabetes register
Visalli, 2003 (63)	900/150	Italy	CC	Q	Medical diagnosis	12	EURODIAB register

PC = prospective cohort, NCC = nested case control, CC = case control, D = diary, I = interview, Q = questionnaire, R = medical records

Figure 19 Risk of bias in observational studies of solid food exposure and TIDM risk



3.2. Outcomes from studies of solid food introduction and TIDM

3.2.1 Solid food introduction at ≥ 3-4 months vs < 3-4 months, and risk of TIDM

Six studies examined the association between delaying introduction of solid food for longer than 3-4 and risk of TIDM (Figure 20). There was extreme statistical heterogeneity (I^2=83.5%) so data were not pooled for meta-analysis. This heterogeneity could not be attributed to a particular study. If the study of Ziegler was excluded, extreme heterogeneity (I^2=86%) remained. Frederikson and Ziegler reported adjusted HR from prospective cohort studies, Ziegler using autoantibodies and Frederikson clinical TIDM for case definition. The other studies reported adjusted (Kostraba, Stene) or unadjusted OR from case control studies using clinical TIDM for case definition. Subgroup and stratified analyses did not show important differences in strength of association and extreme heterogeneity remained in all groups (Table 11).

Figure 20 Introduction of solid food at age ≥3-4 months vs. <3-4 months and TIDM risk

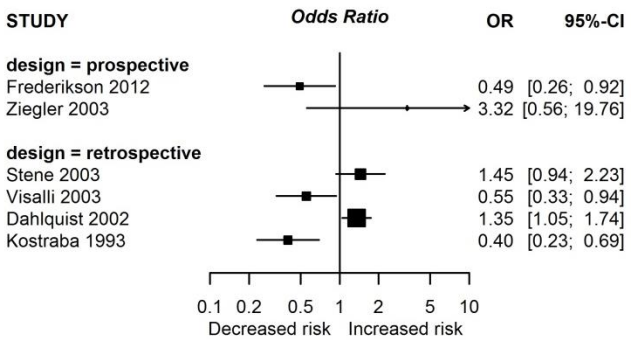


Table 11 Stratified and subgroup analyses of solid food introduction ≥3-4 months vs. <3-4 months and TIDM risk

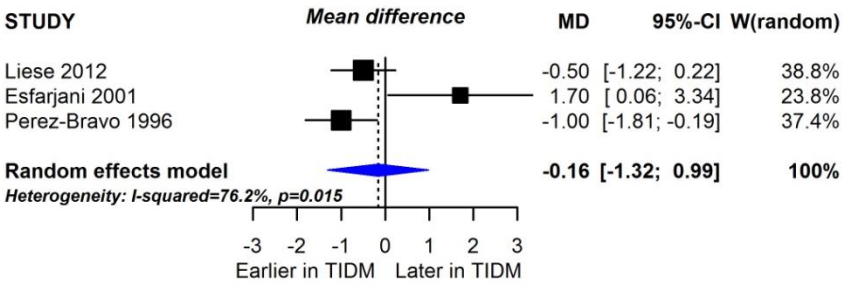
	Number of studies	OR [95% CI]*	I^2 (%)	P-value for between groups difference
Overall (if adjusted NA, unadjusted used)	6	0.83 [0.49-1.40]	83.5	
Adjusted	4	0.82 [0.36-1.87]	83.5	Not tested
Unadjusted	5	0.79 [0.48-1.29]	81.0	
Risk of disease – High	2	1.06 [0.17-6.62]	74.5	0.813
Risk of disease – Normal/Low	4	0.84 [0.46-1.51]	87.2	
Risk of bias – Low	2	0.96 [0.12-7.48]	79.8	0.947
Risk of bias – High/Unclear	4	0.90 [0.54-1.50]	82.2	
Study Design – Prospective	2	1.06 [0.17-6.62]	74.5	0.813
Study Design - Retrospective	4	0.84 [0.46-1.51]	87.2	
Method of diagnosis – clinical	5	0.76 [0.44-1.30]	86.0	0.121
Method of diagnosis – serological	1	3.32 [0.56-19.76]	-	

*Pooled estimate [95%CI] of meta-analysis of studies reporting Odds or Relative risk or Risk ratios or Hazard ratios

3.2.2 Timing of solid food introduction as a continuous variable, and TIDM risk

Three studies compared the mean time of solid food introduction in subjects with T1DM versus unaffected subjects. Pooled data show no overall difference between cases and controls (MD -0.16; 95% CI -1.32, 0.99) with extreme statistical heterogeneity (I^2=76.2%) (Figure 21). All 3 studies reported unadjusted data from case control studies. Heterogeneity was attributable to the study of Esfarjani (32), for unclear reasons, but timing of SF introduction occurred later in the study of Esfarjani than the other 2 studies, and if timing of SF introduction is not normally distributed then analysis of arithmetic mean (sd) may not be appropriate and may have contributed to the heterogeneity.

