National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Health effects of breastfeeding: an update; Annex A and B

Systematic literature review

Annex to:

RIVM report 2015-0043

M. Buijssen et al.

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Health effects of breastfeeding: an update; Annex A and B

Systematic literature review

Annex to:
RIVM Report 2015-0043

Colophon

Marleen Buijssen, Pallas
Rana Jajou, Pallas
Femke (G.B.) van Kessel, Pallas
Marije (J.M.) Vonk Noordegraaf-Schouten, Pallas
Marco J. Zeilmaker, RIVM
Alet H. Wijga, RIVM
Caroline T.M. van Rossum, RIVM

Contact:
Caroline van Rossum
Caroline.van.rossum@rivm.nl

This investigation has been performed by order and for the account ofthe Ministry of Health, Welfare and Sports.

This is a publication of:
National Institute for Public Health and the Environment
P.O. Box 1 | 3720 BA BILTHOVEN
The Netherlands
www.rivm.nl

Contents

Annex A Health outcomes related to the child

A-I Reviews with health outcomes related to the child

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Early onset of Inflammatory bowel disease (Crohn's disease and Ulcerative colitis)	Barclay, 2009 The Journal of Paediatrics Systematic review and meta-analysis[1]	To assess the current evidence for the role of BF in the development of early onset inflammatory bowel disease with a systematic review.	*Inclusion criteria* - Outcomes described for patients exclusively < 16 years old - Early onset with predominantly < 16 years old (>50% <16 years; all <21 years) - When data for patients <16 years old could be extracted separately	Studies published between Jan 1966-Jan 2008 *Number of hits in original search* - Ovid databases Medline (1966-Jan 2008), Old Medline 1951-1965, Cochrane Library (1991- quarter 1, 2008), CAB abstracts 1973-2008, Embase (1980-week 4, 2008), Cinahl (1982-Jan 2008), ACP Journal Club Database / Abstracts of Reviews of Effectiveness (1991- quarter 1, 2008), total, n=72 (after abstract review) - Reference lists and specific hand search, n=7 *Number/designs of included articles for early onset disease* CC studies: n=8 (7 suitable for meta-analysis using data on absolute exposure)	Patients with IBD	*Exposure assessment* NR, however, information available on whether the investigators of the individual papers used a validated method to define BF *Exposure definition* BF was defined as any exposure because definitions and durations of feeding practice varied between studies

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Outcome assessment Information available on whether the investigators of the individual papers used a validated method to define IBD cases (see table II below) *Outcome definition* Defined by specific diagnostic criteria (clinical, radiological, endoscopic and pathological) and standard definitions *Age at diagnosis* < 16 years	*Analysis with Gilat et al. 1987** - IBD: $SOR_{BF\ vs\ no\ BF}$ (95% CI) = 0.69 (0.51-0.94; p = 0.02) - UC: $SOR_{BF\ vs\ no\ BF}$ (95% CI) = 0.72 (0.51-1.02; p = 0.06) - CD: $SOR_{BF\ vs\ no\ BF}$ (95% CI) = 0.64 (0.38-1.07; p = 0.09) - Heterogeneity of this data was moderate to high (I^2 values: IBD 71.4%; UC 43.3%; CD 81.6%) *Analysis excluding Gilat et al. 1987* - IBD: $SOR_{BF\ vs\ no\ BF}$ (95% CI) = 0.60 (0.39-0.91; P = 0.02) - UC: $SOR_{BF\ vs\ no\ BF}$ (95% CI) = 0.61 (0.44-0.84; P = 0.003) - CD: $SOR_{BF\ vs\ no\ BF}$ (95% CI) = 0.65 (0.26-1.15; P = 0.11) - Heterogeneity of studies was still high for all IBD and CD, but not for UC (I^2 values; IBD 73.1%; UC 0% and CD 84%) See figure 2 for the random effect model analysis.	NR	- Meta analysis combining the results of 8 studies was hindered by the lack of OR and Cis of exposure to breast milk in Gilet et al (1987). A random effects model therefore was applied, including this study assuming an OR of 1 for each group in the Gilat et al study (see figure 2 below). *Limitations (pre-defined quality criteria)* - No information about the time of assessing BF data - Not reported whether assessment of outcome was after assessment of exposure - No information was reported about correction for relevant confounders *Other limitations* - Overall quality of included data was poor - A potential recall bias was present in all studies analysed, none of the studies in our review used written evidence of BF - Publication bias may also exist, but this is difficult to assess because of the small number of publications - Failure to use or describe OBD specific diagnostic criteria, which may lead to misclassification of OBD by researchers - None of the included studies described appropriate power calculations
CD: Crohn's disease ; IBD: Inflammatory bowel disease; UC: Ulcerative colitis; *OR of 1 assumed for each group in the study of Gilat et al. 1987			

[1] Three of the included articles in this review were included in the report of RIVM (2007).

Barclay, 2009

Table II. Results of eight studies that include patients with early onset inflammatory bowel disease

Author	Population	Early onset	IBD	Cases (n)	Control source	Control matching	Control subjects (n)	IBD Def	BF def	study rating	Effect size
Koletzko[34] 1991	Canada	Yes	UC	93	Siblings	Sibling with no disease	138	No	Yes	2+	OR UC 0.59 (0.27-1.30)
Bergstrand[26] 1983	Sweden population register	Yes	CD	308	Population register	Age, sex and birth place	308	Yes	No	2+	$P < .01$* OR CD 0.28 (0.14-0.56)
Koletzko[33] 1989	Canada	Yes <18	CD	114	Siblings	Sibling with no disease	180	No	Yes	2+	OR CD 0.28 (0.11-0.71)
Gruber[30] 1996	USA support charity	Yes <22	CD	54	Friends and neighbors	Age matched	90	No	Yes	2+	OR CD 0.60 (0.29-1.27)
Gilat[29] 1987	9 countries	Yes <20	UC/CD	499 UC 197 CD 302	1 = Minor GI disease; 1 = non-GI OPD	Age and sex	998 UC 394 CD 604	No	No	2 −	OR UC 1.00 (0.71-1.41) CD 1.00 (0.76-1.32)
Rigas[37] 1993	USA OPD	Yes <17	UC/CD	107 UC 39 CD 68	From pediatric GI clinic	Seen before or after patient in clinic (age)	202	No	No	2+	OR UC 0.50 (0.25-1.01) CD 0.48 (0.27-0.85)
Urashima[41] 1999	Japan	Yes <15	UC/CD	175 UC 133 CD 42	Healthy hospital controls	Age and sex	392 UC 266 CD 126	Yes	No	2−	OR UC 0.53 (0.32-0.87) CD 0.30 (0.13-0.51)
Baron[25] 2004	France EPIMAD	Yes <17	UC/CD	282 UC 60 CD 222	Random telephone selection	Age, sex, and geographically	282 UC 60 CD 222	Yes	No	2−	OR UC 1.07 (0.52-2.22) CD 1.60 (1.10-2.40)

IBD def, Whether investigators used a validated method to define IBD cases; *BF def*, whether investigators used a validated method to define breastfeeding; GI, gastrointestinal; OPD, outpatients department.

*Bergstrand et al:[26] Although separate data on early-onset group is available, exposure to breast milk is displayed for adult and early-onset group; OR displayed is for all patients and is therefore not included in our meta-analysis. All identified studies were case control studies.

Barclay, 2009

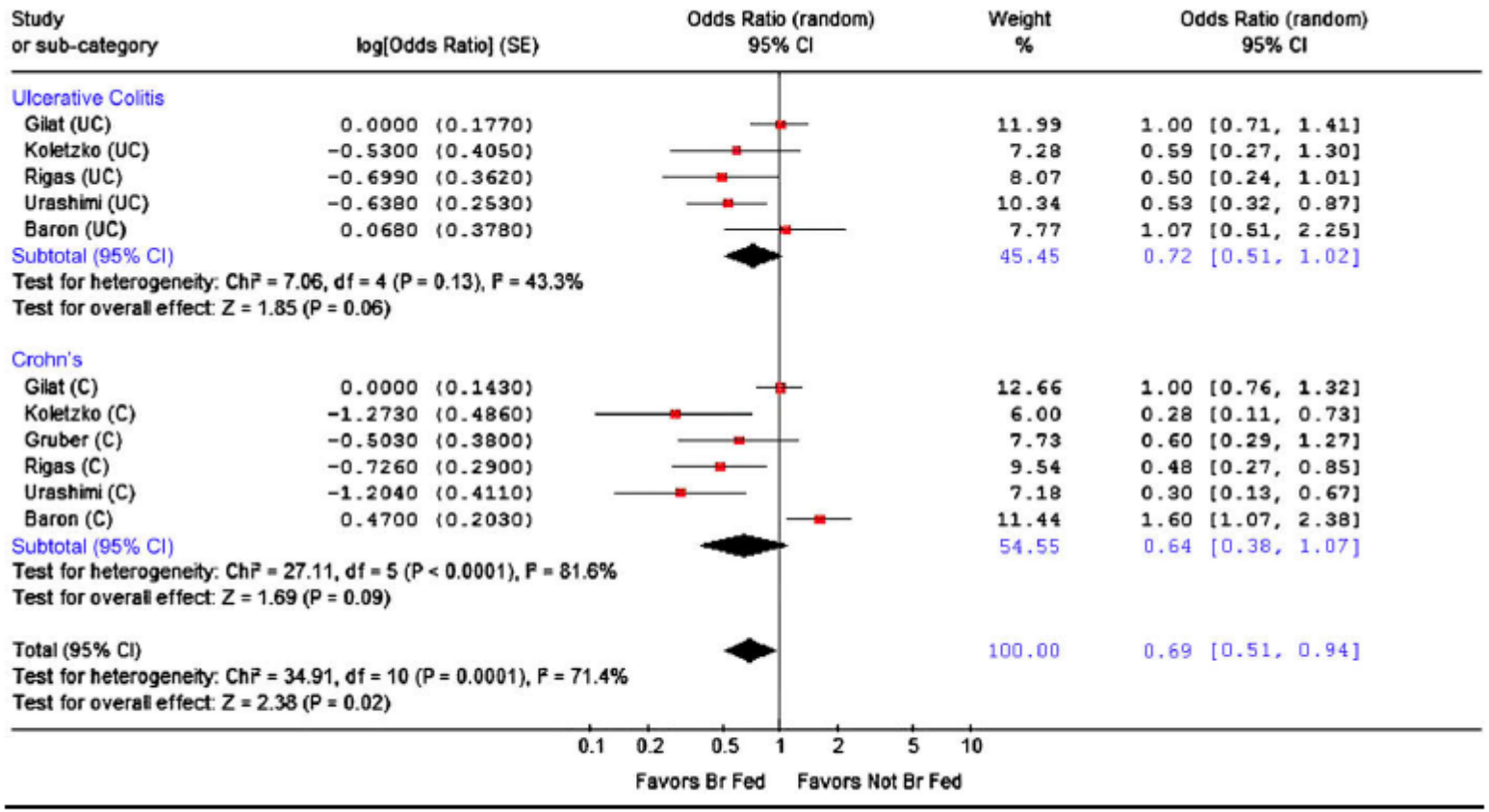


Figure 2. Random effects analysis including all studies for exposure to breast milk on the development of UC, CD, and all IBD (OR of Gilat et al[29] estimated at 1).

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Type 1 diabetes	Cardwell, 2012 Diabetes care Systematic review including pooled analysis[2]	To investigate if there is a reduced risk of type 1 diabetes in children BF or EBF by performing a pooled analysis with adjustment for recognized confounders	*Inclusion criteria* - Human studies - Study identified a group with type 1 diabetes and a group without type 1 diabetes - Study recorded BF in these groups - No language restriction *Exclusion criteria* - Study contained <20 patients with diabetes - Study was family-based	January 1996-1 May 2011 *Number of hits in original search* - MEDLINE: n=238 - Web of Science: n=393 - EMBASE: n=609 *Number of included articles* - Total: n=43 - CC studies: n=40 - CH studies: n=3	Subjects with type 1 diabetes (n=9,874) and subjects without type 1 diabetes 28 included studies were from Europe, 2 from the USA, 1 from Australia and from 1 from Canada. Other studies were from non-western countries	*Assessment* 37 studies ascertained BF data using questionnaires or interviews; other studies used medical or maternity records, or the method was unknown BF data were recalled 0-25 years after birth of the child *Definition* Both exclusive and nonexclusive BF: - Any BF - BF for ≥2 vs <2 weeks - BF for ≥3 vs <3 months

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment Diabetes registers or hospital admissions for diabetes Age at diagnosis ranged from 0 to 23 years *Definition* Occurrence of diabetes determined as described above	*Nonexclusive BF and type 1 diabetes (unadjusted)* OR $_{\text{BF any vs. none}}$ (95% CI) = 0.81 (0.72-0.92; P < 0.001) (n=43) OR $_{\text{BF ≥2 vs <2 wks}}$ (95% CI) = 0.93 (0.81-1.07; P = 0.32) (n=28) OR $_{\text{BF ≥3 vs <3 mo.}}$ (95% CI) = 0.88 (0.78-1.00; P = 0.05) (n=29) *EBF and type 1 diabetes (unadjusted)* OR $_{\text{EBF any vs. none}}$ (95% CI) = 0.74 (0.64-0.84; P < 0.001) (n=33) OR $_{\text{EBF ≥2 vs <2 wks}}$ (95% CI) = 0.75 (0.64-0.88; P = 0.001) (n=20) OR $_{\text{EBF ≥3 vs <3 mo.}}$ (95% CI) = 0.87 (0.75-1.00; P = 0.06) (n=30) Additional analyses with studies of low risk of bias and heterogeneity scores are presented in table 2. - The association for ≥2 vs <2 wks was little altered by adjustment for confounding factors (supplementary table 1) - Stratified analyses for geographic region (European vs non-European) and low and high incidence rate countries did not reveal marked differences in association (supplementary table 2) - There was little evidence of a difference in the association between childhood type 1 diabetes and BF in early diagnosed diabetes and later diagnosed diabetes in studies in which both age groups were available (supplementary table 3)	Analyses were adjusted for the following confounders: maternal diabetes, birth weight, gestational age, maternal age, birth order, Caesarean section and socioeconomic status	- Authors of relevant studies were asked to provide individual participant data or conduct pre-specified analyses *Limitations (predefined quality criteria)* - In the majority of studies BF data were recalled many years after the birth of the child (delay in years ranged from 0 to 25 years) - Only few associations adjusted for confounders - Firm conclusions are difficult to reach because of the marked heterogeneity in the observed associations and the weaknesses inherent in many of the included studies
Mo.: Months; UK: United Kingdom; USA: United States of America; Wks: Weeks.			

[2] Three of the included articles in this review were included in the report of RIVM (2007).

Cardwell, 2012

Table 2—*Pooled analyses of the association between breast-feeding and childhood-onset type 1 diabetes in all studies and in studies with a lower risk of bias*

	All studies						Studies with low risk of bias[d]					
	N[b]	Cases	OR (95% CI)	*P* value	Heterogeneity χ^2 (*P* value)	I^2 in % (95% CI)	N[b]	Cases	OR (95% CI)	*P* value	Heterogeneity χ^2 (*P* value)	I^2 in % (95% CI)
Nonexclusive breast-feeding[a]												
Any vs. none[c]	43	9,874	0.81 (0.72–0.92)	0.001	112.16 (<0.001)	63 (48–73)	16	2,918	1.00 (0.89–1.11)	0.93	15.20 (0.51)	1 (0–53)
≥2 vs. <2 wks[e]	28	6,798	0.93 (0.81–1.07)	0.32	58.32 (<0.001)	54 (29–70)	15	2,343	1.00 (0.87–1.15)	0.99	15.16 (0.37)	8 (0–44)
≥3 vs. <3 mos[e]	29	6,683	0.88 (0.78–1.00)	0.05	87.10 (<0.001)	68 (53–78)	15	2,334	0.99 (0.86–1.14)	0.92	27.00 (0.02)	48 (6–71)
<2 wks[e]	24	6,185	1.00 (ref. cat.)				13	2,045	1.00 (ref. cat.)			
2 wks–4 mos			0.96 (0.83–1.12)	0.60	38.11 (0.03)	40 (2–63)			1.03 (0.86–1.22)	0.77	13.06 (0.37)	8 (0–46)
4–6 mos			0.95 (0.78–1.15)	0.59	43.55 (0.006)	47 (15–67)			1.09 (0.90–1.32)	0.38	7.02 (0.86)	0 (0–57)
>6 mos			0.94 (0.76–1.17)	0.57	69.28 (<0.001)	67 (49–78)			1.09 (0.83–1.44)	0.52	26.75 (0.01)	55 (16–76)
Exclusive breast-feeding[a]												
Any vs. none[c]	33	7,621	0.74 (0.64–0.84)	<0.001	96.22 (<0.001)	67 (52–77)	13	2,187	0.89 (0.78–1.02)	0.09	12.84 (0.38)	6 (0–59)
≥2 vs. <2 wks[f]	20	4,388	0.75 (0.64–0.88)	0.001	45.10 (0.001)	58 (30–74)	12	1,918	0.86 (0.75–0.99)	0.04	11.07 (0.44)	0 (0–58)
≥3 vs. <3 mos[f]	30	7,312	0.87 (0.75–1.00)	0.06	122.64 (<0.001)	76 (66–83)	13	2,190	1.13 (0.96–1.33)	0.15	23.00 (0.03)	43 (0–70)

ref. cat., reference category; wks, weeks; mos, months. [a]For approximate categories used in each study, see Fig. 1 (for any nonexclusive breast-feeding and nonexclusive breast-feeding for 2 weeks) and Fig. 2 (for any exclusive breast-feeding and exclusive breast-feeding for 2 weeks) and Tables 1 and 2 (for any nonexclusive for 3 months or exclusive breast-feeding for 3 months). [b]Number of studies. [c]Any measure of breast-feeding or exclusive breast-feeding versus none. [d]Studies with low risk of bias indicated by footnote in Table 1. [e]Less than 2 week category and <3 month category includes no breast-feeding. [f]Less than 2 week category and <3 month category includes no exclusive breast-feeding.

Cardwell, 2012

Supplementary Table 1. The association between non-exclusive breast feeding (≥ 2 weeks versus < 2 weeks) and exclusive breastfeeding (≥ 2 weeks versus < 2 weeks) with type 1 diabetes after adjustment for various confounders.

Adjusted for	Nos. of studies recording confounder	Nos. of cases in adjusted analysis	Unadjusted OR in studies recording confounder (95% CI)	Adjusted pooled estimate		Heterogeneity	
				OR (95% CI)	P	χ2 (P)	I^2 in % (95%CI)
Non-exclusive breast feeding (≥ 2 weeks versus < 2 weeks)							
Unadjusted	28		0.93 (0.81, 1.07)				
Maternal diabetes	21	6472	0.91 (0.79, 1.06)	0.91 (0.79, 1.05)	0.19	32.29 (0.04)	38 (0, 63)
Birth weight	21	6465	0.90 (0.78, 1.05)	0.90 (0.77, 1.05)	0.19	37.75 (0.01)	47 (12, 68)
Gestational age	18	5297	0.94 (0.80, 1.10)	0.95 (0.80, 1.12)	0.53	28.94 (0.04)	41 (0, 66)
Birth order	19	6660	0.92 (0.79, 1.07)	0.91 (0.79, 1.06)	0.23	31.70 (0.02)	43 (2, 67)
Maternal age	21	6596	0.90 (0.78, 1.05)	0.90 (0.78, 1.04)	0.16	33.57 (0.03)	40 (0, 65)
Caesarean section	16	4147	0.94 (0.80, 1.11)	0.95 (0.81, 1.12)	0.51	20.41 (0.16)	27 (0, 60)
Socio-economic status	8	2313	0.72 (0.62, 0.84)	0.77 (0.66, 0.90)	0.001	2.94 (0.72)	0 (0, 65)
Fully adjusted[a]	24	6822	0.90 (0.79, 1.02)	0.92 (0.80, 1.05)	0.22	32.34 (0.09)	29 (0, 57)
Exclusive breast feeding (≥ 2 weeks versus < 2 weeks)							
Unadjusted	20		0.74 (0.64, 0.88)				
Maternal diabetes	17	3649	0.76 (0.63, 0.91)	0.76 (0.63, 0.91)	0.003	42.20 (<0.001)	62 (36, 78)
Birth weight	17	3545	0.76 (0.63, 0.91)	0.76 (0.64, 0.90)	0.001	34.63 (0.004)	54 (20, 73)
Gestational age	13	2175	0.77 (0.60, 0.98)	0.74 (0.58, 0.96)	<0.001	38.55 (<0.001)	69 (45, 82)
Birth order	16	3560	0.75 (0.62, 0.90)	0.74 (0.62, 0.89)	0.001	39.19 (0.001)	62 (34, 78)
Maternal age	17	3583	0.76 (0.63, 0.91)	0.77 (0.63, 0.93)	0.01	44.54 (<0.001)	64 (40, 79)
Caesarean section	11	1468	0.77 (0.57, 1.04)	0.77 (0.57, 1.05)	0.10	37.26 (<0.001)	73 (51, 85)
Fully adjusted[a]	17	3357	0.76 (0.63, 0.91)	0.78 (0.65, 0.93)	0.01	33.49 (0.01)	52 (17, 73)

CI, confidence interval; OR, odds ratio.

[a] Studies adjusted for as many potential confounders as possible, excludes studies for which adjustments could not be made for any confounders.

Cardwell, 2012

Supplementary Table 2. Sensitivity analyses of the pooled analyses of the association between breast feeding and exclusive breastfeeding and type 1 diabetes by incidence rate and region.

	Pooled estimate				P for interaction [b]	Heterogeneity	
	Studies	Cases	OR (95%CI)	P		χ2 (P)	I^2 in % (95%CI)
Any v none							
European	28	6886	0.82 (0.73, 0.91)	0.02	0.57	43.41 (0.02)	38 (2, 61)
Non-European	15	2988	0.74 (0.53, 1.04)	0.08		68.25 (<0.001)	79 (67, 87)
Low incidence countries[a]	23	4465	0.76 (0.63, 0.92)	0.004	0.31	60.54 (<0.001)	64 (43, 77)
High incidence countries[a]	20	5409	0.87 (0.73, 1.02)	0.09		51.37 (<0.001)	63 (40, 77)
> 2wk v < 2wk							
European	21	5342	0.85 (0.74, 0.98)	0.02	0.02	32.67 (0.04)	39 (0, 64)
Non-European	7	1456	1.21 (0.89, 1.63)	0.22		10.92 (0.09)	45 (0, 77)
Low incidence countries[a]	14	2714	0.91 (0.76, 1.08)	0.27	0.79	18.54 (0.14)	30 (0, 63)
High incidence countries[a]	14	4084	0.96 (0.77, 1.19)	0.69		39.75 (<0.001)	67 (43, 81)
> 3m v < 3m							
European	22	5236	0.86 (0.76, 0.98)	0.02	0.53	59.86 (<0.001)	65 (45, 78)
Non-European	7	1447	0.95 (0.67, 1.34)	0.76		22.16 (0.001)	73 (42, 87)
Low incidence countries[a]	15	2803	0.90 (0.74, 1.08)	0.25	0.85	45.64 (<0.001)	69 (48, 82)
High incidence countries[a]	14	3880	0.87 (0.74, 1.03)	0.11		40.71 (<0.001)	68 (44, 82)
Any exclusive v no exclusive							
European	24	5817	0.79 (0.70, 0.88)	<0.001	0.02	41.35 (0.01)	44 (10, 66)
Non-European	9	1804	0.56 (0.36, 0.88)	0.01		43.78 (<0.001)	82 (66, 90)
Low incidence countries[a]	17	3147	0.72 (0.59, 0.88)	0.001	0.73	41.91 (<0.001)	62 (35, 77)
High incidence countries[a]	16	4474	0.75 (0.63, 0.90)	0.002		54.26 (<0.001)	72 (54, 83)
> 2wk exclusive v < 2wk exclusive							
European	16	3548	0.79 (0.71, 0.88)	<0.001	0.01	16.02 (0.38)	6 (0, 41)
Non-European	4	840	0.59 (0.32, 1.09)	0.09		12.63 (0.01)	76 (35, 91)
Low incidence countries[a]	10	1346	0.80 (0.64, 1.00)	0.05	0.47	14.27 (0.11)	37 (0, 70)
High incidence countries[a]	10	3042	0.72 (0.57, 0.90)	0.004		29.80 (<0.001)	70 (42, 84)
> 3m exclusive v < 3m exclusive							
European	23	5766	0.91 (0.78, 1.05)	0.21	0.23	86.30 (<0.001)	75 (62, 83)
Non-European	7	1546	0.71 (0.46, 1.10)	0.13		32.77 (<0.001)	82 (63, 91)
Low incidence countries[a]	16	3066	0.91 (0.72, 1.15)	0.42	0.67	64.15 (<0.001)	77 (62, 86)
High incidence countries[a]	14	4246	0.83 (0.69, 0.99)	0.04		53.65 (<0.001)	76 (59, 86)

m, month; wk, week.