Figure 21 Timing of solid food introduction as a continuous variable, and TIDM risk



3.2.3 Other studies solid food introduction and TIDM, which couldn't be meta-analysed

Meta-analyses included 1 cohort and 4 case control studies in total, including at least 2264 participants with TIDM. A further 1 nested case control and 7 case control studies reported relevant data which could not be included in meta-analysis, in relation to at least 1825 participants with TIDM. These studies are summarised in Table 12. Two of the case control studies (Kostraba (38, 49), Rosenbauer (49)) showed a significant relationship between early introduction of solid food in TIDM compared to unaffected subjects. 6 studies showed no significant relationship, although solid food introduction was earlier in people with TIDM in 3 of these 6 studies, and similar or unclear in 3.

Table 12 Other studies evaluating timing of solid food introduction and TIDM which couldn't be meta-analysed

First Author and Year of Publication	Design	N/n cases	Age at first solid food introduction	Units	Descriptive measure	Unaffected	TIDM	P value
Kostraba, 1993 (38)	CC	309/142	Continuous	Weeks	Mean	16.9	13.4	**0.01**
Savilahti, 2009 (72)	NCC	6209/45	Continuous	Months	Mean	4	3.7	0.09
Hypponen, 1999 (36)	CC	821/435	Continuous	Months	Average			NS
Majeed, 2011 (39)	CC	395/96	Categorical	>6 vs <6 months				NS
Rabiei, 2011 (69)	CC	300/100	Categorical	>6 vs <6 months	aOR (95% CI)	0.60 (0.27-1.32)		NS
Rosenbauer, 2008 (49)	CC	2631/760	Categorical	>5 vs <5 months	aOR (95% CI)	0.82 (0.64-1.05)		NS
					uOR (95% CI)	0.78 (0.65-0.93)*		**0.006**
Strotmeyer, 2004 (56)	CC	690/247	1-3 months	%		20	13	**<0.05**
			4-6 months	%		48	58	**<0.05**
			7-12 months	%		30	28	NS

* Adjusted data from this study showed no statistically significant difference

4 Conclusions

This report summarises the results of over 60 studies examining the association between total or exclusive breastfeeding duration, timing of solid food introduction and TIDM risk, including over 15,000 people with TIDM. The majority of the studies were case-control design, some of which were nested in cohort studies. Overall we found VERY LOW evidence that increased duration of TBF, and LOW evidence that increased duration of EBF, are associated with reduced risk of TIDM. We found no association between timing of SF introduction and TIDM risk.

Figure 22 Summary of Meta-Analysis findings for Duration of BF and TIDM risk

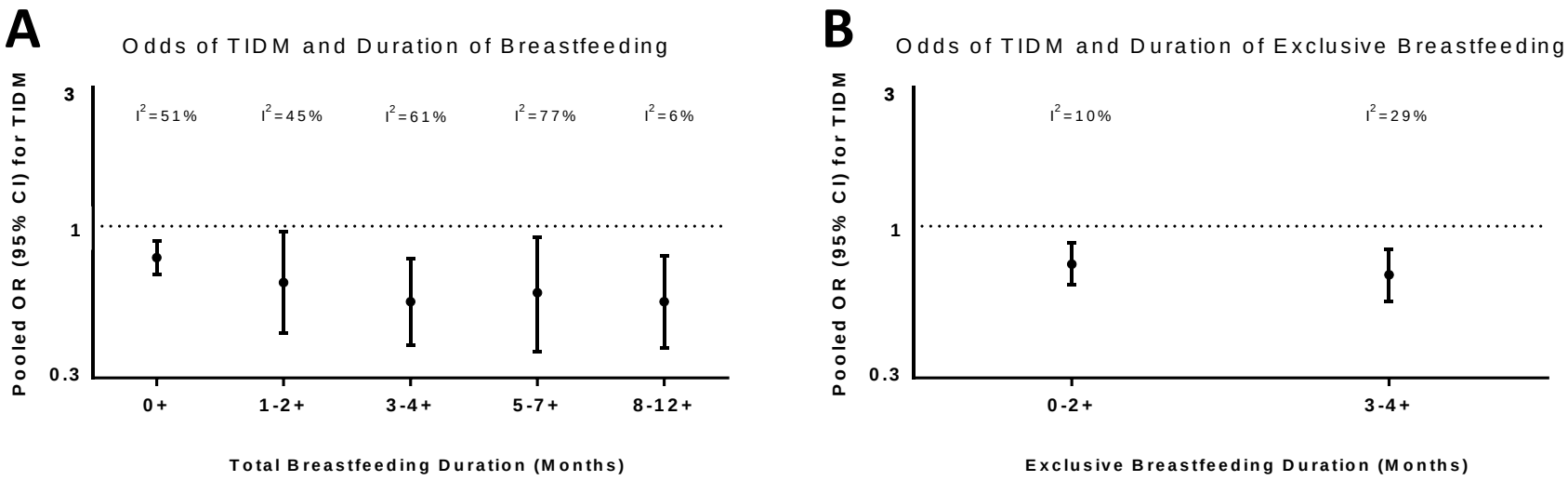


Figure 22. Pooled OR for TIDM in relation to TBF (A) and eBF (B). Bars are 95% CI; I^2 is a measure of statistical heterogeneity.