[a] Low incidence countries (≤ 15 per 100,000 person years) an high incidence countries (>15 per 100,000 person years).

[b] P-value calculated from meta-regression.

Cardwell, 2012

Supplementary Table 3. The association between breast feeding and exclusive breastfeeding and type 1 diabetes by age at diagnosis (restricted to studies which recorded age at diagnosis and included cases diagnosed over 5 and under 5 years).

	Under 5s				Over 5s				P for interaction[b]
	N[a]	Cases	OR (95%CI)	P	N[a]	Cases	OR (95%CI)	P	
Any breast feeding									
> 2wk v < 2wk	22		0.84 (0.65, 1.08)	0.17	22		0.95 (0.82, 1.11)	0.54	0.45
> 3m v < 3m	23		0.86 (0.69, 1.08)	0.19	23		0.90 (0.79, 1.02)	0.09	0.73
Exclusive breast feeding									
> 2wk v < 2wk	18		0.73 (0.58, 0.91)	0.01	18		0.75 (0.60, 0.95)	0.01	0.87
> 3m v < 3m	24		0.86 (0.71, 1.03)	0.10	24		0.90 (0.76, 1.05)	0.17	0.72

[a] Number of studies included in analysis. [b] P-value calculated using standard test for heterogeneity.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Helicobacter pylori	Chak, 2009 Clinical infectious diseases Systematic review and meta-analysis[3]	To conduct a systematic review of the role of BF in *H. pylori* infection and examine potential sources of heterogeneity	*Inclusion criteria* - Studies published in scientific journals that provided information about BF history and *H. pylori* infection status using any diagnostic test *Exclusion criteria* - Studies that did not include relative risks, ORs or 95% CIs or the crude data to calculate them - Case reports and review articles	1984-2007 *Number of hits in original search* Medline, Cochrane library and Lilacs, bibliography search, total: n=583 *Number of included articles* - Total: n=14 - CH studies: n=3 - CC studies: n=1 - CS studies: n=10	General populations with *H. pylori* infections Included studies were from ; 3 UK, 1 Italy, 1 Japan, 2 Brazil, 2 Turkey, 1 USA, 1 Egypt, 1 Vietnam, 1 Germany, 1 Bangladesh	*Assessment* NR Age at assessment was not reported *Definition* BF was defined as reported by the authors; most studies did not define BF and only reported whether mothers breastfed children or not, providing few other details Most studies included any duration of BF; five studies included a duration of ≥4months (of which 4 studies >6 months)

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment Mainly using C-UBT or IgG serologic test; one study used biopsy Age of assessment was not reported, but concerned infants and young children *Definition* Occurrence of *H. pylori* determined as described above	Overall (n=14): SOR $_{\text{BF any vs. none}}$ (95% CI) = 0.78 (0.61-0.99; P = 0.02) *Length of BF* SOR $_{\text{BF ≥4 months vs. none}}$ (95% CI) = 0.81 (0.40-1.66; P = 0.28) (n=5) This result was highly dependent on the individual studies; exclusion of the only study in which an increased risk of BF was observed: SOR = 0.63 (95% CI, 0.32-1.24; P = 0.09) SOR $_{\text{BF NS vs. none}}$ (95% CI) = 0.76 (0.59-0.99; P = 0.02) (n=9) *Middle/low and high-income countries* Middle/low income countries: SOR $_{\text{BF any vs. none}}$ (95% CI) = 0.55 (0.33-0.93; P = 0.01) (n=7) High income countries: SOR $_{\text{BF any vs. none}}$ (95% CI) = 0.93 (0.73-1.19; P = 0.28) (n=7) Stratified analyses were also performed for diagnostic test, study design and study quality (table 2 below)	Authors used adjusted ORs if provided in the article. Five included studies presented data that were not adjusted for any potential confounding variables	- There was no evidence of publication bias according to the results of Egger's test and Begg's test - If a study reported the effects of different durations of BF, authors used the OR for the longest time *Limitations (predefined quality criteria)* - Time of assessing BF was not reported - Few studies defined BF and definitions may have differed - Choice of diagnostic test differed in the included studies: C-UBT vs. IgG serologic test - Five included studies presented data that were not adjusted for any potential confounding variables - Newcastle-Ottawa scale: all CH studies received 7 stars and the CC study 8 stars (both high quality). The CS studies were classified as "lower quality" *Other limitations* - ORs of CS studies and CH studies were similar: biases related to CS studies had limited impact on the results
C-UBT: C-urea breath test; NS: Not specified; USA: United States of America.			

[3] None of the included articles in this review were included in the report of RIVM (2007).

Chak, 2009

Table 2. Summary estimates of effect of breast-feeding on *Helicobacter pylori* infection in subgroup analyses.

Variable	No. of Studies	Summary estimate (95% CI)		Heterogeneity, %[a]	P[b]
		Random-effects model	Fixed-effects model		
All studies	14	0.78 (0.61–0.99)	0.9 (0.83–0.98)	77.48	.00
National economic status					
Middle- and low-income nation	7	0.55 (0.33–0.93)	0.56 (0.44–0.70)	22.81	.00
High-income nation	7	0.93 (0.73–1.19)	0.98 (0.89–1.07)	34.28	.00
Duration of breast-feeding					
≥4 months	5	0.81 (0.40–1.66)	0.77 (0.60–0.99)	23.75	.00
<4 months or not specified	9	0.76 (0.59–0.99)	0.92 (0.84–1.01)	52.09	.00
Diagnostic test[c]					
^{13}C-urea breath test	6	0.67 (0.32–1.39)	0.61 (0.47–0.80)	33.07	.00
IgG serologic test	7	0.91 (0.74–1.11)	0.95 (0.87–1.04)	26.31	.00
Study design[d]					
Cohort[e]	3	0.8 (0.68–0.94)	0.8 (0.68–0.94)	1.47	.83
Cross-sectional	10	0.81 (0.58–1.14)	0.96 (0.86–1.06)	64.07	.00
Study quality[f]					
High quality	4	0.73 (0.52–1.01)	0.77 (0.66–0.91)	8.78	.12
Low quality	10	0.81 (0.58–1.14)	0.96 (0.86–1.06)	64.07	.00

[a] Determined by the χ^2 test.
[b] P value is for the Q statistic.
[c] The study by Süoglu et al. [19] was excluded because it used endoscopic biopsy.
[d] The study by Süoglu et al. [19] was excluded because it was a case-control study.
[e] The random-effects and fixed-effects summary estimates were identical because the χ^2 value was less than the number of degrees of freedom.
[f] Study quality was judged on the basis of the Newcastle-Ottawa scale [12].

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Childhood asthma	Dogaru, 2014 American journal of Epidemiology Systematic review and meta -analysis[4]	- To identify and summarize all publications on BF and the risk of asthma in children from the general population - To use stratified analyses and meta regressions to explore potential sources of heterogeneity	*Inclusion criteria* - Fully reported original studies (CH, CC and CS studies) - Studies performed in the general population - Studies that analysed as outcomes: asthma diagnosis from medical reports or physicians; parental reports of current wheezing, parental reports of treatment for asthma or wheezing; parental reports of doctor diagnosis of asthma and wheezing with or without bronchial hyper responsiveness *Exclusion criteria* - Duplicate reports - Studies in the form of conference proceedings and abstracts - Studies not published in English - Studies performed in special populations like children at risk, or those performed only in children with diagnosed asthma/wheeze that analysed only the association between BF and asthma severity - Studies that did not differentiate between asthma/wheezing conditions and other respiratory or atopic conditions - Studies that analysed only “wheeze ever” as an outcome	Studies published between 1983-2012 *Number of hits in original search* - PubMed and Embase: n= 1,464 - Reference check: n= 18 *Number of included articles* - Studies included in systematic review: n=117 - Studies included in meta-analysis: n=113 *Designs of the included articles* - CH studies: n=57 (unclear whether prospective or retrospective) - CC studies : n=13 - CS studies : n=47	Children with asthma Western (countries from Europe, North America and South America, as well as Australia and New Zealand) and non-western (east Asia, middle east, south Asia and Africa) populations. n=89 studies from western regions and n=28 from non-western regions	*Assessment* - NR - Age at assessment of BF ranged between 0 (during BF in28 studies) till >2 year (after second year in 63 studies) *Definition* NR *Stringent categorization* 3 cut offs for each type of BF: ever vs, never; ≥3-4 months < 3-4 months and ≥6 months vs < 6 months *Flexible categorization* More vs. less BF: priority to highest cut-offs in article, EBF and school-aged subjects

Health Outcome assessment and definition	Results	Confounders	Remarks, limitations
Assessment Ascertained through medical reports and parental reports *Definition* - Asthma ever: Lifelong reports of asthma diagnosis and/or use of asthma/wheeze treatment and /or wheeze accompanied by	*Stringent categorization* *(E)BF and outcomes grouped together: asthma ever, recent asthma and recent wheezing illness* - 0-2 yrs: Median SOR* $_{\text{BF any vs. never}}$ (range) = 0.61 (0.59-0.69) (n=9) - 3-6 yrs: Median SOR $_{\text{BF any vs. never}}$ (range) = 0.79 (0.57-0.89) (n=8) - ≥7 yrs: Median SOR $_{\text{BF any vs. never}}$ (range) = 0.94 (0.86-1.02) (n=9) - 0-2 yrs: Median SOR $_{\text{EBF any vs. never}}$ (range) = 0.67 (0.62-0.69) (n=6) - 3-6 yrs: Median SOR $_{\text{EBF any vs. never}}$ (range) = 0.80 (0.51-0.83) (n=5) - ≥7 yrs: Median SOR $_{\text{EBF any vs. never}}$ (range) = 0.73 (0.65-0.84) (n=3) Web table 2 shows results in detail for BF durations and the 3 outcomes	40/117 studies did not adjust for confounders, the others included up to 24 confounders in their analyses. Only 23/117 studies (20%) adjusted for 3 or more essential confounders. *Adjustments*: - n=31 smoking exposure during pregnancy - n=10 gestational age - n=19 birth weight	- Quality score was based on 1) whether a study reported at least 3 of 7 important potential confounders and 2) whether it satisfied at least 4 of 7 of the selected quality standards suggested by Kramer et al., 1988 - In all analyses, high levels of heterogeneity was found, except for the analyses on ”asthma ever” and “recent asthma” in studies analysing the outcome in children 0-2 years of age and in studies classified as high quality *Limitations(predefined quality criteria)* - Exclusiveness of BF was not well defined - Not reported whether assessment of exposure

[4] Eleven of the included articles in this review were included in the report of RIVM (2007). One of the included articles in this review was included in the review of Kramer (2012). One of the included articles in this review was included in both the review of Hörnell (2013) and Waidyatillake (2013). One of the included articles in this review was included in the review of Waidyatillake (2013). Six of the included articles in this review were included in the review of Hörnell (2013).

<table>
<tr>
<td>bronchial hyper reactivity. From those the ones that reported the condition in the past 12 months were analysed separately as recent asthma.
- Recent wheezing illness: combined recent asthma and recent wheezing (single or multiple episodes in the past 12 months)

Age Categories at outcome assessment were:
0-2 years
3-6 years
≥ 7 years</td>
<td>Flexible categorization
BF and asthma ever, recent asthma and recent wheezing illness (see web table 4)
- Asthma ever: SOR _{BF more vs. less} (95% CI) = 0.79 (0.74-0.84) (n=75)
- Recent asthma: SOR _{BF more vs. less} (95% CI) = 0.76 (0.67-0.86) (n=46)
- Recent wheezing illness: SOR _{BF more vs. less} (95% CI) = 0.81 (0.76-0.87) (n=94)
- SORs (95% CI) by age:
<table>
<tr><th>By age</th><th>Asthma ever</th><th>Recent asthma</th><th>Recent wheezing illness</th></tr>
<tr><td>0-2 years</td><td>0.63 (0.57,0.69)</td><td>0.63 (0.57,0.69)</td><td>0.70 (0.65,0.76)</td></tr>
<tr><td>3-6 years</td><td>0.77 (0.67,0.87)</td><td>0.75 (0.63,0.90)</td><td>0.81 (0.72,0.89)</td></tr>
<tr><td>≥7 years</td><td>0.83 (0.77,0.89)</td><td>0.81 (0.68,0.96)</td><td>0.88 (0.79,0.97)</td></tr>
</table>
Stratified results (flexible categorization)
- SORs (95% CI) stratified for non-western and western countries (Europe, North- and South-America or Australia/New Zealand)
<table>
<tr><th></th><th>Asthma ever</th><th>Recent asthma</th><th>Recent wheezing illness</th></tr>
<tr><td>non-western</td><td>0.72 (0.52,0.99)</td><td>0.72 (0.52,0.99)</td><td>0.75 (0.62,0.91)</td></tr>
<tr><td>western</td><td>0.80 (0.74,0.85)</td><td>0.78 (0.71,0.85)</td><td>0.84 (0.79,0.88)</td></tr>
</table>
- For results stratified for study design, study quality and study age see web table 4

Meta-regression analysis
- Significant effect for age in recent wheezing illness: ratio of ORs _{age ≥7 vs. 0-2 years} (95% CI) = 1.30 (1.09-1.56; P = 0.005); similar, but non-significant ratios of ORs observed for asthma ever and recent asthma
- Other meta-regression analyses for cohort study, Western country, BF definition, BF cut-off, quality score, study after 1990 and analysed outcome were all not significant, see table 3</td>
<td>- n=15 ethnicity
- n= 21 SES
- n=33 family education
- n=15 did not adjust for family history of asthma or allergy</td>
<td>and outcome were blind

Other Limitations
- Not reported about how data on BF were assessed.
- Observational studies included, which are prone to bias
- Publication bias possible, but authors state that the exclusion of conference abstracts and non-English articles did not alter the main results and interoperations.
- 28 of 117 included articles were form non-Western regions.</td>
</tr>
<tr><td colspan="4">UK: United Kingdom. *the median and range of SORs resulted from meta-analysis</td></tr>
</table>

Dogaru, 2014

Web Table 1. Results of meta-analyses [OR (95% CI)] performed in each of the 45 groups of studies, determined by age, outcome, definition of breastfeeding and breastfeeding stringent categorization

		Asthma ever				**Recent asthma**				**Recent wheezing illness**			
		any duration		*exclusive duration*		*any duration*		*exclusive duration*		*any duration*		*exclusive duration*	
Age	BF cut off	pooled OR (CI)	N[1]	pooled OR (CI)	N	pooled OR	N	pooled OR (CI)	N	pooled OR (CI)		pooled OR (CI)	
0-2 years	ever vs. never	0.65 (0.51,0.82)	5	*N/A*		0.65 (0.51,0.82)	5	*N/A*		0.69 (0.57,0.84)	9	*N/A*	
	<3 vs. ≥3mo	0.59 (0.50,0.70)	5	0.62 (0.51,0.74)	6	0.59 (0.50,0.70)	5	0.62 (0.51,0.74)	6	0.61 (0.54,0.69)	7	0.64 (0.55,0.75)	10
	<6 vs. ≥6mo	0.61 (0.50,0.74)	4	0.69 (0.58,0.81)	3	0.61 (0.50,0.74)	4	0.69 (0.58,0.81)	3	0.61 (0.47,0.78)	6	0.69 (0.58,0.81)	3
3-6 years	ever vs. never	0.79 (0.68,0.91)	12	*N/A*		0.86 (0.65,1.13)	5	*N/A*		0.89 (0.73,1.07)	13	*N/A*	
	<3 vs. ≥3mo	0.84 (0.76,0.92)	5	0.81 (0.59,1.11)	12	0.79 (0.70,0.88)	3	0.83 (0.56,1.23)	6	0.75 (0.71,0.80)	6	0.80 (0.69,0.93)	12
	<6 vs. ≥6mo	0.57 (0.38,0.86)	2	0.51 (0.24,1.08)	2	*dropped*[2]	1	*dropped*[2]	1	0.73 (0.59,0.89)	4	0.73 (0.56,0.96)	2
≥7 years	ever vs. never	0.79 (0.68,0.91)	25	N/A		0.96 (0.84,1.10)	13	*N/A*		0.95 (0.87,1.04)	24	*N/A*	
	<3 vs. ≥3mo	0.84 (0.76,0.92)	11	0.73 (0.39,1.36)	6	0.87 (0.73,1.04)	9	0.65 (0.34,1.26)	5	0.92 (0.82,1.03)	12	0.84 (0.57,1.24)	10
	<6 vs. ≥6mo	0.57 (0.38,0.86)	7	*dropped*[2]	0	0.96 (0.86,1.08)	6	*dropped*[2]	0	1.02 (0.96,1.07)	10	*dropped*[2]	1

Note: Each cell represents the results (pooled odds-ratios with CI) of a meta-analysis performed in a group defined by the respective breastfeeding type, breastfeeding cut-off, outcome and age of outcome assessment.
BF=breastfeeding; **N**=number of studies meta-analysed in that particular group; **OR**=odds-ratio; **mo**=months;
[1]N/A: The groups "duration of exclusive breastfeeding, ever versus never" were not considered, as they do not make sense conceptually. If a study reported analyses using these groups, we relocated them to "duration of any breastfeeding, ever versus never".
[2]dropped: the analysis was dropped due to insufficient number of studies in that particular group (less than 2)

Dogaru, 2014

Web Table 4. Results (pooled odds-ratios) of meta-analyses performed in all studies and stratified by age, study design, country and study quality

	Asthma[a] ever			**Recent asthma[a]**			**Recent wheezing illness**		
	pooled ORs (CI)	*I^2 (p-value)*	*N*	*pooled ORs (CI)*	*I^2 (p-value)*	*N*	*pooled ORs (CI)*	*I^2 (p-value)*	*N*
All studies	**0.79 (0.74,0.84)**	*71.37 (<0.001)*	**75**	**0.76 (0.67,0.86)**	*91.58 (<0.001)*	**46**	**0.81 (0.76,0.87)**	*86.58 (<0.001)*	**94**
By age									
0-2 years	0.63 (0.57,0.69)	*0.00 (0.846)*	14	0.63 (0.57,0.69)	*0.00 (0.846)*	14	0.70 (0.65,0.76)	*64.25 (<0.001)*	28
3-6 years	0.77 (0.67,0.87)	*67.44 (<0.001)*	27	0.75 (0.63,0.90)	*66.70 (0.001)*	12	0.81 (0.72,0.89)	*77.40 (<0.001)*	28
≥7 years	0.83 (0.77,0.89)	*74.20 (<0.001)*	40	0.81 (0.68,0.96)	*94.96 (<0.001)*	25	0.88 (0.79,0.97)	*90.55 (<0.001)*	53
By study design									
non-cohort	0.75 (0.67,0.83)	*74.56 (<0.001)*	36	0.70 (0.55,0.90)	*95.58 (<0.001)*	21	0.83 (0.74,0.92)	*90.70 (<0.001)*	50
cohorts	0.82 (0.76,0.89)	*68.51 (<0.001)*	39	0.79 (0.72,0.88)	*68.34 (<0.001)*	25	0.79 (0.73,0.85)	*73.47 (<0.001)*	44
By country[b]									
non-western	0.72 (0.52,0.99)	*97.05 (<0.001)*	14	0.72 (0.52,0.99)	*97.05 (<0.001)*	14	0.75 (0.62,0.91)	*94.78 (<0.001)*	24
western	0.80 (0.74,0.85)	*65.89 (<0.001)*	58	0.78 (0.71,0.85)	*65.56 (<0.001)*	32	0.84 (0.79,0.88)	*71.78 (<0.001)*	70
By study quality									
low	0.80 (0.74,0.87)	*73.59 (<0.001)*	42	0.74 (0.61,0.89)	*94.78 (<0.001)*	24	0.80 (0.72,0.89)	*90.28 (<0.001)*	54
medium	0.76 (0.68,0.86)	*71.88 (<0.001)*	26	0.79 (0.68,0.92)	*76.72 (<0.001)*	18	0.81 (0.72,0.90)	*73.19 (<0.001)*	26
high	0.81 (0.61,1.06)	*48.38 (0.071)*	7	0.68 (0.55,0.84)	*0.00 (0.436)*	4	0.85 (0.77,0.95)	*72.09 (<0.001)*	14
By study age[c]									
before 1990	0.92 (0.84,1.01)	*68.38 (<0.001)*	22	0.86 (0.74,1.00)	*76.32 (<0.001)*	11	0.86 (0.78,0.95)	*69.20 (<0.001)*	24
after 1990	0.73 (0.67,0.79)	*71.24 (<0.001)*	53	0.72 (0.61,0.85)	*92.77 (<0.001)*	35	0.80 (0.74,0.87)	*88.41 (<0.001)*	70

[a]asthma was defined as any of the following factors, alone or in combination, with or without accompanying wheeze: reported asthma diagnosis (parent reports or medical records), use of asthma/wheeze treatment and bronchial hyper-reactivity; the outcomes analysed were recent asthma (last 12 months) asthma ever (life-long)

[b]country from Europe, North- and South-America or Australia/New Zealand3[2] quality score (QC): one point is assigned for adjusting for ≥3 essential confounders (EC: birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socio-economic status and exposure to tobacco smoke pre- and post-partum) and one point for meeting >3 Kramer quality criteria (KC: nonreliance on prolonged BF recall; sufficient duration of BF; sufficient exclusivity of BF; strict diagnostic criteria; adjustment for essential confounders; assessment of dose-effect; assessment o children at high risk)

[c]studies were classified based on the year the study started (for longitudinal studies) or was performed (for cross-sectional studies and case-control studies) , NOT the publication year.

Dogaru, 2014

Table 3. Results of Meta-Regression Performed Using "More versus Less Breastfeeding," 1983–2012[a]

Explanatory Variable	Asthma Ever (n = 75)			Recent Asthma (n = 46)			Recent Wheezing Illness (n = 94)		
	Ratio of ORs[b]	95% CI	P Value	Ratio of ORs[b]	95% CI	P Value	Ratio of ORs[b]	95% CI	P Value
Cohort study	1.031	0.837, 1.271	0.770	1.117	0.803, 1.553	0.500	0.917	0.776, 1.083	0.301
Western country[c]	0.924	0.731, 1.167	0.500	0.976	0.677, 1.407	0.895	1.185	0.980, 1.431	0.079
Age, years[d]									
0–2	1.00	Referent		1.00	Referent		1.00	Referent	
3–6	1.131	0.861, 1.486	0.372	1.271	0.866, 1.866	0.213	1.120	0.907, 1.383	0.288
≥7	1.257	0.972, 1.626	0.080	1.321	0.978, 1.786	0.069	1.300	1.085, 1.558	0.005
Breastfeeding definition[e]									
Any duration	1.00	Referent		1.00	Referent		1.00	Referent	
Exclusive	1.029	0.841, 1.259	0.779	1.009	0.756, 1.347	0.949	0.985	0.815, 1.190	0.874
Breastfeeding cut-off[f]									
Ever vs. never	1.00	Referent		1.00	Referent		1.00	Referent	
≥3–4 vs. <3–4 months	1.060	0.853, 1.318	0.594	0.873	0.617, 1.235	0.431	0.938	0.764, 1.151	0.534
≥6 vs. <6 months	0.985	0.767, 1.265	0.902	0.998	0.703, 1.418	0.993	0.962	0.784, 1.180	0.708
Quality score[g]	0.999	0.865, 1.154	0.988	1.082	0.846, 1.383	0.520	1.055	0.954, 1.167	0.295
Study after 1990	0.764	0.625, 0.934	0.009	0.841	0.602, 1.175	0.520	0.948	0.799, 1.125	0.538
Outcome analyzed									
Wheeze	NA			NA			1.00	Referent	
Asthma	NA			NA			0.907	0.791, 1.041	0.162
Intercept	0.798	0.546, 1.166	0.239	0.680	0.422, 1.096	0.110	0.687	0.506, 0.932	0.016

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

[a] Asthma was defined as a parent report of doctor diagnosis, use of asthma medication, wheeze accompanied by bronchial hyperreactivity, and/or data retrieved from medical records reported at any time in the past ("asthma ever"). Of those, we categorized as "recent asthma" the ones reported in the last 12 months. "Recent wheezing illness" included studies analyzing "recent asthma" and studies analyzing a single or multiple episodes of wheezing reported in the last 12 months.

[b] The meta-regression coefficients are to be interpreted as "ratios of odds ratios" (i.e., the relative change in the pooled odds ratios when the explanatory variable (study characteristic) is different by 1 unit, holding everything else constant). For example, the 1.257 coefficient for school age in the meta-regression for "asthma ever" means that the studies performed at school age yield a pooled odds ratio that is 25.7% larger than studies performed in children 0–2 years of age. In this case, it means that the protective effect of breastfeeding in children 7 or more years of age is lower than that in children 0–2 years of age (the larger OR is closer to 1, representing no effect).

[c] Countries from Europe, North America, and South America, as well as Australia or New Zealand.

[d] Age when the outcome was assessed.

[e] Whether the analysis used duration of any breastfeeding or duration of exclusive breastfeeding.

[f] The stringent categorization of breastfeeding used in analysis (ever vs. never; ≥3–4 vs. <3–4 months; or ≥6 vs. <6 months).

[g] Quality score: 1 point was assigned for adjustment for 3 or more essential confounders (birth weight, gestational age, ethnicity, family history of asthma or allergy, family education, socioeconomic status, and exposure to tobacco smoke pre- or postpartum) and 1 point for meeting more than 3 Kramer quality criteria (nonreliance on prolonged breastfeeding recall, sufficient duration of breastfeeding, sufficient exclusivity of breastfeeding, strict diagnostic criteria, adjustment for essential confounders, assessment of dose effect, and assessment of children with family history of atopy).

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Sudden infant death syndrome (SIDS)	Hauck, 2011 Pediatrics Systematic review and meta-analysis[5]	To perform a meta-analysis to measure the association between BF and SIDS	*Inclusion criteria* - Human studies - No language restriction - Meet all 6 eligibility criteria: 1) Appropriate definition of SIDS 2) Autopsies performed in >98% of cases 3) Adequate description of SIDS ascertainment 4) Matched control subjects 5) Adequate description of control selection 6) Inclusion of sufficient data to calculate ORs and 95% CIs or inclusion of the actual ORs and CIs	January 1996-December 2009 *Number of hits in original search* - Total: n=288 - Ovid Medline: n=265 - Reference lists: n=23 *Number of included articles* Total: n=18, all CC studies	SIDS cases and controls Included studies were from: 4 UK, 3 USA, 3 Tasmania, 2 Germany, 2 New Zealand, 1 Denmark, 1 Denmark, Norway and Sweden, 1 Scotland, 1 Canada	*Assessment* BF was mostly assessed through interviews (n=14). For 4 studies it was only reported that they did not use interview. Time from infant's death or identification of control to time of interview ranged from immediately to 6 weeks (data available for n=9) *Definition* - Any BF: BF of any amount (partial or exclusive) or duration, including BF at discharge from hospital - BF ≥2 months: BF of any amount at the age of 2 months or older - EBF: exclusive BF (i.e., no formula supplementation) for any duration

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment Autopsy Age was not reported *Definition* Determined as described above	*Association BF and SIDS* - SOR $_{\text{BF any vs. none}}$ (95% CI) = 0.40 (0.35-0.44; I^2 = 71%) (n=18) - aSOR $_{\text{BF any vs. none}}$ (95% CI) = 0.55 (0.44-0.69; I^2 = 40%) (n=7) - SOR$_{\geq 2 \text{ mo vs. none}}$ (95% CI) = 0.38 (0.27-0.54; I^2 = 78%) (n=3) - aSOR$_{\geq 2 \text{ mo vs. none}}$ (95% CI); not possible (n=2) - SOR $_{\text{EBF vs. no BF}}$ (95% CI) = 0.27 (0.24-0.31; I^2 = 87%) (n=8) - aSOR $_{\text{EBF vs. no BF}}$; not possible (n=0)	The univariable and multivariable ORs were extracted from each study. Multivariable ORs were presented in 8 studies: adjustment varied between studies.	Five studies did not meet all 6 eligibility criteria and were excluded: failed criteria were listed per excluded study *Limitations (predefined quality criteria)* - Age of BF assessment was not reported, only time after death - Not reported whether assessment of exposure and outcome were blind - No outcome definition was reported - Ten included studies presented data that were not adjusted for any potential confounding variables *Other limitations* - Only a small number of studies presented data on BF duration, and when presented, there were different ways in which duration was defined, which made it difficult to pool the results
SIDS: Sudden infant death syndrome; USA: United States of America.			

[5] One of the included articles in this review was included in the report of RIVM (2007).

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Coeliac disease	Henriksson, 2013 Evidence Based Medicine Systematic review[6]	To update the evidence published in a previous systematic review and meta-analysis that compared the effect of BF on risk of CD	*Inclusion criteria* - English written - Compared risk of CD in people who were BF with risk in those who were not BF or compared risk of CD according to duration of BF - Used histological criteria for diagnosing CD - Controlled for potential confounders by matching in the study design or used risk adjustment in the analysis - Provided sufficient data to allow the reconstruction of 2 x 2 tables to determine RR or OR with 95% CI	June 2004-April 2011 PUBMED, EMBASE and Cinahl were systematically searched *Number of hits in original search* n=164 *Number of included studies* n=4 (see table 2 below) *Designs of included studies* Observational studies: n=3 CC studies: n=1 See table 2 below for the methodology of the included studies.	Patients with CD with mean/median age of 14 months – 8.4 years (see table 2 below). Two studies were from the USA, one from Serbia and one from Spain.	*Assessment* Medical records, interview and questionnaire were used to assess BF exposure *Definition* NR

Health Outcome assessment and definition	Results	Confounders	Remarks, limitations
Assessment Studies were included if they used histological criteria for diagnosing CD *Definition* NR Age *at diagnosis* Not clear	*Duration of BF and later onset of CD (n=3)* - Significant association between longer duration of BF and later onset of CD: 2 studies - No association: 1 study *BF during gluten introduction (n=3)* - BF during gluten introduction significantly delayed the onset of CD (n=3) - Timing of the introduction of gluten into the infant diet is significantly associated with the appearance of CD (n=1)	Studies were included if they controlled for potential confounders by matching in the study design or used risk adjustment in the analysis These factors included: age, sex, ethnicity and infant diet choices	*Limitations (predefined quality criteria)* - No information about the time of assessing BF data was reported - No specific definition of outcome (what histological criteria) was reported - Not reported whether assessment of outcomes was after assessment of exposure. *Other Limitations* The finding should be interpreted with caution: - Studies were of moderate or high risk of bias - Recall bias was possible in one article - Using interviews and questionnaires, as done in most of these studies, misclassification of infant feeding is likely to occur, both of duration of BF and age of introduction of gluten - None of the included studies accounted for socioeconomic status to be a confounding factor although this is a crucial factor for diet choice - The published studies provided only data for narrative presentation, so authors could not conduct a meta-analysis
CD: Coeliac Disease.			

[6] One of the included articles in this review was included in the report of RIVM (2007). One of the included articles in this review was included in the review of Szajewska (2012).

Henriksson, 2013

Table 2 Methodology of included studies (summary)

Reference (country)	Case selection	Control selection	Exposure measurement	Confounding factors considered	Sample size	Age	Methodological quality
Radlovic *et al* (Serbia)	Children with coeliac disease (CD), UniChildrens hospital, Belgrade	Within cohort	Retrospectively analysed medical records	Age, sex	89 cases	7–24 months, median 14 months	B
D'Amico *et al* (the USA)	Children under age 20 with CD, 30 different states, USA	Within cohort	Questionnaire	Age, sex	141 cases	8.4 years	C
Norris *et al* (the USA)	Children with CD, Denver metropolitan area	All CD-negative children in cohort	Interview, questionnaire	Ethnicity, infant diet choices	51 cases, 1509 controls	4.7 years	B
Roman* (Spain)	All new CD-cases 2006-06–2007-05, 39 hospitals, Spain	Children paired for age and sex	Questionnaire	–	993 cases, 744 controls	3.7 years	Not assessed

*A conference report whose abstract was published but not yet the whole study.
A, low risk of bias; B, moderate risk of bias; C, high risk of bias.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Growth, overweight, obesity, diabetes type1 and type 2, infections, cancer, atopic disease, asthma, neurological function and IQ, celiac disease, IBD	Hörnell, 2014 Food & Nutrition Research Systematic review[7]	To review recent scientific data valid in a Nordic setting on the short- and long-term health effects of BF (duration of both any and EBF) and introduction of foods other than breast milk in order to assess the validity of the current Nordic recommendations. A second aim was to provide a background for the planned update on the chapter on BF.	*Inclusion criteria* - English or Nordic language - Study population relevant to the Nordic countries *Exclusion criteria* - Conducted in developing countries - Published before the search dates of the latest systematic review (SLR) or meta-analysis (MA) or included in it. - Preterm babies - Babies non-healthy at inclusion - Non-human studies - No outcome of interest - Exposure not relevant - Only applicable for CH: BF only given as ever-never and BF data collected retrospectively after >3 y of age - Health outcome on maternal health - Commentaries, opinions, letters to the editors or overviews - Graded C in the quality assessment, except 2 SLR with cancer as outcome	January 2000-June 2011 Complementary search covering the period between the first search until the end of December. *Number of hits in original search* 3037 (1,026 abstracts were classified as overviews/reviews but did not include the description SLR of MA and were therefore not included) *Number of included articles* - Total: n=56 - SLR/MA: n=12 - prospective CH: n=44, six studies originating from PROBIT study	Healthy full-term children by healthy mothers	*Assessment* In CH studies: - Daily records - FFQ - Health records - Asked during visits - (telephone) interview In prospective cohorts, BF data had to be recalled ≤3 years after birth. For SLR, recall periods could be longer than 3 years. *Definition* Any BF and EBF

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Assessment Varies per health outcome and between studies Age at diagnosis NR *Definition* Varied between studies. A.o.: - Later overweight and obesity - Diabetes type 1 and diabetes type 2 - Acute otitis media, gastrointestinal infection, lower respiratory infection - Acute lymphocytic leukemia, acute myelogenous leukemia, Hodgkin disease, neuroblastoma, breast cancer, prostate	*EBF and growth in infancy (n=7)* 1/1 SLR no association between EBF and growth 3/6 CH studies found no association between BF, BFD, EBF and growth 1/6 CH study found association between EBF and slower growth 1/6 CH study found that smaller size was strongly associated with increased risks of subsequent weaning and discontinuing EBF 1/6 CH study found that those EBF <4 mo. showed higher weight-for-length z-scores at 6-7 months compared to those EBF for ≥4 mo - Growth in infancy varied only a little between those EBF for 4 mo or 6 mo. *EBF and risk of overweight/obesity (n=4)* 2/2 SLRs found a lower risk of overweight/obesity with longer duration of EBF 1/1 CH study found no consistent association between BFD/EBF and overweight/obesity 1/1 CH study found BMI triceps skinfold thickness and hip circumferences at 6.5y were higher among EBF for 6 mo. compared to EBF for 3 mo.	Adjustments varied between included studies.	- Quality assessed performed using the QAT. C-graded studies were excluded, except 2 SLRs on cancer as the main outcome was low. - Complementary search used to evaluate the conclusion of the SLR, as supporting or not. - Abstract screening according to the guide for conducting SLRs for the 5th edition of the NNR - Some SLR used introduction of solid foods as exposure. These were not presented in the table below. *Limitations (predefined quality*

[7] Four of the included articles in this review were included in the report of RIVM (2007). Three of the included articles in this review were included in the review of Lefebre (2014). Six of the included articles in this review were included in the review of Kramer (2012). Six of the included articles in this review were included in the review of Dogaru (2014). One of the included articles in this review was included in the review of Waidyatillake (2013) and Dogaru (2014).

cancer, colorectal cancer, gastric cancer - (atopic) eczema, atopy, allergy, any sensitization, food allergy, allergic rhinitis, pollen allergy, animal dander allergy, atopic dermatitis - Asthma and wheezing - Development in childhood - Celiac disease - UC and CD	- Probable evidence that EBF >4 mo associated with slower weight gain during later infancy compared with EBF<4 mo. *BF duration and risk of overweight/obesity (n=10)* 1/1 SLR found that BF may be a protective factor against overweight and obesity 8/9 CH studies show lower risk of overweight/obesity with longer BFD 1/9 CH study found no significant association between BF intervention and growth indices - Convincing evidence that longer duration of EBF or any BF is associated with a protective effect against overweight and obesity in childhood and adolescence. - Limited-suggestive evidence that BF is associated with lower risk of overweight/obesity in adulthood. *BF and diabetes mellitus type 1 and type 2 (n=2)* 1/1 SLR found that longer duration of BF may contribute to risk reduction in the development of diabetes mellitus type 1 and type 2. 1/1 SLR found that BF may contribute to risk reduction in the development of diabetes mellitus type 2. 1/1 CH study found no effect of BF on risk of islet cell autoimmunity in children - Probable evidence that any BF had a protective effect against diabetes mellitus type 1 and type 2. - Limited but suggestive evidence that BF duration is associated with protective effect against diabetes mellitus type 1 and type 2. *BF and acute otitis media, gastrointestinal infection, lower respiratory infection (n=7)* 2/3 SLRs found a protective dose/duration-response effect on gastrointestinal or respiratory tract infections. 1 SLR found conflicting results for GI and protective effect of BF for hospitalization due to LRTI 1/2 SLR found that BF was associated with significant reduction in AOM 1/2 SLR found varying results of the effect of BF on AOM 3/3 CH studies found a protective dose/duration-response effect of BF or EBF on gastrointestinal infections 3/3 CH studies found a protective effect of dose/duration-response of BF or EBF on respiratory tract infections 2/2 CH study found no significant association between BF and AOM - Convincing evidence that BF protects infants in industrialized countries against overall infections, AOM, and gastrointestinal and respiratory tract infections. *BF and cancer (n=3)* 2/2 SLR found an association between a history of BFD ≥6 mo. and a reduction in the risk of ALL. 1/1 SLR found a protective effect of BF on AML. 1/1 SLR found that BF was associated with lower risk for Hodgkin disease and neuroblastoma 1/1 SLR found that BF was not associated with prostate, colorectal, gastric, smoking-related cancers, nor overall breast cancer. BF women had a reduced risk of premenopausal breast cancer - Limited but suggestive evidence that BF reduced the risk of childhood leukemia and possible other childhood cancers. The effect on childhood leukemia seems larger with longer BFD (>6 mo.) *BF and atopic disease (n=9)* 1/2 SLRs found a protective effect of EBF >3 mo. on the risk for atopic disease 1/2 SLRs found no effect of EBF >3 mo. on the risk for atopic disease 6/7 CH studies found no protective effect of EBF on the development of atopic disease 1/7 CH study found that EBF increased the risk of eczema after adjustment for demographics, filaggrin variants, parents' eczema and pets at home - Very limited evidence and no conclusion can be drawn for any preventive effects of BF on atopic		*criteria)* - SLRs used in this SLR could include studies with recall periods longer than 3 years. - Definitions of BF varied in the included studies. Often poor definition of EBF. - Included CHs had to be prospective, so exposure is assessed before health outcome. SLRs used in this SLR could include CC studies or retrospective CH. Blinding NR. - Not always corrected for confounding factors in the primary studies. *Other limitations* - Methodology used to assess BF not always clear. - Not clear how many studies are found by the complementary search. -1 SLR on IBD included in RIVM report (2007) *Funding* Work was supported by the Nordic Council of Ministers

	diseases in children. *BF and asthma (n=12)* 1/2 SLR found that BF (>3 mo.) was associated with reduced risk of asthma compared to no BF 1/2 SLR found no association between BF and risk of asthma 2/10 CH studies found no association between BF and later risk of allergic disease. 1/10 CH study found an u-shaped association between BF and wheeze, asthma or lung function 6/10 CH studies found association between BF and reduced risk of asthmatic symptoms 1/10 CH study found no reduction in risk of asthma when comparing BF intervention with control areas - Limited evidence and no conclusions can be drawn for the association between BF and asthma/wheezing. *Complementary search (n=3):* did not change the conclusion as they had differing results *BF and IQ and neurological development (n=7)* 1/1 SLR found little or no evidence for positive association between BF and later cognitive performance of the child. 4/6 CH studies found positive association between BF and increased IQ or developmental scores. 2 CH studies found stepwise increase with longer duration of BF with highest IQ points or developmental scores with BF >6 mo. Positive results were found in the PROBIT-study. 2/6 CH found no association between EBF or BF and increased IQ or developmental scores - Probable evidence that BF is beneficial for IQ and development scores of children, with increase benefit with increasing duration. *Complementary search (n=1):* Supported the conclusion that BF is beneficial for neurodevelopment. *BF and celiac disease (n=1)* 1/1 SLR found negative association between BF and celiac disease. The risk was especially reduced if the child was still BF when gluten was introduced. - Probable evidence for BF as protective factor for celiac disease, if gluten is introduced in small amounts while still BF. Unclear whether the protection only delays the onset of celiac disease or if it provides permanent protection. *BF and IBD (n=1)* 1/1 SLR found that BF had a statistically significant protective role against ulcerative colitis and an even greater role against Crohn's disease - Probable evidence that BF provides protection against IBD.		
ALL: Acute lymphocytic leukemia; AML: Acute myelogneous leukemia; AOM: Acute otitis media; BMI: Body mass index; CD: Crohn's disease; FFQ: Food frequency questionnaire; GI: Gastrointestinal infection; IBD: Inflammatory bowel disease; IQ: Intelligence quotient; LRI: Lower respiratory infection; MA: Meta-analyses; NNR: Nordic Nutrition Recommendations; PROBIT: Promotion of Breastfeeding Intervention Trial; QAT: Quality Assessment Tools; UC: Ulcerative colitis.			

Overview included SLR/MA

Author, year Design	Countries	Number and type of included studies Study population	Exposures	Outcomes	Effect/association	Comments
Akobeng, 2006 SLR + meta-analysis	Germany, Italy (2), Sweden (3)	6 included; 6 CC (retrospective) Total 1131 cases (varying between	BF; various definitions and therefore not combined	Celiac disease	Being BF at introduction of gluten decreased the risk of getting celiac disease (pooled OR 0.48, 95% CI 0.40-0.59) Not clear whether BF delays onset of CD or provides permanent protection	Characteristics of excluded papers not given, conflict of interest only stated for the authors not the included studies.

Author, year Design	Countries	Number and type of included studies Study population	Exposures	Outcomes	Effect/association	Comments
		7-491) + 3493 controls (varying between 73-1949				Strengths: Included only studies based on histologically confirmed coeliac disease. Various definitions of breastfeeding were used in the primary studies and exact timing and amount of gluten consumed was not given
Dujits, 2009 SLR	Industrialized countries (defined by the World Bank as *High income*)	21 included; 4 CC, 16 follow-up, 1 RCT GI: 40 518 (8 out of 21 studies about gastrointestinal infection) LRI: 60 377 (16 out of 21 studies about LRI)	BF; various definitions	Overall infections, gastrointestinal or respiratory tract infections in infancy. The included studies varies between 0-30 days and 0-24 months.	GI: 6 out of 8 studies suggested BF had a protective effect, and the size varied according to duration and exclusiveness of BF. LRI: 13 out of 16 studies concluded BF had a protective effect Five studies combined BFD and EBF. All those studies observed a protective dose/duration-response effect on gastrointestinal or respiratory tract infections.	Discusses publication bias, but no calculation. No description of the methodology used to assess dietary intake.
Ip, 2009 SLR + meta-analysis	Developed countries (varying nr for different outcomes)	32 primary studies on infant health outcomes, 28 SLRs or meta-analysis AOM: ca 300 – ca 15000, most a few thousands per study. GI: 6599 LRI: 3201 breastfed and 1324 non-breastfed subjects. ALL: 3266 subjects Atopy: 4 158 participants. Asthma: 8183 term infants Cognitive performance: NR Overweight: 488,731 subjects + 61 studies of which number NR T1DM: 9 447 cases and 38 957 controls	BF; Most studies did not differentiate between exclusive and partial BF. All definitions of EBF accepted, but conclusions qualified with respect to the definitions used	AOM, nonspecific gastroenteritis, severe lower respiratory tract infections, atopic dermatitis, asthma (young children), obesity, type 1 and 2 diabetes, childhood leukemia, CVD risk (serum cholesterol, blood pressure), cognitive performance	AOM: Pooled aOR of risk for AOM when comparing ever BF with never BF was 0.77 (95% CI 0.64-0.91). EBF for 3 or 6 mo compared with never BF pooled adjusted OR was 0.50 (0.36-0.70). GI: Summary crude OR for the 14 cohort studies were 0.36 (95% CI 0.32-0.41, heterogeneity, p<0.01), and for the 2 case-control studies 0.54 (0.36-0.41, heterogeneity, p=0.35). LRI: Summary RR 0.28 (95% CI 0.14-0.54) of hospitalization due to LRTI <1 y in those EBF 4 mo or more compared with FF. ALL/AML: BF ≤6 mo vs never BF: ALL OR 0.91. 95% CI 0.83-1.00), BF >6 mo vs never BF: ALL OR 0.80. 95% CI 0.71-0.91). Association between a history of BF of at least 6 months duration and a reduction in the risk of both ALL and AML Atopy: OR 0.58 (95% CI 0.41-0.92) when comparing EBF > or <3 mo in children with a family history of atopy. Asthma: BF for >=3 mo associated with reduced risk of asthma compared to not BF in children without family history (OR 0.73, 95% CI 0.59-0.92). Cognitive performance: Little or no evidence for an association between breastfeeding in infancy and cognitive performance in childhood. Overweight: A history of BF is associated with a reduced risk for obesity later in life. T1DM: Two meta-analysis of fair quality including a total of 17 CC reported OR 1.23 (95% CI 1.12-1.35)	