In spite of the growing number of epidemiological studies examining the association between breastfeeding, solid food introduction and risk of TIDM, there are very few systematic reviews analysing this relationship. The current report probably provides the most comprehensive description of eligible studies on breastfeeding and TIDM to date. A recent literature review by Hornell and colleagues (74) concluded that prolonged breastfeeding had a protective effect against the risk of TIDM. The authors based their conclusions on an earlier paper by Ip and colleagues (75) and on a single prospective study, also included in our report (2).

In our search for existing systematic reviews we identified two existing reviews of this area, by Patelarou et al (76) and by Cardwell et al (77). Both were scored below the recommended AMSTAR cut-off point for a high quality systematic review (24 and 31, respectively) and therefore were excluded from our Overview and we have not directly included their data in this report. Cardwell's meta-analysis of individual patient data from 43 observational studies reported no clear association between TBF for more than 2 weeks (28 studies; OR = 0.93, 95% CI 0.81 to 1.07) or for more than 3 months (29 studies; OR = 0.88, 95% CI 0.78 to 1.00) and TIDM. They found a protective effect of EBF >2 weeks on risk of TIDM albeit with very high statistical heterogeneity (17 studies; aOR = 0.78, 95% CI 0.65, 0.93; I^2=52%), but no such effect for EBF >3 months. Cardwell's analysis differs from ours because they acquired individual patient data from the majority of the 43 included studies, including confounders, so that they could do adjusted analyses where possible. Due to their methods they were able to include larger numbers of studies in individual meta-analyses of specific cut-off durations. They did not however identify as many studies as our review, so had increased risk of publication bias from the methods used. They also only explored 2 time cut-offs i.e., 2 weeks and 3 months for their analyses. For example in their analysis of EBF >2 weeks versus shorter they included 13 distinct studies in meta-analysis – of these, 1 study was not included in our review (78) because relevant data were only available through contact with the authors. In contrast we included 28 separate studies in our analysis of EBF duration, although a maximum of 6 studies could be included in meta-analysis of EBF duration and TIDM at any given time cut-off, due to lack of individual patient data. Our finding that TBF durations of ≥5-7 and 8-12 months are associated with reduced TIDM risk was not explored by Cardwell et al, and theirs was not a systematic review including all

available data but rather a details analysis of studies well known to the authors. The review by Patelarou *et al* (76) was methodologically weaker, only identifying 28 studies.

In the current report, the pooled data suggest reduced risk of TIDM is associated with increased duration of total or exclusive breastfeeding duration. Some meta-analyses showed significant statistical heterogeneity across studies, especially for TBF, which remained largely unexplained after subgroup and stratified analyses. There was no evidence for a difference between adjusted and unadjusted analyses, suggesting that confounding bias may not be a major issue for studies of TBF/EBF and TIDM. There was however reduced heterogeneity in some analyses when analysing retrospective and prospective studies separately, and in some analyses these 2 subgroups were significantly different i.e. retrospective studies showed more positive findings than prospective studies. The use of serology for outcome assessment in some of the prospective studies, often with shorter time between exposure and outcome assessment, may account for the reduced evidence for association between TBF/EBF and TIDM seen in prospective compared with retrospective studies. The relationship between serological diabetes and clinical diabetes is only moderately strong - approximately 60% of people with ≥2 diabetes-associated antibodies develop clinical TIDM over a 10 year follow up period (79).

Evidence for an association was strongest for EBF and TIDM, where both meta-analysed and non meta-analysed data suggested prolonged EBF is associated with reduced TIDM risk, with low or moderate statistical heterogeneity and no significant difference between prospective and retrospective studies. Possible explanations for this association are reduced gastrointestinal infection, an established effect of prolonged EBF duration and a proposed risk factor for TIDM; or reduced cow's milk exposure in infancy, also proposed as a risk factor for TIDM (80, 81). We found no evidence that timing of SF introduction is relevant.

Overall these data support an association between longer TBF and EBF duration and reduced risk of TIDM, and no association between delayed solid food introduction until after 3-4 months and risk of T1DM. The association seen with prolonged TIDM suggests a protective effect against infection as the most likely mechanism, rather than an adverse effect of early CM introduction, since other parts of this systematic review series have not identified a relationship between timing of CM introduction, or use of hydrolysed infant formula, and risk of TIDM.

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