Author, year Design	Countries	Number and type of included studies Study population	Exposures	Outcomes	Effect/association	Comments
		T2DM in later life: 76 744 subjects			and 1.43 (1.15-1.77) respectively for the risk of T1DM if BF <3 mo vs >=3 mo. 5 of 6 later published studies reported similar results. T2DM in later life: Pooled adjusted OR 0.61 (95% CI 0.44-0.85) for those BF compared with FF.	
Klement, 2004 SLR	8+ (UK, Sweden, Canada, US, Japan, Italy, Israel + "9 countries (Europe, North America and Mediterranean)"	17 included; 15 retrospective CC, 2 unknown UC: 27-713 cases and 98-713 controls/study CD: 24-1396 cases and 90-1396 controls/study	BF; various definitions	Inflammatory bowel disease (Ulcerative colitis and/or Crohn disease)	Pooled OR for Crohns disease 0.67 (95% CI 0.52-0.86) Pooled OR for ulcerative colitis 0.77 (0.61-0.96)	Most of the included studies relied on long recall for the breastfeeding data. Only two had data from infancy, but then only breastfeeding at maternity ward. However, breastfeeding was only documented as ever-never, and this kind of recall from mothers tend to be accurate. Included in RIVM report, 2006.
Kramer 2002 (updated 2009) SLR + meta-analysis	Country stated only for some studies; Belarus, Iran, Nigeria, Honduras, Finland, Austria (11 developing +11 developed countries)	2 clinical trials, 20 observational Growth: A)4388 B)3450 C)3430 D)3455 AOM: 3762 GI: 3482 LRI: 510 Wheezing: 3993 Asthma: 552	BF; EBF 6 mo vs. EBF 3-4 mo with MBF	Child health, growth and development	Growth: Infants EBF ≥6 months had no observable deficits in growth: A) Weight gain 3-8 mo: pooled WMD of -12.45 (95% CI -23.46 to -1.44) g/mo (data id heterogeneity) B) Weight gain 8-12 mo: pooled WMD was -1.82 (95% CI -16.72 to +13.08) g/mo C) Length gain 3-8 mo: pooled analysis yielded a WMD of -0.4 (95% CI -0.7 to 0.0) mm/mo D) Length gain 8-12 mo: slightly but significantly higher length gain in the EBF group (WMD +0.9 (95% CI +0.3 to +1.4)) mm/mo AOM: EBF 6 mo vs. EBF 3-4 mo with MBF afterwards: varying results GI: EBF 6 mo vs. EBF 3-4 mo with MBF afterwards: RR 0.67; 95% CI 0.46 to 0.97 LRI: EBF 6 mo vs. EBF 3-4 mo with MBF afterwards: no reduced risk (pooled RR 0.91; 95% CI 0.82 to 1.02) Wheezing in the EBF group: pooled RR 0.79 (95% CI 0.49 to 1.28) Asthma at five to six years: pooled RR was 0.91 (95% CI 0.61 to 1.36)	Included in RIVM report, 2006.
Martin RM, 2005a Cohort-study + Meta-analysis	Most studies based in Europe or North America; France (2), Austria, UK (4), US (3), N-Ireland, Germany (2),	26 included; 2 CH/nested CC, 24 CC NR	Ever or EBF vs never BF, various durations of BF, separate meta-analysis of prolonged BF > 6-8 mo vs never BF, 2 studies examined EBF vs	Childhood cancers (all cancers and specific cancers)	Lower risks associated with having been BF: ALL: 9% (95% CI 5 2–16%) Hodgkin's disease: 24% (3–40%) Neuroblastoma: 41% (22–56%). There was little evidence that BF was associated with acute nonlymphoblastic leukemia, non-Hodgkin's lymphoma, central nervous system cancers, malignant germ cell tumors, juvenile bone tumors, or other solid cancers.	No duplicate study selection and data extraction, 85 % relied on long-term recall, only 8% examined breastfeeding exclusivity and control response rates were under 80% in over half. Included in summary due to few studies with outcome

Author, year Design	Countries	Number and type of included studies Study population	Exposures	Outcomes	Effect/association	Comments
	Sweden, United Arab Emirates, Canada, New Zealand, Scotland, Russia, US/Canada/Australia, US/Canada (2), Greece, Shanghai, Italy, The Netherlands		never BF.			cancer.
Martin RM, 2005b SLR + meta-analysis	NR	14 included; 11 CC, 3 CH/nested CC studies + Boyd Orr CH	Ever or EBF vs never BF, various durations of BF, separate meta-analyses comparing any or EBF of > 6 mo with never BF were undertaken	Adult cancer (all cancers and specific cancers)	No association between BF and breast cancer (regardless of menopausal status) (RR = 0.94, 95% CI = 0.85 to 1.04). However, BF women had a reduced risk of premenopausal breast cancer (RR = 0.88, 95% CI = 0.79 to 0.98) but not of postmenopausal breast cancer (RR = 1.00, 95% CI = 0.86 to 1.16).	No duplicate study selection and data extraction. (Stated that one author extracted the data on two separate occasions to check the consistency of data extraction), infant feeding was assessed in adulthood for most studies included. Included in summary due to few studies with outcome cancer.
Monasta, 2010 SLR	Not stated in all SLR reviewed. But when done the original studies were mostly conducted in N-USA and Western Europe.	22 SLR + 58 papers in further search Varies	BF; EBF and BFD	Overweight and obesity in childhood or later in life They evaluated whether no or short BF was one of five factors associated with overweight and obesity in childhood and/or adult life.	1) OR 0.78 (95%CI:0.71-0.85); 2) OR 0.96 (95%CI:0.94-0.98); 3) OR 0.78 (95%CI:0.72-0.84); 4) range OR 0.86 (95%CI:0.81-0.91) – OR 0.93 (95CI:0.88-0.99) 5) lower BMI w/BF OR 0.04 (95%CI: (0.05) – (-0.02)); 6) OR 0.75 (95%CI:0.71-0.79).	Publication bias not assessed, some characteristics not included, methodology of dietary intake not exact
Yang 2009 SLR + meta-analysis	(probably) developed countries. Not stated.	21 studies with 27 study populations Total 34227	BF; duration at least 3 months, EBF (no other milk products, solids etc added to infants diet in first 3 mo) + never BF or BF < 3 mo	Atopic dermatitis during childhood (follow-up 1 y to 7 y)	Summary OR 0.89 (95% CI 0.76-1.04) – for the effect of EBF on the risk of AD	Discusses publication bias, but no calculation. Several characteristics of included studies reported, but not all. Characteristics of excluded papers not given

AD: Atopic dermatitis; ALL: Acute lymphocytic leukemia; AML: Acute myelogneous leukemia; AOM: Acute otitis media; aOR: Adjusted OR; BMI: Body mass index; CD: Crohn's disease; GI: Gastrointestinal infection; LRI: Lower respiratory infection; RCT: Randomized controlled trial; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; UC: Ulcerative colitis; UK: United Kingdom; US: United States; WMD: Weighted mean difference.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Weight and length gain, asthma and atopic diseases, GI, URTI and LRTI, otitis media, caries, cognitive ability	Kramer, 2012 Cochrane Database of Systematic Reviews Systematic literature review including pooled analysis[8]	1) to assess the effects on child health, growth, and development, and on maternal health, of EBF for 6 mo. vs. EBF for 3-4 mo. with MBF (introduction of complementary liquid or solid foods with continued BF) thereafter through 6 mo. 2) to assess the child and maternal health effects of prolonged (>6 mo.) EBF vs. EBF through 6 mo. and MBF thereafter	*Inclusion criteria* - Controlled clinical trials and observational studies - All languages - Studies of (or including) low birth weight infants were not excluded, provided that such infants were born at term (≥37 weeks) - Studies with internal comparison group - Comparison must be on one group of infants who received EBF for >3 mo. but <7 mo. and MBF until ≥6 mo. and another group of infants who received EBF for ≥6 mo. *Exclusion criteria* - Studies comparing EBF and MBF from birth	Original review 2000: 1966-August 2000 Update review 2007: 2000-December 2006 Current update review: January 2007-June 2011 *Used databases* - Cochrane, Medline, Embase, CINAHL, BIOSIS, African index medicus, IMEMR, LILACS - Experts in the field were contacted *Number of hits in original search* Original review 2000: n=2,668 Update review 2007: n=835 Current review: n=3,425 *Number of included articles* Total, n=10 studies (26 articles), all observational studies	Healthy infants 3 USA, 1 Sweden, 1 the Netherlands, 1 Finland, 1 Belarus, 1 Australia, 1 pooled sample of developed countries, 1 pooled sample of mid-to high-SES infants from 2 developed and 3 developing countries	*Assessment* NR Age at assessment: NR *Definition* The definitions of EBF and MBF are described per included study. - Complementary foods used in MBF included juices, formula, other milks, other liquids, or solid foods. - Although the WHO defines EBF as BF with no supplemental liquids or solid foods other than medications or vitamins, few studies strictly adhered to the WHO's definition

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment NR Age at assessment: NR *Definition* NR	*Objective 1* Tables for the following outcomes are presented below: - Weight and length gain - Asthma and atopic diseases - GI, URTI and LRTI: in addition to the table one study (data not shown) reported substantially lower aORs (vs. a never-BF group) for both URTI and LRTI in their EBF group compared with their MBF group in the first 6 mo. of life but not for mo. 7-12 - Otitis media - Death	Results in tables are unadjusted. Comments on adjusted analyses are presented under the tables	- 6/10 studies included in this review included >1 publication. In total, 26 publications were included on the 10 studies, but it is not reported whether some of these publications were on non-relevant health outcomes only - Authors also searched for articles in developing countries (n=11), but as all results were presented stratified, only the results for developed countries are presented here - Other health outcomes presented in the review were: head circumference, sleeping time, essential amino acid concentration, leg length, triceps skinfold thickness, subscapular skinfold thickness, waist circumference, hip circumference, systolic blood pressure and diastolic blood pressure, and haemoglobin, serum ferritin, lipoprotein, apoprotein and triglyceride concentration - Original review (1996-2000) was included in the RIVM report

[8] Five of the 26 publications for the 10 studies included in this review were included in the report of RIVM (2007). One of the included publications in this review was included in both the RIVM report (2007) and Dogaru (2014). Six of the publications in this review were included in the review of Hörnell (2013).

	- Caries - Cognitive ability *Objective 2* One study reported: "no differences in the overall rates of gain in weight and length" for the first year of life in infants who were EBF >6 mo. vs. those EBF <6 mo. and MBF thereafter (actual data not reported)		*Limitations (predefined quality criteria)* - Age at BF assessment was not reported - It was not reported whether exposure and outcome assessment were blind - Outcome definition was not reported - Presented results in the tables were not adjusted for confounding
GI: Gastrointestinal infection; LRTI: Lower respiratory tract infection; Mo.: Months; URTI: Upper respiratory tract infection; WHO: World Health Organization.			

Kramer, 2012

Weight and length gain

Outcome	MD (95% CI)	RR (95% CI)	Nr of studies
Monthly weight gain (g/mo.)			
- 3-8 months	-7.95 (-31.84-15.93)		4
- 6-9 months	21.11 (-44.70-86.91)		2
- 8-12 months	-1.82 (-16.72-13.08)		3
Monthly length gain (cm/mo.)			
- 3-8 months	-0.03 (-0.11-0.06)		4
- 6-9 months	-0.04 (-0.10-0.01)		2
- 8-12 months	0.09 (0.03-0.14)		3
Weight-for-age z-score			
- at 6 months	-0.09 (-0.16- -0.02)		1
- at 9 months	-0.10 (-0.18- -0.02)		1
- at 12 months	-0.09 (-0.17- -0.01)		1
Length-for-age z-score			
- at 6 months	-0.12 (-0.20- -0.04)		1
- at 9 months	-0.14 (-0.22- -0.06)		1
- at 12 months	-0.02 (-0.10- 0.06)		1
Weight-for-length z-score			
- at 6 months	0.02 (-0.07-0.11)		1
- at 9 months	0.03 (-0.06-0.12)		1
- at 12 months	-0.08 (-0.17-0.01)		1
Weight-for-age z-score < -2			
- at 6 months		0.92 (0.04-19.04)	1
- at 9 months		1.52 (0.16-14.62)	1
- at 12 months		1.15 (0.13-10.31)	1
Length-for-age z-score < -2			
- at 6 months		1.53 (0.84-2.78)	1
- at 9 months		1.46 (0.80-2.64)	1
- at 12 months		0.66 (0.23-1.87)	1
Weight-for-length z-score < -2			
- at 6 months		0.31 (0.02-5.34)	1
- at 9 months		1.14 (0.24-5.37)	1

- at 12 months		1.15 (0.13-10.31)	1
Height at 6.5 years	0.10 (-0.40-0.60)		1
BMI at 6.5 years	0.20 (0.02-0.38)		1

MD: Mean difference; RR: Risk ratio

Kramer, 2012

Asthma and atopic diseases

Outcome	RR (95% CI)	Nr of studies
Atopic eczema in first 12 months	0.65 (0.27-1.59)	2
Food allergy at year 1 (by history)	0.19 (0.08-0.48)	1
Food allergy at year 1 (by double challenge)	0.77 (0.25-2.41)	1
≥2 episodes of wheezing in first 12 months	0.79 (0.49-1.28)	2
Atopic eczema at 5-7 years	0.86 (0.47-1.58)	2
Hay fever at 5-7 years	0.80 (0.39-1.65)	2
Asthma at 5-7 years	1.02 (0.72-1.44)	3
Food allergy at 5 years	0.61 (0.12-3.19)	1
Allergy to animal dander at 5 years	0.81 (0.24-2.72)	1
Positive skin-prick test to house dust mite at 6.5 years	0.86 (0.62-1.20)	1
Positive skin-prick test to cat dander at 6.5 years	0.86 (0.60-1.24)	1
Positive skin-prick test to birch pollen at 6.5 years	0.80 (0.55-1.18)	1
Positive skin-prick test to mixed northern grasses at 6.5 years	0.71 (0.50-1.01)	1
Positive skin-prick test to Alternaria at 6.5 years	0.74 (0.47-1.17)	1
Any positive skin-prick test at 6-7 years	0.95 (0.81-1.11)	2

RR: Risk ratio

Kramer, 2012

Infections

Outcome	RR (95% CI)	Nr of studies
≥1 episodes of GI in first 12 months	0.67 (0.46-0.97)*	1
Hospitalization for GI in first 12 months	0.79 (0.42-1.49)	1
≥1 episodes of URTI in first 12 months	1.07 (0.96-1.20)	1
≥2 episodes of URTI in first 12 months	0.91 (0.82-1.02)	2
≥4 episodes of URTI in first 12 months	0.82 (0.52-1.29)	1
≥1 episodes of LRTI in first 12 months	1.07 (0.86-1.33)	1
≥2 episodes of RTI in first 12 months	0.90 (0.79-1.03)	1
Hospitalization for RTI	0.75 (0.60-0.94)**	2

GI: Gastrointestinal infection; LRTI: Lower respiratory tract infection; RR: Risk ratio; RTI: Respiratory tract infection; URTI: Upper respiratory tract infection

*Significant result was maintained after adjustment for geographic region, urban versus rural location, maternal education, and number of siblings in the household: aOR (95% CI)=0.61 (0.41-0.93); a mixed-level multivariate Poisson model was used to estimate the adjusted incidence density ratio (IDR) by age period: 0-3 mo. (when both groups received EBF) IDR (95% CI)=0.97 (0.46-2.04) and 3-6 mo. (feeding differed) IDR (95% CI)=0.35 (0.13-0.96)

**crude risk in one study became non-significant after adjustment for geographic region, urban versus rural location, maternal education and cigarette smoking, and number of siblings in the household: aOR (95% CI)=0.96 (0.71-1.30)

Kramer, 2012

Otitis media

Outcome	MD (95% CI)	RR (95% CI)	Nr of studies
N episodes of otitis media in first 12 months	-0.04 (-0.49-0.41)		1
≥1 episodes of otitis media in first 12 months		1.28 (1.04-1.57)	2
Frequent otitis media in first 12 months		0.81 (0.43-1.52)	1

MD: Mean difference; RR: Risk ratio

Kramer, 2012

Caries

Outcome	RR (95% CI)	Nr of studies
Any dental caries (decayed, missing, or filled teeth) at 6 years	0.98 (0.94-1.03)	1
Any incisor caries (decayed, missing, or filled teeth) at 6 years	0.91 (0.72-1.16)	1

RR: Risk ratio

Kramer, 2012

Cognitive ability

Outcome	MD (95% CI)	Nr of studies
Wechsler cognitive ability test at 6.5 years: vocabulary	0.50 (-0.57-1.57)	1
Wechsler cognitive ability test at 6.5 years: similarities	0.30 (-0.56-1.16)	1
Wechsler cognitive ability test at 6.5 years: matrices	-0.20 (-1.07-0.67)	1
Wechsler cognitive ability test at 6.5 years: block designs	1.30 (0.40-2.20)*	1
Wechsler cognitive ability test at 6.5 years: verbal IQ	0.50 (-0.95-1.95)	1
Wechsler cognitive ability test at 6.5 years: performance IQ	0.80 (-0.55-2.15)	1
Wechsler cognitive ability test at 6.5 years: full-scale IQ	0.80 (-0.58-2.18)	1
Teacher's academic rating at 6.5 years: reading	-0.10 (-0.19- -0.01)*	1
Teacher's academic rating at 6.5 years: writing	-0.12 (-0.20- -0.04)*	1
Teacher's academic rating at 6.5 years: mathematics	-0.04 (-0.12-0.04)	1
Teacher's academic rating at 6.5 years: other subjects	-0.10 (-0.17- -0.03)*	1
Parent's behaviour rating at 6.5 years: total difficulties	0.30 (-0.16-0.76)	1
Parent's behaviour rating at 6.5 years: emotional symptoms	0.10 (-0.09-0.29)	1
Parent's behaviour rating at 6.5 years: conduct problems	0.0 (-0.13-0.13)	1
Parent's behaviour rating at 6.5 years: hyperactivity/inattention	0.20 (-0.01-0.41)	1
Parent's behaviour rating at 6.5 years: peer problems	0.10 (-0.05-0.25)	1
Parent's behaviour rating at 6.5 years: prosocial behaviour	0.10 (-0.05-0.25)	1
Teacher's behaviour rating at 6.5 years: total difficulties	0.10 (-0.46-0.66)	1
Teacher's behaviour rating at 6.5 years: emotional symptoms	0.0 (-0.18-0.18)	1
Teacher's behaviour rating at 6.5 years: conduct problems	0.0 (-0.17-0.17)	1
Teacher's behaviour rating at 6.5 years: hyperactivity/inattention	-0.10 (-0.37-0.17)	1
Teacher's behaviour rating at 6.5 years: peer problems	0.10 (-0.08-0.28)	1
Teacher's behaviour rating at 6.5 years: prosocial behaviour	-0.10 (-0.33-0.13)	1

MD: Mean difference

*Result no longer significant after adjustment for clustering and for other potential confounders

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Overweight and obesity	Lefebvre, 2014 Journal of the American Association of Nurse Practitioners Systematic literature review[9]	To explore the current evidence of the effect of BF on childhood obesity and provide recommendation for the nurse practitioner as a primary care provider	*Inclusion criteria* - Any country - Written in English - Examining the association between BF and childhood obesity *Exclusion criteria* - Case reports	January 2005 – March 2012 *Number of hits in original search* PubMed, CINAHL, and Medline, total n=483 *Number of included articles* n=21 n=8 prospective CH n=13 other designs	107,177 persons, with ages varying from infancy to adults 1 Kuwait, 3 Brazil, 2 Germany, 2 Australia, 4 USA, 2 the Netherlands, 1 Iran, 1 (England, Wales and Northern Ireland), 1 Sweden, 1 Ireland, 1 Northern Mariana Islands, 1 Singapore, 1 NR	*Assessment* Current BF information, n=6 Retrospective BF information, n=15 Age range at assessment not clear from characteristics table *Definition* NR

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment Height and weight measurements Questionnaires Age at assessment: childhood to 19 years (age range not clear from characteristics table), but 25-42 years in one study *Definition* BMI was the primary outcome in most studies	*BF and childhood obesity* - 10/21 studies: no significant effect - 11/21 studies: significant inverse effect *BFD and childhood obesity* - Any (vs. none) BF is protective against childhood obesity (n=1) - Protective effect on childhood obesity provided by BF is dependent on duration (n=9); protective effect found for: • BFD $_{\geq 4 \text{ mo. vs } <4 \text{ mo.}}$ (n=4) • BFD $_{\geq 6 \text{ mo.}}$ (n=2) • BFD $_{1\text{-}3 \text{ mo.}}$ (n=1) • BFD $_{9 \text{ mo. vs. } <3 \text{ mo.}}$ (n=1; effect in girls only) • BFD $_{\geq 24 \text{ mo. vs. } 12\text{-}24 \text{ mo.}}$ and BFD $_{12\text{-}24 \text{ mo. vs. } <12 \text{ mo.}}$ (n=1) *EBF and childhood obesity* - Duration of EBF has an effect of childhood obesity (n=3); protective effect found for: • EBFD $_{\geq 6 \text{ mo.}}$ and EBFD $_{\geq 24 \text{ mo.}}$ (=1) • EBFD $_{\geq 24 \text{ mo. vs. } 12\text{-}24 \text{ mo.}}$ and EBFD $_{12\text{-}24 \text{ mo. vs. } <12 \text{ mo.}}$ (n=1) • For children with EBF $_{<3 \text{ mo.}}$ there was a decreased risk of overweight with increased duration of EBFD (n=1)	Each of the included studies controlled for some confounding variables; 3 studies adjusted for ≤5 confounders	*Limitations (predefined quality criteria)* - Retrospective collection of BF data in 15/21 studies - No definition of BF reported - No information about blinding reported, outcome measured after BF assessment, or simultaneously - Limited outcome definition reported - All studies adjusted for confounders, though 3 studies adjusted for ≤5 confounders. None of the studies controlled for all confounders considered relevant by the authors; authors conclude that the relation between BF and childhood obesity remains unclear because of confounding maternal, child, cultural, genetic and environmental variables *Other limitations* - In one study it appeared that the association between BF and childhood obesity was related to the statistical model used to obtain the results (significant effect in logistic model, but no effect in linear regression model) - Broad age range in included studies (infancy to 45 years) - 14 different countries - Different questionnaires in collecting the data - Different study designs
Mo.: Months; Vs.: Versus.			

[9] Two of the included articles in this review were included in the report of RIVM (2007). Three of the included articles in this review was included in the review of Hörnell (2013).

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Coeliac disease	Szajewska, 2012 Alimentary Pharmacology & Therapeutics Systematic review [10]	To summarise current knowledge concerning the possible relationship between early feeding practices and the risk of developing CD	*Exclusion criteria* - Letters to the editor, abstracts, proceeding from scientific meeting, reviews (unless a full set of data was available) - Retrospective design with no control group	CENTRAL (Cochrane library), MEDLINE, EMBASE (up to July 2012) Additional manual search on all references from identified studies and key review articles *Number of hits in original search* NR *Number of included articles* - Total: n=12 - CC: n=7 (6 CCs included from 2 SLRs) - Prospective CH: n=3 - Record linkage study: n=1 - RCT: n=1 (as the outcomes of the RCT were not relevant, data from this study was not presented in this table)	In prospective studies, infants at population risk or increased risk of developing CD (defined by HLA status, first-degree relative with CD or type 1 DM). In retrospective studies, cases should have a diagnosis of CD 1,500 cases and 265,344 controls all studies except RCT All western countries (Sweden 4x, Italy 2x, Germany 2x, combination Italy/Germany, USA, UK)	*Assessment* Questionnaire, interview, maternity records Age at assessment of BF ranged between 0 (directly after birth) till 14.9y *Definition* - ever BF vs. never BF - EBF vs. PBF - Short BFD vs. long BFD - BF at gluten introduction vs. not

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Assessment Reported to a CD national register. In retrospective studies small bowel biopsy or positive serology indicative of CD Age at outcome assessment NR, but at last 14.9y *Definition* CD was diagnosed according to the original ESPGHAN criteria.	*Ever BF vs. never BF (n=2)* - OR $_{\text{ever BF vs. never BF}}$ (95% CI)= 1.99 (1.12-3.51; P=0.015) (n=1) - Lower risk of CD in ever BF children vs never BF children (n=1) *EBF vs. any BF and coeliac disease (n=3)* - No evidence that EBF vs. FF or MBF reduces the risk of CD or delays the onset of symptoms (n=3) *BFD and coeliac disease (n=11). See table 1* - Longer duration of BF protects against CD (n=5/6) - Short-term BF not associated with increased risk for CD (n=5/5) *BF at time of gluten introduction and coeliac disease (n=5). See table 2* - Significantly reduced risk of CD when started receiving gluten in children who were BF (n=3) - No significant association found (n=2) - SOR $_{\text{BF at time gluten introduced vs. not BF at time gluten introduced}}$ (95% CI) = 0.48 (0.40-0.59) (n=4)	Adjustments varied between included studies	*Limitations (predefined quality criteria)* - In the majority of studies BF data were recalled many years after the birth of the child (delay in years till 14.9 years) - Some studies did not make any distinction between EBF and any BF. No definition of EBF, PBF provided - Not reported whether assessment of health outcome was after assessment of exposure. Blinding NR, but probably not *Other limitations* - Most studies were nonrandomised, retrospective or observational in design and thus produce inconclusive results and the potential for parental recall bias - Different diagnosis of CD was used
CD: Coeliac disease; CENTRAL: Cochrane Central Register of Controlled Trials; DM: Diabetes mellitus; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology, and Nutrition; HLA: Human Leukocyte Antigen; UK: United Kingdom; USA: United States of America; Vs.: Versus; Y: Years.			

[10] One of the included articles in this review were included in the report of RIVM (2007). One of the included articles in this review was included in the review of Henriksson (2013).

Szajewska, 2012

Table 1 | Duration of breastfeeding and coeliac disease

	Reference	*N*	Duration of BF	Effect size	Effect
Studies included in the systematic review by Akobeng *et al.*[26]	Auricchio 1983[16]	505	Breastfed <30 days or bottle-fed has higher risk of CD than breastfed >30 days	OR 4.05 (2.2–7.27)	Short BF predisposing
	Ascher 1997[15]	81	BF in cases vs. controls: 6.5 (range 1.5–9) months vs. 5 (0–14) months	N.S.	No effect
	Falth-Magnusson 1996[18]	336	Median BF duration: 2.5 months (CD) vs. 4 months (control)	$P < 0.003$	Short BF predisposing
	Greco 1988[19]	2150	BF <90 days 5 times more likely to develop CD	OR 4.97 (3.5–6.9)	Short BF predisposing
	Ivarsson 2002[20]	1272	Children <2 years: median BF duration 5 months for CD vs. 7 months for controls	$P < 0.001$	Short BF predisposing
			Children >2 years	N.S.	No effect
	Peters 2001[22]	280	Risk of developing CD decreased by 63% for children BF >2 months vs. BF <2 months	OR 0.37 (0.21–0.64)	Short BF predisposing
Decker 2010[17]		157 cases + 862 controls	The rate of BF in patients with CD (86.6%) was higher compared with control subjects (76.5%)	OR 1.99 (1.12–3.51).	No effect
			The average duration of BF – 5.18 months (CD) vs. 5.25 months (controls)	N.S.	
Norris 2005[21]		1560 (51 developed autoimmunity)	No protective effect of breastfeeding. BF duration in CD autoimmunity-positive children was 8.3 (8.8) months and BF duration in CD autoimmunity-negative children was 6.7 (6.8) months	OR 1.02 (0.99–1.05)	No effect
Roberts 2008[23]		248 521 (cases $n = 90$)	No significant association between CD and BF	N.S.	No effect
Welander 2010[24]		Cases $n = 44$/controls $n = 9364$	No associations between breastfeeding duration, age at gluten introduction, and future CD (biopsy verified)	N.S.	No effect
Ziegler 2003[25]		1610 (27 developed autoimmunity)	No trend in antibodies to tissue transglutaminase C was observed for the duration of BF.	N.S.	No effect

Szajewska, 2012

Table 2 | Breastfeeding at the time of gluten introduction

Reference	Design		OR	Effect	Strengths/Limitations
Akobeng 2006[26]	Meta-analysis of case-control studies	Ascher	1.54 (0.27–10.56)	No effect	Not clear whether BF provides long-term protection or just delays the symptoms.*
		Falth-Magnusson	0.35 (0.17–0.66)	Protective	
		Ivarsson	0.5 (0.4–0.64)	Protective	
		Peters	0.46 (0.27–0.78)	Protective	
		Pooled	0.48 (0.4–0.59)	Protective	
Norris 2005[21]	Prospective observational study		HR 1.32 (0.76–2.28)	No effect	Prospective design; however, small number of subjects in whom the outcome measures occurred; use of CD autoimmunity as a surrogate for biopsy-diagnosed CD.

* Comment applies to all studies listed under Akobeng 2006.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Lung growth and function	Waidyatillake, 2013 Expert Rev Clin Immunol Systematic review[11]	- To appraise all available data on the possible effect of BF on lung function - To determine the most likely pathway by which BF influences lung function development	*Inclusion criteria* - Studies that examined the association between some form of BF as the exposure variable (either total or exclusive) and at least one lung function parameter measured as outcome *Exclusion criteria* - Lung function parameters not reported with regard to BF - High-risk cohorts	NR, but performed on 13-06-15 *Number of hits in original search* MEDLINE (PubMed): n=292 *Number of included articles* n=10	Most studies assessed outcomes in children and adolescents, but 2 studies measured outcomes in adults *Countries* 4 studies from the UK, 2 studies from Sweden, 2 studies from the USA, 1 study from 20 countries, and 1 study from which the country was unknown	*Exposure assessment* NR Age at assessment ranged from birth to 79 years (7 at birth, 2 in teenagers, 1 in adults) *Exposure definition* BF was described in various ways. Three studies examined total duration of BF as the exposure variable, 2 studies examined EBF duration, and 5 studies examined duration of BF without defining if it was exclusive or total

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Health outcome assessment The methods used to measure lung function were spirometry and peak expiratory flow meter. Two studies measured lung function repeatedly on 2 occasions, while all the others measured lung function at only one time point. The age at lung function measurement ranged from 4 – 79 years among the various studies *Health outcome definition* A wide range of parameters were assessed among the studies: FVC, FEV_1, FEV_1/FVC, FEF_{50}, and FEF_{25-75}	*BF and FEV_1 (table 2)* CH (*duration, ref no or shorter BF)*: - 3/6 studies observed a positive association - 3/6 studies observed no association CS *(non vs any)*: - 1/3 studies observed a positive association - 2/3 studies observed no association *BF and FVC (table 3)* CH (*duration, ref no or shorter BF)*: - 3/4 studies observed a positive association - 1/4 studies observed no association CS *(non vs any)*: - 1/1 study observed no association *BF and FEV_1/FVC (table 4)* CH (*duration, ref no or shorter BF)*: - 1/4 studies observed a positive association - 3/4 studies observed no association *BF and peak flow (table 5)*	3 studies assessed the evidence of possible effect of mediators: - 1 study suggested that weight gain in the first year of life may mediate the effect of BF on FVC - Tennant et al. found no evidence of effect mediation by a range of factors (birth weight, number of lower respiratory tract infections, smoking pattern, and body fat) of the BF/lung function relationship - 1 study that assessed the potential mediating effects of atopy, asthma and lower respiratory tract infections did not find any evidence to support these as proposed mechanisms for the effect of BF	*Limitations (predefined quality criteria)* - Clear definition of BF not reported - Not reported whether assessment of outcome was after assessment of exposure - Health outcomes not well defined (not cut-off values reported for the parameters) - Not all included studies corrected for confounders *Other limitations* - Only papers published in English were included (publication bias) - Lack of consistency between the studies among the classification of exposure and also in terms of which lung function parameters showed beneficial effects - The studies measured lung function at age 4 years and above. Though technically difficult, it is possible to measure the lung function in very young children, and this should be considered in future research, as the effect of BF may be particularly pronounced in early life - As BF is an area which is highly influenced by social and cultural factors, it remains possible that studies with negative or null effects may not have been published. This may have resulted in an overestimation of the potential benefits of BF on lung function in

[11] One of the included articles in this review was included in the report of RIVM (2007). One of the included articles in this review was included in the review of Hörnell (2013) and Dogaru (2014). One of the included articles in this review was included in the review of Dogaru (2014).

	CH (*duration, ref no or shorter BF)*: - 2/4 studies observed a positive association - 2/4 studies observed no association CS *(non vs any)*: - 1/1 study observed a positive association		this review
FEV_1: Forced expiratory volume in one second; FEF: Forced expiratory flow; FVC: Forced vital capacity; UK: United Kingdom, USA: United States of America			

Waidyatillake, 2013

Table 2. Results for the forced expiratory volume in 1 second.

Study (year)	Patients' lung function measured in total population (n/N) Age at lung function (years)	Breastfeeding exposure[†‡§]	Results (FEV_1 in ml) β	95% CI	p-value	Effect	Ref.
Birth cohort studies							
Tennant *et al.* (2008)	403/1142 49–51	Continuous (per week)[§]	NR	NR	0.62#	Not associated	[1]
		Binary[§]				Increased FEV_1	
		≥4 weeks	Ref				
		<4 weeks	-245	-416, -74	<0.01		
Ogbuanu *et al.* (2009)		Categorical[†]				Increased FEV_1	[30]
	1033/1456 10	Not breastfed	Ref				
		<2 months	14.3	-27.4, 56.0[¶]	0.50		
		2–4 months	16.8	-31.2, 64.8[¶]	0.49		
		>4 months	39.5	0.1, 78.8[¶]	0.05		
Soto-Ramirez *et al.* (2012)	1121/1456 18	Continuous (per week)[§]	1.2	0.1, 2.4[¶]	0.03	Increased FEV_1	[28]
Guilbert *et al.* (2007)	616/1246 11; 479/1246 16	Categorical[†]					[27]
		At 16 years				Not associated	
		≤2 months	Ref				
		2 < 4 months	20	-41, 81[¶]	0.50		
		≥4 months	27	-42, 96[¶]	0.40		
Dogaru *et al.* (2012)		Categorical[†]				Not associated	[26]
	773/6808	Not breastfed	Ref				
	8.5–14	≤3 months	-20	NR	0.36		
		4–6 months	-2	NR	0.95		
		>6 months	25	NR	0.29		
Kull *et al.* (2010)	1838/4089 8	Categorical[†]				Not associated	[29]
		<4 months	Ref				
		≥4 months	17.2	-5.1, 39.4	NR		
Cross-sectional studies							
Shaukat et al. (2005)	2305/6843 35–79	Categorical[§]				Not associated	[34]
		None	Ref				
		Any	5.5	-8.7, 20.0	NR		

Waidyatillake, 2013

Table 2. Results for the forced expiratory volume in 1 second (cont.).

Study (year)	Patients' lung function measured in total population (n/N) Age at lung function (years)	Breastfeeding exposure[†‡§]	Results (FEV_1 in ml)			Effect	Ref.
			β	*95% CI*	*p-value*		
Cross-sectional studies (cont.)							
Nagel *et al.* (2009)		Categorical[§]	FEV_1 % predicted mean ratio			Increased FEV_1, but only in affluent countries	[32]
	4888/54943	Affluent countries	Mean ratio				
	8–12	None	Ref				
		Any	1.11	1.02, 1.20	NR		
		Nonaffluent countries					
		None	Ref				
		Any	0.89	0.68, 1.17	NR		
Lee *et al.* (2005)	58/58 5–7 years	Categorical[§]	Mean	SD		Not associated	[33]
		<6 months	1100	200	0.30		
		>6 months	1100	300			

[†]Total duration.
[‡]Exclusive duration.
[§]Undefined.
[¶]Original paper presented SE. Review authors estimated CI.
[#]Parameter estimates and confidence intervals not provided.
FVC_1: Forced vital capacity in one second; NR: Not reported; SE: Standard error.

Waidyatillake, 2013

Table 3. Results for the forced vital capacity.

Study (year)	Patients' who underwent lung function in total population (n/N) Age at lung function (years)	Breastfeeding exposure[†‡§]	Results (FVC in ml) β	95% CI	p-value	Effect	Ref.
Birth cohort studies							
Ogbuanu *et al.* (2009)	1033/1456 10	Age 10 years				Increased FVC	[30]
		Categorical[†]					
		Not breastfed	Ref				
		<2 months	9.6	-34.3, 53.5[¶]	0.67		
		2 <4 months	6.9	-43.5, 57.3[¶]	0.79		
		>4 months	54.0	12.6, 95.4[¶]	0.01		
Soto-Ramirez *et al.* (2012)	1121/1456 18	Age 18 years Continuous (per week)[§]	1.5	0.3, 2.6[¶]	0.01	Increased FVC	[28]
Guilbert *et al.* (2007)	616/1246 11; 479/1246 16	Categorical[†]				Increased FVC	[27]
		At 11 years	NR	NR	<0.01*		
		At 16 years					
		≤1 month	Ref				
		2 < 4 months	43	-28, 114[¶]	0.2		
		≥ 4 months	103	25, 181[¶]	0.01		
Dogaru *et al.* (2012)	773/6808 8.5–14	Categorical[†]				Not associated	[26]
		Not breastfed	Ref				
		≤3 months	-39	NR	0.12		
		4–6 months	-10	NR	0.76		
		>6 months	24	NR	0.37		
Cross-sectional studies							
Shaukat *et al.* (2005)		Catergorical[§]					[34]
	2305/6843	None	Ref				
	35–79	Any	4.9	-8.3, 18.0	NR	Not associated	

[†]Total duration.
[‡]Exclusive duration.
[§]Undefined.
[¶]Original paper presented SE. Review authors estimated CI.
*Parameter estimates and confidence intervals not provided.
FVC: Forced vital capacity; NR: Not reported; SE: Standard error.

Waidyatillake, 2013

Table 4. Results for the ratio between forced expiratory volume one to forced vital capacity.

Study (year)	Patients' who underwent lung function in total population (n/N) Age at lung function (years)	Breastfeeding exposure[†,‡,§]	Results (the ratio between FEV_1/FVC %)			Effect	Ref.
			β	*95% CI*	*p-value*		
Birth cohort studies							
Ogbuanu *et al.* (2009)	1033/1456 10	10 years				Not associated	[30]
		Categorical[†]					
		Not breastfed	Ref				
		<2 months	0.28	-0.56, 1.40[¶]	0.62		
		2 <4 months	0.57	-0.70, 1.84[¶]	0.38		
		>4 months	-0.40	-1.44, 0.64[¶]	0.45		
Soto-Ramirez *et al.* (2012)	1121/1456 18	Age 18 years Continuous (per week)[§]	<-0.01	-0.02, 0.02[¶]	0.92	Not associated	[28]
Guilbert *et al.* (2007)	616/1246 11; 479/1246 16	Categorical[†]				Decreased ratio	[27]
		At 11 years	NR	NR	<0.01*		
		At 16 years					
		≤1 months	Ref				
		2 < 4 months	-0.70	-1.88, 0.48[¶]	0.20		
		≥4 months	-1.90	-3.08, -0.72[¶]	<0.01		
Dogaru *et al.* (2012)	773/6808 8.514	Categorical[†]				Not associated	[26]
		Not breastfed	Ref				
		≤3 months	0.70	NR	0.06		
		4–6 months	0.30	NR	0.45		
		>6 months	0.20	NR	0.56		

[†]Total duration.
[‡]Exclusive duration.
[§]Undefined.
[¶]Original paper presented SE. Review authors estimated CI.
*Parameter estimates and confidence intervals not provided.
FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; NR: Not reported; SE: Standard error.

Waidyatillake, 2013

Table 5. Results of the peak expiratory flow rate.

Study (year)	Patients' who underwent lung function in total population (n/N) Age at lung function (years)	Breastfeeding exposure[†‡]	Results (PEFR in ml/s) β	95% CI	p-value	Effect	Ref.
Birth cohort studies							
Dogaru *et al.* (2012)	773/6808 8.5–14	Categorical[†]				Not associated	[26]
		Not breastfed	Ref				
		≤3 months	-10.0	NR	0.87		
		4–6 months	15.0	NR	0.84		
		>6 months	77.0	NR	0.22		
Ogbuanu *et al.* (2009)	1033/1456 10	Categorical[†]				Increased PEFR	[30]
		Not breastfed	Ref				
		<2 months	114.7	-22.9, 252.3[¶]	0.10		
		2 < 4 months	143.4	-14.5, 301.3[¶]	0.08		
		>4 months	180.8	51.3, 310.3[¶]	0.01		
Kull *et al.* (2004)	2965/4089 4	At 4 years (PEFR < median)				Not associated	[31]
		Categorical[†]	OR				
		0–2 months	1				
		3–4 months	0.98	0.73, 1.01	NR		
		≥4 months	0.94	0.69, 1.30	NR		
Kull *et al.* (2010)	2564/4089 8	At 8 years				Increased PEFR	[29]
		Categorical[§]	β				
		<4 months	Ref				
		≥4 months	73.3	12.0, 135.3	NR		
Cross-sectional studies							
Lee *et al.* (2005)	58/58 5–7	Categorical[§]	Mean	SD		Increased PEFR	[33]
		<6 months			140	30	0.01
		>6 months			165	40	

[†]Total duration.
[‡]Exclusive duration.
[§]Undefined.
[¶]Original paper presented SE. Review authors estimated CI.
[*]Parameter estimates and confidence intervals not provided.
FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; NR: Not reported; SE: Standard error.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Hodgkin Lymphoma	Wang, 2013 Asian Pacific Journal of Cancer Prevention Systematic review and meta-analysis [12]	to synthesize current evidence derived from all case-control and cohort studies regarding the association between BF and the risk of childhood Hodgkin lymphoma.	*Inclusion criteria* - Published in the English language - The exposure of interest was BF - The outcome of interest was childhood Hodgkin lymphoma - Estimates of the relative risk ratio or OR with 95% Cis or reported data to calculate these measures *Exclusion criteria* - No data on childhood Hodgkin lymphoma as outcome - Duplicate report Two other criteria were not clear in the article	PubMed, Embase (up to April 10, 2013) Reference lists were systematically searched for relevant articles *Number of hits in original search* - Unique hits: n=532 *Number of included articles* - Total: n=10, all case-control studies - Population-based CC: n=9 - Hospital-based CC: n=1	1,618 cases and 8,181 controls. Estimated year of birth was between 1960 and 2004 for all participants. Western (Europe 5x, North America 2x) and non-western (Asia 3x) countries	*Assessment* NR NR, but age range was between 0-17y *Definition* - Any BF - Never BF (includes BF duration of <1 month and 1-2 months for 2 studies) - BFD 0-6 months - BFD >6 months

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Assessment NR NR, but age range was between 0-17y *Definition* Childhood Hodgkin lymphoma	*BF and childhood Hodgkin lymphoma* - SOR $_{\text{BF vs. never BF}}$ (95% CI)= 0.79 (0.58-1.08) P for heterogeneity = 0.12, I^2= 35.70% - SOR $_{\text{BFD 0-6 mo. vs. never BF}}$ (95% CI)= 1.03 (0.78-1.37; P=0.82) (n=6) - SOR $_{\text{BFD >6 mo. vs. never BF}}$ (95% CI)= 0.80 (0.46-1.39; P=0.42) (n=6) P for between subgroups = 0.43 *BF and childhood Hodgkin lymphoma , stratified for geographic region*	Nothing reported on confounders, but for the associations, maximally adjusted ORs were used as for the sensitivity analysis minimally adjusted ORs were used.	- 5 studies were categorized as higher-quality study (7 or more stars) and 4 were lower-quality study, using the 9-star Newcastle-Ottawa Scale. - No clear evidence of publication bias with the statistical tests used (Begg's rank correlation and Egger's regression test) *Limitations (predefined quality criteria)* - BF data were recalled retrospectively - No definition of BF provided - Assessment of health outcome was after assessment of exposure. Blinding NR, but probably not - Health outcome not well-defined - Confounders NR

[12] Three of the included articles in this review were included in the report of RIVM (2007).

	- North America: $SOR_{BF\ vs.\ never\ BF}$ (95% CI)= 0.66 (0.49-0.89) (n=2) - Asia: $SOR_{BF\ vs.\ never\ BF}$ (95% CI)= 0.29 (0.12-0.70) (n=3) - Europe: $SOR_{BF\ vs.\ never\ BF}$ (95% CI)= 1.10 (0.84-1.45) (n=5) P for between subgroups = 0 *Dose-response analysis and childhood Hodgkin lymphoma, random-effects model* - Along with the increase in BFD, point estimates of the effect decreased: P=0.44 See figure 4.		*Other limitations* - None of the included studies reported the dosage and frequency of BF. - Definition of BF and measurement methods varies across the included studies - Residual confounding effects by factors that were not controlled or adjusted among the included studies might have influenced the observed results.
Mo.: Months; Y: Years.			

Wang, 2013

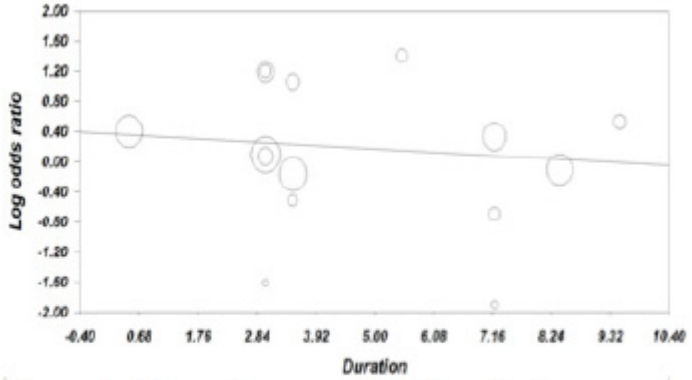


Figure 4. 4 Dose-Response Relationship Between the Breastfeeding Duration and Odds Ratios of Childhood Hodgkin Lymphoma. The breastfeeding duration was modeled with a linear trend in a random-effects meta-regression model. White circles represent individual study

A-II Primary articles with health outcomes related to the child

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
BMI, obesity, asthma, hyperactivity, parental attachment, behavioural compliance, reading comprehension, vocabulary recognition, math ability, memory based intelligence, and scholastic competence (all C)	Colen, 2014 Social Science & Medicine USA Prospective cohort study 1986-2010	To examine the association between infant feeding practices and child health and wellbeing	*Setting* NLSY79 cohort, a nationally representative cohort containing information on 12,686 young men and women *Study population* Singleton children born to original NLSY79 female respondents, who were between 4 and 14 yrs for the years between 1986 and 2010 and born after 1978 (so prospective BF data was available) *Sample size* Full sample: n=8,237 Sibling sample: n=7,319 Discordant sibling sample: n=1,773 (see remarks)	*Age at enrolment* 4-14 yrs *Age at assessment of outcome* 4-14 yrs Mean age: - Full sample: 8.9 yrs - Sibling sample: 8.9 yrs - Discordant sibling sample: 8.9 yrs	*Assessment* Interview; prospective data collection from birth (within two years after birth) *Definition* BF: NR BF status: - yes: BF for any length - no: no BF BF duration: in weeks	*Assessment* Interview; further information in table 1 below *Definition* Definitions for the following outcomes are reported in table 1 below

Results	Confounders	Remarks, limitations
BF status and 11 health outcomes See table 3 and 4 below - Full sample: Significant protective effect of BF on 9 outcomes: BMI, obesity, hyperactivity score, parental attachment, math skills, reading recognition, vocabulary word identification, digit recollection and scholastic competence ($P < 0.05$); protective effect on behavioural compliance ($P < 0.10$); significant negative effect on asthma ($P < 0.05$) - Sibling sample: Similar to full sample; but no significant effect on hyperactivity - Discordant sibling sample: Regression coefficients are attenuated, and some even changed signs; none remained significant ($P < 0.05$) *BF duration and 11 health outcomes* Overall, same patterning as BF status, see table 5	All models: Age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care Within-family estimates: also within family fixed effects	- Full sample: all respondents who were interviewed at least once between 1986 and 2010 - Sibling sample: NLSY children for which a sibling was also assessed - Discordant sibling sample: siblings who were differently fed in infancy (comparison within rather than across families) *Limitations (predefined quality criteria)* - No definition of BF reported - Outcome assessment was after exposure assessment; not reported whether assessment was blind *Other limitations* - Due to social desirability, women might exaggerate the extent through which they BF. However, because of prospective data collection this effect is probably limited - Sibling comparisons are a powerful methodological strategy to reduce selection bias, but can only account for unobserved potential confounders that differ across, not within, families
BMI: Body mass index; NLSY79: National Longitudinal Study of Youth, 1979 Cohort; USA: United States of America.		

Colen, 2014

Table 1
Description of long-term child wellbeing outcomes.

Measure	Age range	Objective	Format	Method of assessment
Body Mass Index	4–14 years	To measure weight to height ratio. BMI is considered to be reliable indicator of body fat for most people.	Measurements of height and weight obtained during interview. BMI calculated by dividing current weight by height squared. Reported in kilograms per squared meters (kg/m2).	63.96% obtained by interviewer; 33.29% obtained via maternal report; and 2.76% obtained by child report.
Obesity	4–14 years	To determine if respondent's BMI is exceeds the 95th percentile.	Dichotmous variable coded as 1 if child's BMI is at or exceeds 95th percentile for age- and sex-specific distributions and 0 if child's BMI falls below the 95th percentile.	All calculations based on sex-specific BMI-for-age growth charts for the U.S. generated by the Centers for Disease Control (CDC) and conducted by NLSY staff.
Asthma	4–14 years	To measure whether the respondent currently has asthma	Dichotomous variable coded as 1 if parent reported that child has asthma and 0 if parent reported child does not have asthma.	Maternal Report
Hyperactivity[a]	4–14 years	To measure the frequency and range of childhood behavioral problems attributable to hyperactivity	Subset of six questions from Behavior Problem Index (BPI): (1) has difficulty concentrating or paying attention; (2) is easily confused or seems to be in a fog; (3) is impulsive or acts without thinking; (4) has a lot of difficulty getting his/her mind off certain thoughts; and (5) is restless or overly active and cannot sit skill. Answer of "not true" is given value of 0 and answers of "sometimes true" or "often true" are given value of 1.	Maternal report
Parental attachment	4–7 years	To measure aspects of the child's usual behavior related to secure/insecure parental attachment.	Subset of seven questions based on Campos and Kagan's Compliance Scale: (1) trouble soothing child; (2) child stays close when playing; (3) child copies your actions; (4) child upset when you leave; (5) child is demanding; (6) child is empathetic; (7) child wants to help with things.	Maternal report
Behavioral compliance	4–7 years	To measure aspects of the child's usual behavior regarding following/not following household rules.	Subset of seven questions based on Campos and Kagan's Compliance Scale: (1) child resists eating meals; (2) child obeys when told to eat; (3) child resists going to bed; (4) child obeys going to bed; (4) child protests TV rules; (6) child obeys TV rules.	Maternal report
PIAT math[a]	5–14 years	To measure academic achievement in mathematics as taught in mainstream education for children ages 5 through 14.	Test consisting of 84 multiple-choice items of increasing difficulty, beginning with such early skills as recognizing numerals and progressing to measuring advanced concepts in geometry and trigonometry.	Interviewer assessment
PIAT reading[a]	5–14 years	To measure word and letter recognition as well as pronunciation ability for children ages 5 through 14.	Test of 84 questions of increasing difficulty; child matches letters, names letters, and reads single words aloud.	Interviewer Assessment
Peabody picture vocabulary[a,b]	4–14 years	To measure hearing and receptive vocabulary for Standard American English.	Interviewer says a word and the child points to 1 of 4 pictures that best portrays the word's meaning.	Interviewer Assessment
Wechsler Intelligence Scale (WISC)[a,b]	7–14 years	To measure child's short-term auditory memory and ability to manipulate verbal information from temporary storage	Digits Forward: The child listens to and repeats a sequence of numbers said by the interviewer. Digits Backwards: The child listens to a sequence of numbers and repeats them in reverse order.	Interviewer Assessment
Scholastic competence[b]	8–14 years	To measure child's sense of self-competence in the domain of academic skills.	Six item Likert scale measure that asks child, "How true of you is this statement?" (1) Some kids feel they are very good at school work; (2) Some kids feel they are just as smart as other kids their age; (3) Some kids are pretty slow in finishing their school work; (4) Some kids often forget what they learn; (5) Some kids do very well at their school work; (6) Some kids have trouble figuring out the answers in school.	Child Report

Source: National Longitudinal Survey of Youth, 1979 – Children's sample (NLSY-Childrens).
[a] Dependent variables are standardized by age.
[b] Age range did vary slightly over time.

Colen, 2014

Table 3
Unadjusted means and (sample sizes) for select child wellbeing outcomes by breastfeeding status (yes/no), 1986–2010: All NLSY Children and sibling subsamples.

	Full sample[a]			Sibling sample[b]			Discordant sibling sample[b]		
	Breastfed		Not breastfed	Breastfed		Not breastfed	Breastfed		Not breastfed
Body Mass Index	17.83 (15,518)	***	18.55 (17,984)	17.78 (13,911)	***	18.47 (16,120)	18.40 (3471)		18.59 (3733)
Obesity (%)	11.91 (15,518)	***	17.38 (17,984)	11.63 (13,911)	***	17.03 (16,120)	16.36 (3471)		18.14 (3733)
Asthma (%)	7.91 (17,150)	+	6.79 (18,382)	7.43 (14,981)		6.40 (15,673)	7.95 (3768)		8.89 (3718)
Hyperactivity score[c]	101.79 (16,312)	***	104.68 (17,515)	101.91 (14,277)	***	104.47 (14,949)	102.97 (3582)		103.81 (3543)
Parental attachment	19.94 (5386)		19.29 (5715)	20.04 (4801)		19.39 (5095)	19.68 (1160)		19.54 (1193)
Behavioral compliance	25.19 (5358)		24.65 (5716)	25.23 (4778)		24.67 (5095)	24.93 (1166)		24.88 (1182)
PIAT math skills[c]	106.87 (13,783)	***	100.11 (15,113)	107.11 (12,114)	***	100.38 (12,968)	102.39 (3093)	+	101.06 (3042)
PIAT reading recognition[c]	109.36 (13,734)	***	103.35 (15,043)	109.58 (12,069)	***	103.43 (12,906)	106.30 (3078)	+	104.81 (3027)
Peabody picture vocabulary test[c]	100.40 (7639)	***	90.43 (8762)	100.91 (6666)	***	90.97 (7476)	94.54 (1743)		93.26 (1766)
Wechsler Intelligence Scale (WISC)[c]	10.38 (7039)	***	9.58 (8122)	10.38 (6317)	***	9.55 (7287)	9.91 (1579)		9.61 (1666)
Scholastic competence	178.63 (5015)	***	169.39 (7084)	178.49 (4568)	***	169.05 (6393)	173.27 (1266)		169.84 (1414)

Source: National Longitudinal Survey of Youth, 1979 – Children's Sample (NLSY-Children).
Notes: All data are weighted to reflect the complex sampling design of the NLSY79 study.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; +$p < 0.10$.
[a] The full sample is weighted using longitudinal custom probability weights provided by the NLSY.
[b] We calculate weights for the sibling sample by dividing the average custom weight of all siblings within a given family by the total number of siblings from that family.
[c] Dependent variables are standardized by age.

Colen, 2014

Table 4
Unstandardized coefficients and corresponding standard errors for breastfeeding initiation (yes/no) from regression models predicting select outcomes among NLSY Children aged 4–14, 1986–2010.

	Between-family estimates						Within-family estimates		
	Model 1			Model 2			Model 3		
	Full sample[a]			Sibling sample[a]			Sibling sample[b]		
	b		S.E.	*b*		S.E.	*b*		S.E.
Body Mass Index	−0.449	*** (33,502)	0.094	−0.413	*** (30,031)	0.101	−0.141	(30,031)	0.188
Obesity	−0.342	*** (33,502)	0.066	−0.369	*** (30,031)	0.074	−0.173	(30,031)	0.164
Asthma	0.261	* (34,663)	0.106	0.237	* (30,998)	0.117	0.023	(30,998)	0.222
Hyperactivity[c]	−0.631	* (32,973)	0.314	−0.355	(29,513)	0.348	−0.572	(29,513)	0.549
Attachment	0.277	* (11,101)	0.113	0.223	+ (9896)	0.122	−0.047	(9896)	0.205
Compliance	0.227	+ (11,074)	0.119	0.307	* (9873)	0.129	−0.204	(9873)	0.221
PIAT math[c]	2.175	*** (28,179)	0.312	2.066	*** (25,293)	0.331	0.646	(25,293)	0.601
PIAT reading[c]	2.019	*** (28,068)	0.346	2.001	*** (25,190)	0.370	0.868	(25,190)	0.690
Peabody picture vocabulary[c]	3.250	*** (15,969)	0.444	3.181	*** (14,342)	0.474	0.686	(14,342)	0.865
Wechsler Intelligence Scale[c]	0.329	*** (15,161)	0.084	0.311	** (13,604)	0.092	0.221	(13,604)	0.178
Scholastic competence	2.789	* (12,099)	1.204	2.363	+ (10,961)	1.304	−0.353	(10,961)	2.757

Source: National Longitudinal Survey of Youth, 1979 – Children's sample (NLSY-Childrens).
Notes: All data are weighted to reflect the complex sampling design of the NLSY79 study.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; + $p < 0.10$.
[a] Controls measured at the date of interview include: year, age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care.
[b] Models include all control variables listed above as well as within family fixed effects.
[c] Dependent variables are standardized by age.

Colen, 2014

Table 5

Unstandardized coefficients and corresponding standard errors for breastfeeding duration (in weeks) from regression models predicting select outcomes among NLSY Children aged 4–14, 1986–2010.

	Between-family estimates						Within-family estimates		
	Model 1			Model 2			Model 3		
	Full sample[a]			Sibling sample[a]			Sibling sample[b]		
	b		S.E.	*b*		S.E.	*b*		S.E.
Body Mass Index	−0.007	** (33,502)	0.002	−0.007	** (30,031)	0.003	0.005	(30,031)	0.003
Obese	−0.007	** (33,502)	0.002	−0.006	* (30,031)	0.002	0.001	(30,031)	0.004
Asthma	0.004	* (34,663)	0.002	0.004	+ (30,998)	0.002	0.006	(30,998)	0.008
Hyperactivity[c]	−0.020	** (32,973)	0.007	−0.017	* (29,513)	0.008	−0.015	(29,513)	0.012
Attachment	0.009	*** (11,101)	0.003	0.008	** (9896)	0.003	0.005	(9896)	0.004
Compliance	0.005	+ (11,074)	0.003	0.006	+ (9873)	0.003	0.009	+ (9873)	0.005
PIAT math[c]	0.059	*** (28,179)	0.008	0.056	*** (25,293)	0.008	0.012	(25,293)	0.012
PIAT reading[c]	0.047	*** (28,068)	0.009	0.048	** (25,190)	0.009	0.008	(25,190)	0.014
Peabody picture vocabulary[c]	0.084	*** (15,969)	0.012	0.087	*** (14,342)	0.013	0.007	(14,342)	0.021
Wechsler Intelligence Scale[c]	0.007	*** (15,161)	0.002	0.006	* (13,604)	0.002	−0.005	(13,604)	0.003
Scholastic competence	0.119	*** (12,099)	0.029	0.126	*** (10,961)	0.032	0.015	(10,961)	0.058

Source: National Longitudinal Survey of Youth, 1979 – Children's Sample (NLSY-Childrens).

Notes: All data are weighted to reflect the complex sampling design of the NLSY79 study.

***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; + $p < 0.10$.

[a] Controls measured at the date of interview include: year, age, sex, race, marital status, region, insurance coverage, family income, mother's education, and mother's employment. Controls measured at the time of birth include: preterm birth, birth order, mother's age, family income, mother's education, mother's employment, smoked during pregnancy, drank during pregnancy, and timely prenatal care.

[b] Models include all control variables listed above as well as within family fixed effects.

[c] Dependent variables are standardized by age.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Multiple sclerosis	Conradi, 2012 Multiple sclerosis journal Germany Case-control study 2006-2009	To investigate a possible association between BF and occurrence of MS	*Setting* MS ambulatory center in the Charité – Universitätsmedizin Berlin *Study population* Patients aged 18 to 80 years with CIS, relapsing-remitting, secondary progressive and primary progressive MS at different stages of disease. Controls were selected from two general practitioners. *Sample size* Cases: n=245 Controls: n=296	*Age at enrolment* Median age (IQR) Cases: 46 year (37-54) Controls: 40 year (27-54) *Age at assessment of outcome* NR	*Assessment* Mothers or relatives of patients and controls provided information about BF *Definition* NR - No BF (ref) - BFD ≤4 months - BFD >4 months	*Assessment* NR *Definition* Cases: MS was according to the revised 2005 McDonalds criteria or CIS Controls had no MS, CIS, any other inflammation of the CNS or a severe medical or psychiatric disorder.

Results	Confounders	Remarks, limitations
BF (as dichitomous variable) and probability of multiple sclerosis - aOR $_{\text{BF vs. no BF}}$ (95% CI) = 0.58 (0.35-0.94; P = 0.028) - aOR $_{\text{BFD ≤4 mo. vs. no BF}}$ (95% CI) = 0.87 (0.49-1.52; P = 0.614) - aOR $_{\text{BFD >4 mo. vs. no BF}}$ (95% CI) = 0.51 (0.29-0.88; P = 0.016) See table 1 for univariate outcomes.	Age, gender, number of older siblings, number of inhabitants in place of domicile at age 0-6, day-care attendance between ages 0 and 3	*Limitations (predefined quality criteria)* - BF data was assessed 18-80 years after birth - No clear definition of BF was provided. Duration of BF was specified - Assessment of BF was done after the health outcome was known . Blinding not reported - No data on environmental risk factors for MS included in questionnaire *Other limitations* - 39.6% patients and 37.8% controls were not able to answer questions on the duration of BF
CIS: Clinically isolated syndrome; CNS: Central nerve system; MS: Multiple sclerosis.		

Conradi, 2012

	Univariate		
	OR	95% CI	p-value#
Breastfed	0.45	0.29–0.69	<0.0005
Breastfed no	1.00		
Breastfed ≤ four months	0.75	0.46–1.24	0.311
Breastfed > four month	0.37	0.23–0.61	<0.0005

§: stepwise backward selection; #: Fisher's exact test; OR: odds ratio; CI: confidence interval.

Table 1. Results of univariate analysis for BF as a dichotomous risk factor for the probability of MS adjusted for the independent MS-predictors and as categorical factor

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Neonatal weight loss	Davanzo, 2013 Journal of Human Lactation Italy Retrospective cohort study January 1-August 15, 2007	To assess the extent of neonatal weight loss and its association with selected clinical variables in a population of healthy term infants cared for using a specific protocol on weight loss	*Setting* Regular nursery of the Institute for Maternal and Child Health – IRCCS "Burlo Garofolo" (Trieste, Italy) *Study population* Consecutively admitted healthy term neonates *Sample size* n=1,003	*Age at enrolment* Directly after birth *Age at assessment of outcome* NR, but every day all infants were weighed. Healthy infants were routinely discharged at ≥36h. Babies with weight loss >10% were discharged when they regained enough weight to fall below 10% weight loss	*Assessment* Routine categorization by the neonatologist at the discharge visit based on a review of the medical records from birth through hospital discharge *Definition* WHO definitions (WHO, 2008) for EBF, PBF, CF and NBF For the analysis: - BF = EBF + PBF - FF = CF + NBF	*Assessment* Review of hospital records: naked weighing between 8-10 AM every day by a nurse using an electronic scale *Definition* - Weight at birth - Weight at hospital discharge - Maximum weight loss (both in absolute and percentage terms) reached at any time during the hospital stay -Weight loss more than the safest upper limit defined as 8% (Livingstone et al.)

Results	Confounders	Remarks, limitations
BF and mean weight loss(SD) FF infants: 255 ± 93g or 7.5% ± 2.4% BF infants: 215 ± 73g or 6.3% ± 2.0% P < 0.001 *Feeding at discharge and neonatal weight loss ≥8% before discharge* - Total: $OR_{FF\ vs.\ BF}$ (95% CI) = 3.94 (2.94-5.27) $aOR_{FF\ vs.\ BF}$ (95% CI) = 3.65 (2.67-4.99) - Vaginal deliveries (n=795): $OR_{FF\ vs.\ BF}$ (95% CI) = 5.54 (3.19-6.47) $aOR_{FF\ vs.\ BF}$ (95% CI) = 4.81 (3.32-6.98)	Season, type of delivery, birth weight, jaundice treated and not treated with phototherapy, length of hospital stay, hypernatremia (>150 mEq/L), and hypoglycaemia (blood glucose < 45 mg/dL)	*Limitations (predefined quality criteria)* - Assessment of BF data was after the assessment of health outcome. Not reported whether exposure and outcome assessment were blind - Only a limited number of variables related to weight loss were studies, which hindered the value of multivariate analysis (e.g. no control for maternal factors, both clinical and socio-demographic) *Other limitations* - Retrospective design: it is possible that the decision for FF was made after weight loss occurred *Conflict of interest* - The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The study was approved by the Research Commission of the IRCCS "Burlo Garofolo," Trieste, and funded by the grant RC 18/09 of the same Institute
CF: Complimentary breastfeeding; NBF: No breastfeeding; PBF: Predominant breastfeeding		

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
CNS tumours	Harding, 2007 British Journal of Cancer UK Case-control study Scotland: 1991-1994 England, Wales: 1992-1994	To investigate infant feeding habits in relation to risk of childhood CNS tumours	*Setting* Nationwide, population-based *Study population* Children diagnosed with CNS tumours before 15 years of age, and two matched controls per case (birth month/year and study region) Recruitment cases: NR (probably in UKCCS Investigators, 2000). Controls: randomly selected from health authorities/health boards. *Sample size* Cases: n=633 Control: n=7,621	*Age at enrolment* NR *Age at assessment of outcome* NR	*Assessment* Mothers of case and control subjects were interviewed using a questionnaire detailing whether they had ever BF, including dates and durations, whether they had ever used formula milk, whether they sterilised bottles and feeding utensils, and the age at which solid food was introduced *Definition* NR Duration of BF categories: ever BF, BF < 1 month, 1-6 months and > 6 months	*Assessment* A pathological review provided detailed classification of tumours *Definition* Any CNS tumour as well as according the specific classification of the tumour: - All CNS tumours - Glioma (plus subgroup pilocytic astrocytoma) - Ependyoma - Medulloblastoma/PNET - Other CNS tumours

Results	Confounders	Remarks, limitations
All CNS tumours - aOR $_{\text{BF ever vs. never}}$ (95% CI) = 1.01 (0.85, 1.21) - aOR $_{\text{BF <1 mo. vs. never}}$ (95% CI) = 1.11 (0.86, 1.42) - aOR $_{\text{BF 1-6 mo. vs. never}}$ (95% CI) = 0.94 (0.75, 1.19) - aOR $_{\text{BF >6 mo. vs. never}}$ (95% CI) = 1.03 (0.83, 1.28) P for trend = 0.72 *CNS tumour diagnostic subgroups* No significant associations were observed between ever BF and any diagnostic subgroup, nor between duration of BF and any diagnostic subgroup (table 1) *Further analyses* None of the further analyses of sterilisation or age at introduction of solid food showed a significant effect for all CNS tumours or any diagnostic subgroup (results not shown), although an increased risk associated with sterilising feeding utensils did approach significance (OR 1.54, P=0.067, CI: 0.97-2.45)	Age, sex, region, and deprivation index	- UKCCS includes all types of cancer; the matched controls for all cancer cases were included in this study *Limitations (predefined quality criteria)* - Time of assessing BF data was after diagnosis of the tumour - No definition of BF reported *Other limitations* - The UKCCS is subject to participation bias; responding controls are generally from less deprived areas and therefore are not completely representative of the underlying population. Areas of higher deprivation display a lower level of BF which is also shown in the results of this study - Recall bias is possible, with the possibility of differential reporting between cases and controls. Self-reporting of BF habits are known to lack accuracy, though it is unclear whether this differs between cases and controls
CNS: Central nervous system; Mo.: Months; UK: United Kingdom; UKCCS: The UK childhood cancer study		

Harding, 2007

Table I Numbers of subjects (*n*) and ORs for association between breastfeeding and childhood CNS tumours by diagnostic group

				Ever breastfed (duration)				
	Exposure	**Never breastfed**	**Ever breastfed**	**< 1 month**	**1–6 months**	**>6 months**	**Unknown**	***P*-value for trend****
Controls	*n* (%)	2495 (35.9)	4460 (64.1)	1014 (14.6)	1599 (23.0)	1842 (26.5)	5	
All CNS tumours	*n* (%)	231 (36.5)	402 (63.5)	101 (16.0)	134 (21.2)	167 (26.4)	0	0.72
	OR (95% CI)	1.00	1.01 (0.85–1.21)	1.11 (0.86–1.42)	0.94 (0.75–1.19)	1.03 (0.83–1.28)		
Glioma	*n* (%)	122 (35.2)	225 (64.8)	55 (15.9)	70 (20.2)	100 (28.8)	0	0.59
	OR (95% CI)	1.00	1.08 (0.86–1.38)	1.14 (0.82–1.60)	0.95 (0.70–1.30)	1.19 (0.89–1.58)		
Pilocytic astrocytoma[a]	*n* (%)	67 (41.9)	93 (58.1)	27 (16.9)	29 (18.1)	37 (23.1)	0	0.17
	OR (95% CI)	1.00	0.82 (0.59–1.15)	1.02 (0.64–1.61)	0.71 (0.45–1.13)	0.80 (0.52–1.23)		
Ependyoma	*n* (%)	23 (35.4)	42 (64.6)	13 (20.0)	11 (16.9)	18 (27.7)	0	0.77
	OR (95% CI)	1.00	1.01 (0.59–1.73)	1.41 (0.70–2.82)	0.72 (0.35–1.51)	1.03 (0.54–2.00)		
Medulloblastoma/PNET	*n* (%)	53 (35.6)	96 (64.4)	25 (16.8)	36 (24.2)	35 (23.5)	0	0.61
	OR (95% CI)	1.00	1.01 (0.71–1.45)	1.16 (0.71–1.89)	1.07 (0.69–1.67)	0.88 (0.56–1.37)		
Other CNS tumours	*n* (%)	33 (45.8)	39 (54.2)	8 (11.1)	17 (23.6)	14 (19.4)	0	0.22
	OR (95% CI)	1.00	0.77 (0.47–1.25)	0.65 (0.30–1.42)	0.89 (0.49–1.64)	0.69 (0.36–1.34)		

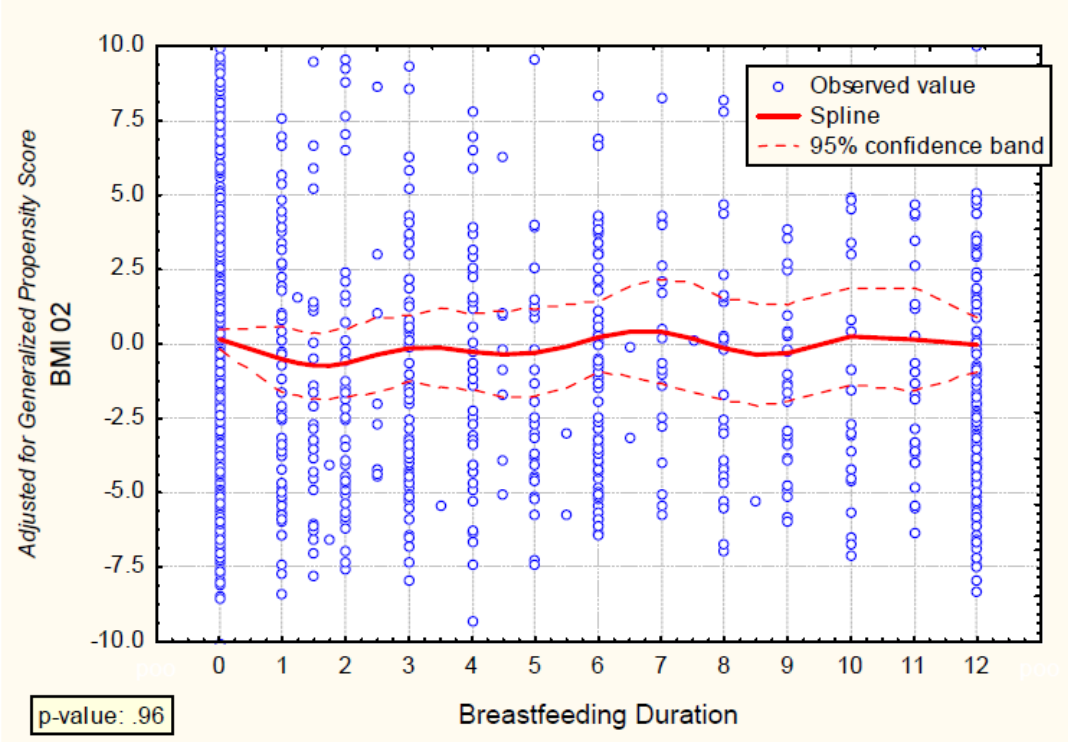
CNS = central nervous system; OR = odds ratio. [a]Subgroup of glioma. **P-value derived from fitting a linear trend across categories in a logistic regression model. Logistic regression analyses adjusted for age, sex, region, and deprivation index.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
BMI	Jiang, 2013 Health Services Research USA Retrospective cohort study Two waves: 1997 and 2002	To estimate the effect of BF duration on childhood obesity	*Setting* PISD, representative sample of US families *Study population* CDS: Children born to PISD families between 1984 and 1997 who lived with their biological mother at the time of the 1997 interview *Sample size* n=3,271	*Age at enrolment* 4 mo.-13 yrs *Age at assessment of outcome* 5-18 yrs	*Assessment* In-person interview in 1997 *Definition* BF: NR BF duration: ranges from 0-12 mo. Durations >12 mo. were truncated at 12 mo.	*Assessment* In-person interview in 2002 - 99% direct measurement of height and weigh - 1% height and weight reported as recorded at the child's last doctor's visit *Definition* BMI: calculated using height and weight

Results	Confounders	Remarks, limitations
BFD and BMI Model / Effect / SE / P Unadjusted / -0.120 / 0.030 / <0.0001 Linear regression adjusted / 0.004 / 0.036 / 0.92 GPS adjusted linear regression / -0.0004 / 0.041 / 0.99 GPS adjusted GAM / / / 0.99 Figure 1 below describes the estimated, adjusted relationship between mo. of BF and BMI (P = 0.96)	- Child's age at the 1997 survey, race and ethnicity, child's gender, number of siblings, first born to the mother, preterm, born small for gestational age, mother-rated child's health at birth as compared to other babies, HOME scale (measure of cognitive stimulation and emotional support that parents provide to their children) - Maternal characteristics: IQ, education, age at time of child's birth, enrolment in WIC program of Medicaid during pregnancy, employment, marital status, head of household (yes/no), household income	*Limitations (predefined quality criteria)* - Time of assessing BF data could be up to 13 years retrospective - No definition of BF reported - Outcome assessment after exposure assessment, no information about blinding - GPS only controls for observed confounding. Other factors, such as maternal BMI and weight gain during pregnancy, may play a confounding role *Other limitations* - Use of a retrospective cohort, which is subject to recall bias
BMI: Body mass index; CDS: Child development supplement; GAM: Generalized additive model; GPS: Generalized propensity score; HOME: Home Observation for Measurement of the Environment; Mo.: Months; PISD: the Panel Study of Income Dynamics; USA: United States of America.		

Jiang, 2013

Figure 1: Relationship between Breastfeeding Duration and Subsequent Childhood Obesity



Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Metabolic syndrome	Martin, 2014 Circulation Belarus Long-term follow up of an RCT[13] 1996-2010	To investigate the effects of an experimental intervention to promote increased duration of exclusive BF on cardiometabolic risk factors in childhood	*Setting* Maternity hospitals and their associated polyclinics (outpatient health clinics following up both well and ill children): 31 sites *Study population* Infants born at term (≥37 wks gestation) in 1996-1997 (healthy, singleton, birth weight ≥2,500g, Apgar score ≥5 at 5 minutes; mothers initiated BF, no condition that would interfere with BF) with follow-up data at 11.5 yrs (fasted ≥8h and did not have diabetes) *Sample size* n=13,616	*Age at enrolment* At birth *Age at assessment of outcome* Median 11.5 years (SD: 0.50; IQR: 11.3-11.8)	*Assessment** BF was assessed at routine well-child visits at 1, 2, 3, 6, 9, and 12 months *Definition** EBF according to WHO definitions: no solids, non-breast milk, or water or other liquids (other than vitamins or medications) BF duration (BFD): <3 months (reference), ≥3 to <6 months, and ≥6 months	*Assessment* Follow-up at dedicated research visits by specially trained paediatricians *Definition* Binary outcome for presence or absence of metabolic syndrome according to recommendations of the European Group for the Study of Insulin Resistance (Balkau, 1999): raised insulin levels (fasting values ≥75th sample percentiles for sex and pubertal stage, as in other studies) and at least 2 of the following metabolic abnormalities based on population reference values: - hyperglycemia (whole blood fasting values ≥5.6 mmol/L; - hypertension (systolic blood pressure ≥90th percentile for age, sex, and height); - dyslipidemia (apolipoprotein A values ≤10th percentile for age, sex); - abdominal obesity (waist circumference ≥90th percentile for age, sex).

Results	Confounders	Remarks, limitations
BFD and metabolic syndrome, instrumental variable analysis aOR $_{\text{EBFD 3 to <6 mo. vs. <3 mo.}}$ (95% CI) = 1.91 (0.72-5.05) aOR $_{\text{EBFD ≥6 mo. vs. <3 mo.}}$ (95% CI) = 2.33 (0.52-9.68) P for trend = NR *BFD and metabolic syndrome, observational analysis* aOR $_{\text{EBFD 3 to <6 mo. vs. <3 mo.}}$ (95% CI) = 1.09 (0.86-1.39) aOR $_{\text{EBFD ≥6 mo. vs. <3 mo.}}$ (95% CI) = 1.14 (0.68-1.89) P for trend = 0.43 Cluster-adjusted analyses are presented in the table below	Stratum-level variables (urban vs. rural and East vs. West Belarus), and child age at follow-up, sex, birth weight, and both maternal and paternal education	- Trial: control group (continuation of BF practices) and treatment group (Baby Friendly Hospital Initiative to promote and support BF) - To assess whether results of previous observational studies could be reproduced, authors conducted observational analyses (i.e. disregarding randomization status) - Differences in mean (or ratio of means) (95% CI) between BFDs were also presented for systolic blood pressure, diastolic blood pressure, glucose, insulin, HOMA-IR, HOMA-B, adiponectin and ApoA1. - Authors mention supplemental data for duration of any BF, however these results are not presented in the article and are not presented here *Limitations (predefined quality criteria)* - Assessment of outcome was after BF assessment; it is not reported whether this assessment was blind *Other limitations:* NR
ApoA1: Apolipoprotein A1; HOMA-B and -IR: Homeostasis model assessment of ß-cell function and insulin resistance; Mo.: Months; Wks: Weeks; Yrs: Years. *the current article provided limited information on exposure assessment and definition, so information is obtained from Kramer, 2001		

[13] Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, Collet JP, Vanilovich I, Mezen I, Ducruet T, Shishko G, Zubovich V, Mknuik D, Gluchanina E, Dombrovskiy V, Ustinovitch A, Kot T, Bogdanovich N, Ovchinikova L, Helsing E; PROBIT Study Group (Promotion of Breastfeeding Intervention Trial). Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA*. 2001;285:413–420

Table (adjusted from table 3 and 4 in original article): Instrumental variable estimates and observational associations of duration of BF and metabolic syndrome

	Cluster adjusted*				Further adjusted for baseline factors**			
	<3 mo.	3 to <6 mo.	≥6 mo.	P	<3 mo.	3 to <6 mo.	≥6 mo.	P
Instrumental variable analysis								
Metabolic syndrome	1.0 (ref)	1.84 (0.66-5.15)	2.32 (0.47-11.43)	-	1.0 (ref)	1.91 (0.72-5.05)	2.23 (0.52-9.68)	-
Observational analysis								
Metabolic syndrome	1.0 (ref)	1.08 (0.85-1.37)	1.09 (0.65-1.81)	0.52	1.0 (ref)	1.09 (0.86-1.39)	1.14 (0.68-1.89)	0.43

*Units of randomization (clusters) were maternity hospitals and their associated polyclinics

**Adjusted for stratum-level variables (urban versus rural and East versus West Belarus), and for child age at follow-up, sex, birth weight, and both maternal and paternal education.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Breast cancer	Nichols, 2008 Epidemiology USA Case-control study 2002-2006	To explore whether maternal age and birth order associations for breast cancer risk vary according to exposure to breast milk in infancy	*Setting* Wisconsin *Study population* Women aged 20-69 with incident diagnosis of invasive breast cancer who had a listed telephone number and driver's license. Controls were randomly selected within 5-year age strata, using lists of licensed drivers from Wisconsin Department of Transportation, with no personal history of breast cancer. *Sample size* Cases: n=2016 Controls: n=1960	*Age at enrolment* NR, but between 20 and 69 years *Age at assessment of outcome* NR, but between 20 and 69 years	*Assessment* Structured telephone interviews, self-reported information on whether subjects were breastfed in infancy *Definition* NR	*Assessment* Review of state-mandated cancer registry *Definition* Cases: Incident diagnosis of invasive breast cancer, definition NR

Results	Confounders	Remarks, limitations
BF during infancy and invasive breast cancer aOR $_{\text{BF vs. no BF}}$ (95% CI) = 0.83 (0.72, 0.96) Age adjusted associations between BF during infancy and invasive breast cancer can be found in the table 2. *BF during infancy and invasive breast cancer, restricted to first-born women (Cases: n=557; Controls: n=514)* aOR $_{\text{BF vs. no BF}}$ (95% CI) = 0.97 (0.74, 1.29)	Age, birth order, age at menarche, age at first birth, parity, menopausal status, age at menopause, postmenopausal hormone use, family history of breast cancer in a mother or sister, height, weight at age 20, weight gain since age 20 and mammography screening	*Limitations (predefined quality criteria)* - BF data were recalled many years after birth as included women were aged ≥20 years - No definition or duration of BF provided - Assessment of BF was done after the disease outcome was known . Blinding not reported - Diagnosis of invasive breast cancer not further specified

Nichols, 2008

TABLE 2. Associations of Early Life Factors With Invasive Breast Cancer

	Cases (n = 2016)		Controls (n = 1960)			
Characteristic	No.	%[a]	No.	%[a]	OR (95% CI)[b]	OR (95% CI)[c]
Breast-fed in infancy						
No[e]	1014	50.3	920	46.9	1.00	1.00
Yes	634	31.4	681	34.7	0.87 (0.76–1.01)	0.83 (0.72–0.96)
Unknown/missing	368	18.3	359	18.3		

[a]Due to missing values, some categories do not sum to 100%.
[b]Odds ratios adjusted for age.
[c]Odds ratios adjusted for age, age at menarche, age at first birth, parity, menopausal status, age at menopause, postmenopausal hormone use, family history of breast cancer, height, weight at age 20, weight gain, mammography use, and whether breast-fed in infancy.
[d]In multivariable models, both birth order and maternal age are adjusted for simultaneously when evaluating the effect of either variable.
[e]Reference category.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definitions	Outcome assessment and definitions
Non-alcoholic fatty liver disease	Nobili, 2009 Archives of Disease in Childhood Italy Retrospective cohort study January 2003-September 2007	To investigate the association between early type of feeding (BF vs. FF and duration of BF) and later NAFLD development	*Setting* Liver Unit of the "Bambino Gesù" Pediatric Hospital (Rome, Italy) *Study population* Consecutively enrolled Caucasian children (3-18 years) with NAFLD *Sample size* n=191	*Age at enrolment* 3.3-18.0 years *Age at assessment of outcome* NR	*Exposure assessment* Review of clinical charts *Exposure definition* NR	*Outcome assessment* Liver histology by a biopsy. Steatosis, inflammation, hepatocyte ballooning and fibrosis were scored using the NAFLD Clinica Research Network criteria. Features of steatosis, lobular inflammation and hepatocyte ballooning were combined to obtain the NAFLD activity score (NAS) *Outcome definition* - NAFLD comprises steatosis, NASH and cirrhosis - NASH: patients with NAS ≥5

Results	Confounders	Remarks, limitations
Histological findings(see table 3) NAS: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.12 (0.07-0.20) Steatosis: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.15 (0.08-0.25) Inflammation: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.24 (0.12-0.50) Ballooning: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.15 (0.09-0.26) Fibrosis: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.28 (0.17-0.49) *Multivariate analysis in all children* NASH: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.04 (0.01-0.10; P < 0.001) Fibrosis: OR $_{\text{BF vs. no BF}}$ (95% CI) = 0.32 (0.16-0.65; P < 0.001) *Multivariate analysis for BFD in breastfed children (n=91)* NASH: OR $_{\text{per month BF}}$ (95% CI) = 0.70 (0.001-0.87; P = 0.001) Fibrosis: OR $_{\text{per month BF}}$ (95% CI) = 0.86 (0.75-0.98; P = 0.025)	Multivariable analysis adjusted for age, waist circumference, gestational age and neonatal weight	*Limitations (predefined quality criteria)* - Not clear what time after birth BF data from the clinical charts were reported - No clear definition of BF duration and exclusiveness was reported - Not reported whether assessment of exposure and outcome were blind. Assessment of BF data was after assessment of the health outcome *Other limitations* - Authors state that even though some environmental confounders were taken into account, they could into exclude that the early type of feeding and prolonged BF, are just surrogate indicators of other risk factors.
HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDL: High-density lipoprotein; NAFLD: Non -alcoholic fatty liver disease; NAS: NAFLD activity score; NASH: Non-alcoholic steatohepatitis.		

Nobili, 2009

Table 3 Distribution of histological findings after liver biopsy in breastfed and not breastfed children

	Breastfed								Not breastfed								Breastfed versus not breastfed
Score	0	1	2	3	4	5	6	7	0	1	2	3	4	5	6	7	OR (95% CI)*†
NAS	–	8	31	34	13	2	3	0	–	0	11	8	22	20	30	9	0.12 (0.07 to 0.20)
Steatosis	–	46	37	8	–	–	–	–	–	14	32	54	–	–	–	–	0.15 (0.08 to 0.25)
Inflammation	18	67	6	0	–	–	–	–	5	73	20	2	–	–	–	–	0.24 (0.12 to 0.50)
Ballooning	66	21	4	–	–	–	–	–	34	18	48	–	–	–	–	–	0.15 (0.09 to 0.26)
Fibrosis	42	44	5	0	–	–	–	–	21	62	3	14	–	–	–	–	0.28 (0.17 to 0.49)

*$p<0.001$ for all values (likelihood-ratio test).
†Obtained from ordinal logistic regression using a continuation ratio model.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Asthma, wheeze and atopic eczema	Nwaru, 2013 Clinical & Experimental Allergy UK Prospective cohort study	To investigate the associations between duration of BF and the timing of introduction of complementary foods during the first 6 mo. and parental-reported asthma, wheeze and atopic eczema up to 10 years of age	*Setting* An antenatal clinic (SEATON birth cohort) *Study population* Singletons born to 2,000 healthy pregnant women attending the clinic, at median 12 weeks gestation *Sample size* n=1,924	*Age at enrolment* At birth *Age at assessment of outcome* At ages 1, 2, 5, and 10 years	*Assessment* Prospective data collection with a card *pro forma*: mothers recorded dates in the 6 mo. from birth at which FF was introduced, BF was stopped and the dates of introducing complementary foods (fruit juice, cows' milk/milk products, rice/cereal, vegetables, fruits, biscuits/bread, meat, fish and eggs) *Definition* - Ever BF: if the child was ever given breast milk - Duration of EBF: BF but no FF or complementary foods - Total BF: duration of any BF - FF - Time of introduction of fruit juice, rice/cereals, fruits, vegetables, milk products, biscuits and bread, meat, fish and egg	*Assessment* Postal questionnaires (with a single reminder) completed by the parents; questions were those used in ISAAC *Definition* - Wheeze ever - Wheeze in the last 12 mo. - Wheeze in the absence of colds - Doctor diagnosis of asthma - Doctor diagnosis of eczema

Results	Confounders	Remarks, limitations
BF and asthma, wheezing and eczema in the past 12 mo. up to the age of 10 years Unadjusted results and results for FF and time of introduction of complementary foods is presented in tables 5 and 6 below Stratification of the results by the presence of eczema by 6 months of age and family atopic history did not substantially differ from the results of the whole study population (supplementary tables not available in the article).	Maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods	*Limitations (predefined quality criteria)* - Outcome assessment after exposure assessment, no information on blinding - Limited definition of health outcome *Other limitations* - No information on infant feeding beyond 6 mo. The data may be unable to capture the true variation in the overall timing of infant feeding - Possibility that results are a consequence of type II error - Some complementary food groups overlapped somewhat in their constituent food components, limiting the ability of this study to demonstrate associations with individual food groups

	Asthma		Wheezing		Wheezing without cold		Eczema	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No BF	1		1		1		1	
BF $_{ever}$	0.81	0.59-1.13	0.99	0.78-1.26	1.02	0.72-1.45	1.06	0.83-1.35
BF $_{<2.25\ mo.}$	0.90	0.61-1.35	1.11	0.84-1.49	1.30	0.86-1.96	1.12	0.84-1.51
BF $_{\geq 2.25\ mo.}$	0.76	0.53-1.09	0.90	0.69-1.17	0.86	0.58-1.28	1.04	0.81-1.51
EBF $_{<3.73\ mo.}$	0.77	0.52-1.11	0.91	0.70-1.19	0.97	0.66-1.44	0.93	0.71-1.21
EBF $_{\geq 3.75\ mo.}$	0.87	0.60-1.28	1.09	0.82-1.43	1.09	0.73-1.65	1.25	0.95-1.64

ISAAC: International Study of Asthma and Allergies in Childhood; Mo.: Months; SEATON: Study of Eczema and Asthma To Observe the influence of Nutrition; UK: United Kingdom.

Nwaru, 2013

Table 5. Associations between breastfeeding, introduction of foods and the risk of wheeze up to the age of 10 years

Duration of breastfeeding and age at introduction of complementary foods, months	Wheeze in the past 12 months OR (95% CI)*		Wheeze without cold in the past 12 months OR (95% CI)*	
	Unadjusted†	Adjusted‡	Unadjusted†	Adjusted‡
Child ever breastfed				
No	1	1	1	1
Yes	0.85 (0.68–1.06)	0.99 (0.78–1.26)	0.87 (0.63–1.22)	1.02 (0.72–1.45)
P-value	0.150	0.920	0.420	0.901
Exclusive BF				
No BF	1	1	1	1
Lower median < 3.75	0.84 (0.65–1.08)	0.91 (0.70–1.19)	0.90 (0.61–1.30)	0.97 (0.66–1.44)
Upper median ≥ 3.75	0.86 (0.67–1.11)	1.09 (0.82–1.43)	0.85 (0.58–1.25)	1.09 (0.73–1.65)
P-value	0.353	0.420	0.703	0.822
Total BF				
No BF	1	1	1	1
Lower median < 2.25	1.06 (0.81–1.41)	1.11 (0.84–1.49)	1.25 (0.84–1.87)	1.30 (0.86–1.96)
Upper median ≥ 2.25	0.74 (0.58–0.94)	0.90 (0.69–1.17)	0.70 (0.48–1.01)	0.86 (0.58–1.28)
P-value	0.007	0.297	0.009	0.114
Formula feeding				
Yes	1	1	1	1
No	0.62 (0.46–0.84)	0.70 (0.50–0.97)	0.55 (0.34–0.90)	0.70 (0.42–1.15)
P-value	0.002	0.033	0.016	0.160
Time of starting formula feeding				
Lower median < 0.5	1	1	1	1
Upper median ≥ 0.5	0.80 (0.64–1.00)	0.77 (0.56–1.07)	0.75 (0.54–1.05)	0.75 (0.47–2.00)
No formula feeding	0.55 (0.40–0.76)	0.58 (0.38–0.87)	0.48 (0.29–0.80)	0.57 (0.31–1.04)
P-value	0.001	0.029	0.013	0.187
Introduction of juice				
Lower median < 4.50	1	1	1	1
Upper median ≥ 4.50	0.89 (0.71–1.11)	1.11 (0.86–1.41)	0.71 (0.52–0.98)	0.91 (0.63–1.29)
P-value	0.287	0.426	0.040	0.583
Introduction of rice/cereal				
Lower median < 3.75	1	1	1	1
Upper median ≥ 3.75	0.91 (0.74–1.12)	1.05 (0.84–1.31)	0.94 (0.68–1.28)	1.09 (0.79–1.51)
P-value	0.393	0.688	0.688	0.587

Table 5. (continued)

Duration of breastfeeding and age at introduction of complementary foods, months	Wheeze in the past 12 months OR (95% CI)*		Wheeze without cold in the past 12 months OR (95% CI)*	
	Unadjusted†	Adjusted‡	Unadjusted†	Adjusted‡
Introduction of fruits				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	1.09 (0.88–1.34)	1.10 (0.89–1.37)	1.13 (0.83–1.53)	1.15 (0.84–1.58)
P-value	0.422	0.376	0.440	0.374
Introduction of vegetables				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	0.95 (0.77–1.17)	0.99 (0.79–1.22)	0.97 (0.71–1.33)	1.05 (0.76–1.44)
P-value	0.612	0.894	0.852	0.786
Introduction of milk prod.				
Lower median < 5.75	1	1	1	1
Upper median ≥ 5.75	1.11 (0.88–1.41)	1.13 (0.88–1.44)	0.98 (0.70–1.39)	0.97 (0.68–1.39)
P-value	0.371	0.341	0.922	0.888
Introduction of biscuits/bread				
Lower median < 6.00	1	1	1	1
Upper median ≥ 6.00	1.00 (0.80–1.25)	1.00 (0.79–1.26)	0.95 (0.68–1.32)	0.90 (0.64–1.27)
P-value	0.980	0.999	0.764	0.551
Introduction of meat				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	0.92 (0.75–1.14)	0.92 (0.74–1.15)	1.13 (0.81–1.56)	1.18 (0.84–1.64)
P-value	0.471	0.473	0.472	0.341
Introduction of fish				
Lower median < 5.25	1	1	1	1
Upper median ≥ 5.25	0.95 (0.74–1.21)	0.92 (0.72–1.19)	0.94 (0.65–1.36)	0.91 (0.63–1.33)
P-value	0.653	0.546	0.749	0.643
Introduction of eggs				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	0.95 (0.75–1.20)	1.00 (0.78–1.27)	0.90 (0.64–1.27)	0.89 (0.63–1.27)
P-value	0.678	0.997	0.555	0.529

*Analysed using binomial generalized estimating equations with exchangeable correlation structure.

†Included time as a covariate.

‡Adjusted for time, maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods.

Nwaru, 2013

Table 6. Associations between breastfeeding, introduction of foods and the risk of eczema and asthma up to the age of 10 years

Duration of breastfeeding and age at introduction of complementary foods, months	Doctor-diagnosed eczema in the past 12 months OR (95% CI)*		Doctor-diagnosed asthma in the past 12 months OR (95% CI)*	
	Unadjusted	Adjusted†	Unadjusted	Adjusted†
Child ever breastfed				
No	1	1	1	1
Yes	0.95 (0.76–1.20)	1.06 (0.83–1.35)	0.67 (0.50–0.90)	0.81 (0.59–1.13)
P-value	0.678	0.632	0.009	0.216
Exclusive BF				
No BF	1	1	1	1
Lower median < 3.75	0.90 (0.69–1.16)	0.93 (0.71–1.21)	0.69 (0.49–0.97)	0.77 (0.52–1.11)
Upper median ≥ 3.75	1.01 (0.79–1.31)	1.25 (0.95–1.64)	0.65 (0.46–0.92)	0.87 (0.60–1.28)
P-value	0.538	0.049	0.031	0.366
Total BF				
No BF	1	1	1	1
Lower median < 2.25	1.10 (0.82–1.46)	1.12 (0.84–1.51)	0.85 (0.59–1.25)	0.90 (0.61–1.35)
Upper median ≥ 2.25	0.90 (0.71–1.15)	1.04 (0.81–1.35)	0.58 (0.42–0.81)	0.76 (0.53–1.09)
P-value	0.289	0.735	0.003	0.305
Formula feeding				
Yes	1	1	1	1
No	0.77 (0.59–1.00)	0.83 (0.63–1.10)	0.51 (0.34–0.78)	0.65 (0.41–1.03)
P-value	0.046	0.202	0.002	0.070
Time of starting formula feeding				
Lower median < 0.5	1	1	1	1
Upper median ≥ 0.5	0.97 (0.78–1.22)	0.93 (0.68–1.29)	0.70 (0.51–0.94)	0.72 (0.47–1.12)
No formula feeding	0.75 (0.56–1.00)	0.79 (0.54–1.15)	0.43 (0.28–0.67)	0.52 (0.30–0.90)
P-value	0.114	0.404	0.001	0.068
Introduction of juice				
Lower median < 4.50	1	1	1	1
Upper median ≥ 4.50	0.89 (0.71–1.10)	0.97 (0.77–1.23)	0.63 (0.48–0.85)	0.83 (0.60–1.16)
P-value	0.282	0.812	0.002	0.276
Introduction of rice/cereal				
Lower median < 3.75	1	1	1	1
Upper median ≥ 3.75	1.04 (0.85–1.27)	1.21 (0.97–1.50)	0.77 (0.58–1.02)	0.95 (0.70–1.29)
P-value	0.690	0.085	0.071	0.760

Table 6. (continued)

Duration of breastfeeding and age at introduction of complementary foods, months	Doctor-diagnosed eczema in the past 12 months OR (95% CI)*		Doctor-diagnosed asthma in the past 12 months OR (95% CI)*	
	Unadjusted	Adjusted†	Unadjusted	Adjusted†
Introduction of fruits				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	1.07 (0.87–1.30)	1.10 (0.90–1.36)	1.05 (0.79–1.38)	1.08 (0.80–1.45)
P-value	0.537	0.355	0.755	0.633
Introduction of vegetables				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	0.95 (0.78–1.16)	0.99 (0.80–1.22)	0.91 (0.69–1.21)	0.98 (0.73–1.32)
P-value	0.602	0.941	0.523	0.883
Introduction of milk prod.				
Lower median < 5.75	1	1	1	1
Upper median ≥ 5.75	1.15 (0.92–1.43)	1.16 (0.92–1.46)	0.99 (0.73–1.34)	0.91 (0.66–1.25)
P-value	0.228	0.210	0.944	0.560
Introduction of biscuits/bread				
Lower median < 6.00	1	1	1	1
Upper median ≥ 6.00	1.21 (0.97–1.51)	1.34 (1.06–1.69)	0.89 (0.66–1.19)	0.96 (0.69–1.32)
P-value	0.093	0.016	0.425	0.779
Introduction of meat				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	1.00 (0.81–1.23)	1.03 (0.83–1.28)	0.91 (0.68–1.21)	0.98 (0.72–1.32)
P-value	0.986	0.774	0.518	0.891
Introduction of fish				
Lower median < 5.25	1	1	1	1
Upper median ≥ 5.25	0.99 (0.78–1.26)	0.99 (0.77–1.27)	0.80 (0.58–1.11)	0.83 (0.59-1.16)
P-value	0.934	0.952	0.179	0.276
Introduction of eggs				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	0.88 (0.70–1.10)	0.91 (0.72–1.15)	0.70 (0.52–0.94)	0.78 (0.57–1.08)
P-value	0.264	0.412	0.018	0.137

*Analysed using discrete-time hazard model.

†Adjusted for maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Body fatness	Peneau, 2014 Journal of Pediatrics France Prospective cohort study 1984 – 2004	To investigate whether BF is correlated with body fatness in adulthood	*Setting* Healthy infants and toddlers born in 1984 were invited for a free health examination at age 10 mo., 2 yrs, and 4 yrs at a health center for children. *Study population* 222 subjects who finished at least 2 visits (at 10 mo, 2 yrs, or 4yrs) were invited to participate in the ELANCE prospective study on nutrition and growth. *Sample size* n=73	*Age at enrolment* New-borns *Age at assessment of outcome* 20 years	*Exposure assessment* Face-to-face interviews with children's mothers *Exposure definition* BF: any kind of BF, including PBF regardless of duration No BF: BF was never initiated	*Health outcome assessment* Body measurements performed in health centre for adults by a trained investigator following standard procedures. *Health outcome definition* - BMI: NR - SF: measured at subscapular site - FM: derived from analyser manufacturer's equations

Results							Confounders	Remarks, limitations
BF and BM, SF, FMI							Mother's BMI and father's profession (unskilled/semiskilled vs skilled/professional) and early nutrition: nutritional intake at ages 10 months and 2 years (ie, total energy and % energy from each nutrient).	*Limitations (predefined quality criteria)* - Not reported whether assessment of exposure and outcome were blind - Health outcome was not well defined *Other limitations* - Selection bias may have been introduced into the study if the mothers who completed at least 2 visits for their children were better able to BF or feed their children with healthy food. It may underestimate the association between BF and body fatness. - Misclassification of the exposure is also possible. Although the author defined BF as any breastfeeding including partial breastfeeding, regardless of duration, mothers who fed their children for a short period may still report it as no BF.
BF (yes vs no)	BMI, kg/m^2		SF		FM			
Adjustments	β (95%CI)	p	β (95%CI)	p	β (95%CI)	p		
Adjustment for nutritional intake at age 10 months*								
Proteins	-0.228 (-1.95-1.49)	0.79	-20.16 (-43.9-3.59)	0.094	-1.14 (-4.33-2.04)	0.48		
Lipids	-0.606 (-2.26-1.05)	0.47	-23.33 (-46.7-0.06)	0.051	-1.89 (-4.94-1.16)	0.22		
carbohydrates	-0.618 (-2.32-1.09)	0.47	-22.74 (-46.4-0.98)	0.060	-1.92 (-5.07-1.22)	0.23		
Adjustment for nutritional intake at age 2 years*								
Proteins	-0.771 (-2.36-0.92)	0.38	-25.12 (-47.95- -2.30)	0.032	-2.25 (-5.36-0.86)	0.15		
Lipids	-0.891 (-2.52-0.74)	0.28	-28.25 (-50.28- -6.21)	0.013	-2.83 (-5.86-0.20)	0.066		
carbohydrates	-0.865 (-2.51-0.78)	0.30	-28.27 (-50.64- -5.90)	0.014	-2.76 (-5.86-0.33)	0.079		
*Other confounders adjusted were sex, mothers' BMI, father's occupation and energy (kcal) -Unadjusted outcomes can be found in table 2.								
BMI: Body mass index; SF: Skinfold thickness; FM: Fat mass.								

Peneau, 2014

Table II. Multiple linear regression models for breastfeeding predicting anthropometry and body composition at age 20 years, adjusted for the usual confounding factors and nutritional intakes at age 10 months (n = 73) or age 2 years (n = 68) in the ELANCE longitudinal study

	Breastfeeding (yes vs no)	BMI, kg/m^2		Subscapular SF, %*		FM (BIA), kg†	
Model	**Adjustments**	**β (95% CI)**	***P***	**β (95% CI)**	***P***	**β (95% CI)**	***P***
1	Sex	−0.029 (−1.73 to 1.67)	.97	−19.18 (−42.5 to 4.14)	.11	−0.64 (−3.81 to 2.53)	.69
2	Model 1 + mothers' BMI + father's occupation	−0.413 (−2.12 to 1.29)	.63	−22.58 (−45.6 to 0.47)	.055	−1.52 (−4.64 to 1.60)	.33
	Adjustment for nutritional intake at age 10 months						
3	Model 2 + energy, kcal	−0.431 (−2.11 to 1.25)	.61	−22.70 (−45.8 to 0.40)	.054	−1.54 (−4.63 to 1.56)	.32
4a	Model 3 + proteins, %	−0.228 (−1.95 to 1.49)	.79	−20.16 (−43.9 to 3.57)	.094	−1.14 (−4.33 to 2.04)	.48
4b	Model 3 + lipids, %	−0.606 (−2.26 to 1.05)	.47	−23.33 (−46.7 to 0.06)	.051	−1.89 (−4.94 to 1.16)	.22
4c	Model 3 + carbohydrates, %	−0.618 (−2.32 to 1.09)	.47	−22.74 (−46.4 to 0.98)	.060	−1.92 (−5.07 to 1.22)	.23
	Adjustment for nutritional intake at age 2 years						
5	Model 2 + energy, kcal	−0.772 (−2.39 to 0.85)	.34	−25.35 (−47.88 to −2.83)	.028	−2.36 (−5.44 to 0.72)	.13
6a	Model 5 + proteins, %	−0.721 (−2.36 to 0.92)	.38	−25.12 (−47.95 to −2.30)	.032	−2.25 (−5.36 to 0.86)	.15
6b	Model 5 + lipids, %	−0.891 (−2.52 to 0.74)	.28	−28.25 (−50.28 to −6.21)	.013	−2.83 (−5.86 to 0.20)	.066
6c	Model 5 + carbohydrates, %	−0.865 (−2.51 to 0.78)	.30	−28.27 (−50.64 to −5.90)	.014	−2.76 (−5.86 to 0.33)	.079

*Percent subscapular SF change between non–breastfed infants and breastfed infants.[23]
†For FM (BIA), height at age 20 years was added into all models.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Develop-mental delay	Sacker, 2006 Pediatrics UK Cross-sectional study 2000 – 2001	To investigate whether the duration and exclusivity of BF affects the likelihood of gross and fine motor delay in infants and to examine the effect of factors that might explain any observed differences	*Setting* MCS, which includes infants born in the UK during a 12-month period that spanned 2001-2002 *Study population* Term singleton infants who weighed >2,500 g at birth and were not placed in a special care infant unit and whose mothers participated in the first survey of the MCS *Sample size* n=14,660	*Age at enrolment* NR *Age at assessment of outcome* 9 months on average	*Assessment* A survey that involved home visits by interviewers when the CH member was aged 9 months on average *Definition* Categories based on UK infant feeding guidelines at time of survey: - Never BF: never initiated BF - Short duration: BF < 2 mo. - Intermediate duration: BF 2-4 mo - Prolonged PBF: BF ≥4 mo. with supplementary feeds or solids started <4 mo. - Prolonged EBF: BF ≥4 mo. with supplementary feeds or solids started >4 mo.	*Assessment* - A survey that involved home visits by interviewers when the CH member was aged 9 months on average - The questionnaire items on developmental milestones assessed gross motor coordination and fine motor coordination (adapted from the Denver Developmental Screening test *Definition* - Delay in the developmental milestones: infant has not reached a milestone that 90% of singleton MCS infants in that age group have reached, i.e.: - Gross motor coordination › Infant can sit up without being supported › If infant is put down on the floor, he or she can move about from one place to another › Infant can stand up while holding onto something, such as furniture › Infant can walk a few steps on his or her own - Fine motor coordination › Infant grabs objects using the whole hand › Infant passes a toy back and forth from one hand to another › Infant can pick up a small object using forefinger and thumb only › Infant puts his or her hands together

Results			Confounders	Remarks, limitations
BF and fine and gross motor delay			- Biological: birth weight, gestation in weeks, mother's age in years, and smoking during pregnancy - Socioeconomic: the National Statistics Socio-economic Class, mother's educational qualifications, mother's employment status, and partnership status - Psychosocial: mother's Malaise Inventory score (a measure of psychological distress), mother's postnatal attachment score, and the mother's attitude toward child care, other caregivers, and the child's time spent being cared for by others	*Limitations (predefined quality criteria)* - Exposure and outcome assessed at same time point, no information on blinding *Other limitations* - None
	Fine motor delay	*Gross motor delay*		
BF (ref = never BF)	aOR (95% CI)	aOR (95% CI)		
Short BF	0.94 (0.75–1.17)	0.81 (0.69–0.96)		
Intermediate BF	0.84 (0.61–1.16)	0.75 (0.58–0.96)		
Prolonged PBF	0.78 (0.58–1.04)	0.80 (0.65–0.98)		
Prolonged EBF	0.93 (0.74–1.16)	0.67 (0.54–0.84)		
Unadjusted ORs and ORs adjusted for biological, socioeconomic and psychological confounders separately are presented in table 3.				
MCS: Millennium Cohort Study; UK: United Kingdom; Mo.: Months.				

Sacker, 2006

TABLE 3 Odds (95% CIs) of Developmental Delay According to Duration of Breastfeeding for 14 660 Millennium Cohort Infants With No Missing Information on the Confounding Factors

Breastfeeding Pattern	Unadjusted	Adjusted for Biological Factors[a]	Adjusted for Socioeconomic Factors[b]	Adjusted for Psychosocial Factors[c]	Adjusted for All Factors
Gross motor delay					
1. Never breastfed	1.00	1.00	1.00	1.00	1.00
2. Short duration	0.79 (0.67–0.93)	0.78 (0.66–0.92)	0.83 (0.70–0.98)	0.82 (0.70–0.97)	0.81 (0.69–0.96)
3. Intermediate duration	0.72 (0.56–0.93)	0.70 (0.54–0.89)	0.78 (0.61–1.00)	0.77 (0.60–0.98)	0.75 (0.58–0.96)
4. Prolonged partial	0.78 (0.63–0.96)	0.76 (0.61–0.94)	0.81 (0.66–1.00)	0.81 (0.66–0.99)	0.80 (0.65–0.98)
5. Prolonged exclusive	0.68 (0.56–0.83)	0.65 (0.54–0.80)	0.69 (0.56–0.85)	0.71 (0.58–0.86)	0.67 (0.54–0.84)
Wald test	$P = .0005$	$P = .0001$	$P = .005$	$P = .005$	$P = .002$
Fine motor delay					
1. Never breastfed	1.00	1.00	1.00	1.00	1.00
2. Short duration	0.83 (0.67–1.04)	0.87 (0.70–1.09)	0.93 (0.74–1.16)	0.87 (0.70–1.09)	0.94 (0.75–1.17)
3. Intermediate duration	0.71 (0.52–0.98)	0.77 (0.56–1.06)	0.83 (0.61–1.14)	0.77 (0.56–1.05)	0.84 (0.61–1.16)
4. Prolonged partial	0.62 (0.47–0.83)	0.71 (0.54–0.93)	0.74 (0.55–0.99)	0.69 (0.52–0.92)	0.78 (0.58–1.04)
5. Prolonged exclusive	0.73 (0.59–0.92)	0.83 (0.66–1.05)	0.86 (0.69–1.08)	0.83 (0.66–1.04)	0.93 (0.74–1.16)
Wald test	$P = .005$	$P = .11$	$P = .30$	$P = .09$	$P = .49$

[a] Mother's age at birth, birth weight, gestation, and smoking during pregnancy.
[b] Social class, mother's educational qualifications, mother's employment status, and lone parenthood.
[c] Malaise Inventory, postnatal attachment, parenting views, number of siblings, care while working, and hours cared for by others.

Annex B Health outcomes related to the mother

B-I Reviews with health outcomes related to the mother

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Diabetes type 2	Aune, 2014 Nutrition, Metabolism & Cardiovascular Diseases Systematic review and meta-analysis [14]	To clarify the size of the association, if there is a dose-response relationship between greater BF and type 2 diabetes risk, potential confounding from other risk factors, and whether this partly might be explained by reduced postpartum weight retention by comparing risk estimates adjusted and not adjusted for BMI	*Inclusion criteria* - Prospective cohort, case-cohort, nested case-control design - Investigate the association between BF and maternal risk of type 2 diabetes - Estimates of relative risk (HR, RR, OR) available with 95% CI - Quantitative measure of BF duration for dose-response analysis - Total number of cases and person-years *Exclusion criteria* - Review, letters, news articles, erratum, protocols, cross-sectional studies - Offspring risk of diabetes - Not relevant outcome or data	PubMed, EMBASE, Ovid databases (up to September 19th 2013) Additional manual search on the references of the identified reports *Number of hits in original search* - Unique hits: n=2,424 - PubMed: n=1,224 - Embase: n=2,055 - Ovid-Medline: n=1,035 *Number of included articles* - Total: n=5 (6 studies), all cohorts	10,842 women with diabetes type 2 among 273,961 participants. Participants were women with gestational diabetes mellitus, American nurses and women from the general population Western (USA 2x, Germany 1x, Australia 1x) and non-western (China 1x) countries	*Assessment* 5 studies retrospectively by questionnaire at baseline, 1 study prospectively NR, but one study assessed BF directly after birth *Definition* BF, BFD per child, total BFD

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Assessment NR NR, but one prospective study included *Definition* Maternal diabetes mellitus type 2	*BFD and type 2 diabetes* - $SRR_{\text{high vs. low BFD}}$ (95% CI)= 0.68 (0.57-0.82). See figure 2. P for heterogeneity = 0.001, I^2= 74.7% *BF and type 2 diabetes (n=2; 3 studies), by BMI correction* - Non-BMI adjusted results: $SRR_{\text{high vs. low BFD}}$ (95% CI)=0.82 (0.69-0.99) - BMI-adjusted results: $SRR_{\text{high vs. low BFD}}$ (95% CI)=0.74 (0.58-0.94) *Dose-response analysis and type 2 diabetes* - $SRR_{\text{per 12 mo. increase in lifetime duration of BF}}$ (95% CI)= 0.91 (0.86-0.96) (n=4) See figure 3A P for heterogeneity = 0.001, I^2= 80.9%	Adjustments varied per included studies. All studies adjusted for at least age, BMI and smoking (during pregnancy).	- Study quality scores were relatively high and quite homogenous - No evidence of publication bias with the statistical tests used *Limitations (predefined quality criteria)* - In 5/6 studies BF data were recalled retrospectively. - No definition of BF provided - Not reported whether assessment of health outcome was after assessment of exposure. Blinding NR, but

[14] One of the included articles in this review were included in the report of RIVM (2007). Two of the included articles in this review were included in the review of Jäger (2014).

	- SRR $_{\text{per 3 mo. increase in BFD per child}}$ (95% CI)= 0.89 (0.77-1.04) (n=3) See figure 4A P for heterogeneity = 0.001, I^2= 80.9% - Evidence of nonlinearity by total lifetime duration of BF and BFD per child, both $P_{\text{nonlinearity}} < 0.0001$. Reduction in risk was steeper when increasing BFD from a short duration. See figure 3B and 4B respectively *Stratification for geographic location, BFD and type 2 diabetes* - Europe: SRR $_{\text{high vs. low BFD}}$ (95% CI) = 0.54 (0.34-0.85) (n=1) - America: SRR $_{\text{high vs. low BFD}}$ (95% CI) = 0.77 (0.63-0.94) (n=3) - Asia: SRR $_{\text{high vs. low BFD}}$ (95% CI) = 0.68 (0.52-0.89) (n=1) - Australia: SRR $_{\text{high vs. low BFD}}$ (95% CI) = 0.58 (0.50-0.68) (n=1) P for heterogeneity between subgroups with meta-regression analysis 0.71 For more subgroup analysis see table 2		probably not - Health outcome not well-defined *Other limitations* - Number of studies included was moderate - None of the studies included in the analysis reported whether BF history had been validated.
BMI: Body mass index; USA: United States of America.			

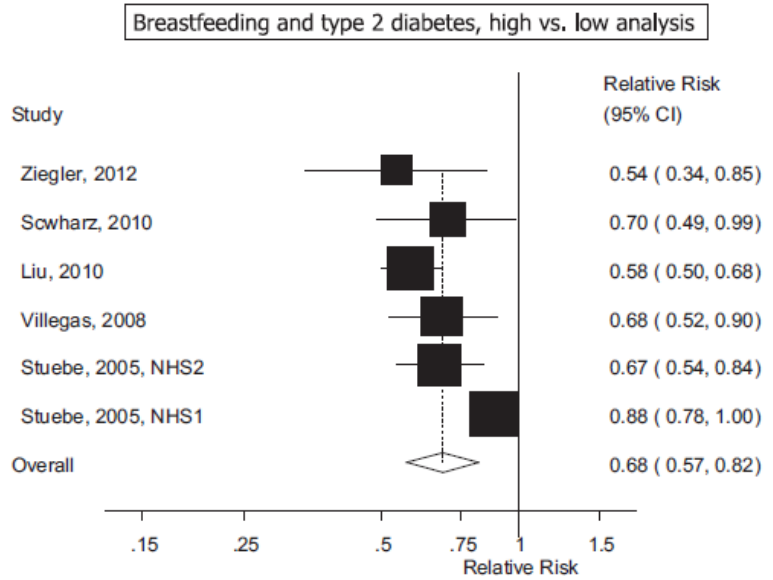


Figure 2 Breastfeeding and type 2 diabetes, high vs. low analysis.

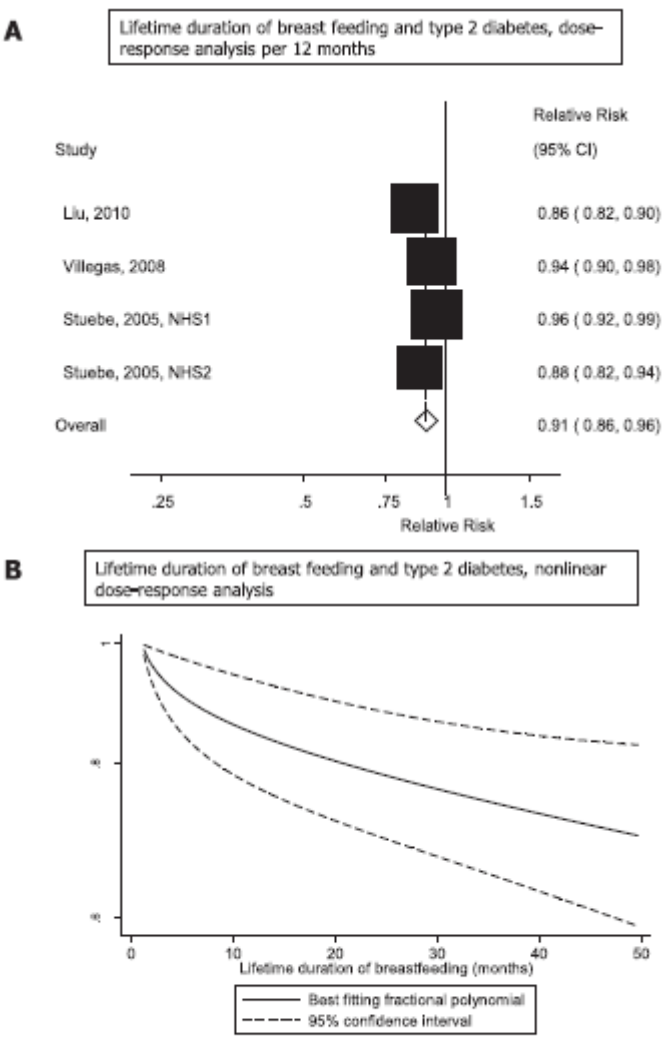


Figure 3 Lifetime duration of breastfeeding and type 2 diabetes. A) Linear dose–response analysis per 12 months. B) Nonlinear dose–response analysis.

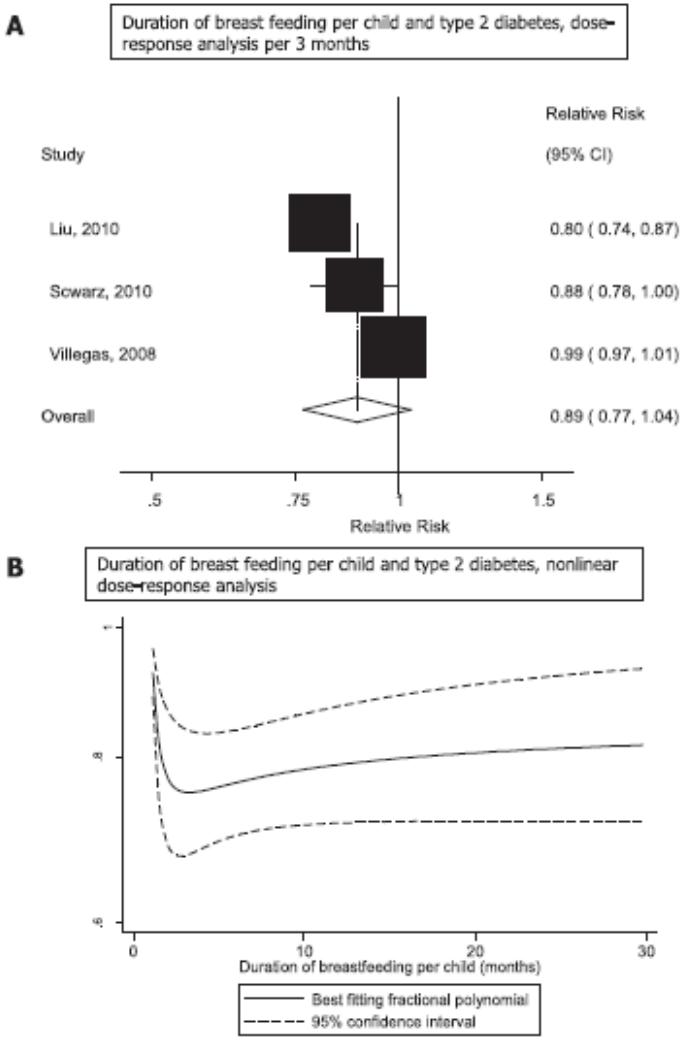


Figure 4 Duration of breastfeeding per child and type 2 diabetes. A) Linear dose–response analysis per 3 months. B) Nonlinear dose–response analysis.

Table 2 Subgroup analyses of breastfeeding and type 2 diabetes risk, highest vs. lowest analysis.

		Reference no.	*n*	RR (95% CI)	I^2 (%)	P_h[a]	P_h[b]
All studies		14–18	6	0.68 (0.57-0.82)	74.7	0.001	
Geographic location							
Europe		18	1	0.54 (0.34-0.85)			0.71
America		14–15	3	0.77 (0.63-0.94)	61.6	0.07	
Asia		16	1	0.68 (0.52-0.89)			
Australia		17	1	0.58 (0.50-0.68)			
Number of cases							
Cases <1000		15,16,18	3	0.66 (0.54-0.80)	0	0.64	0.67
Cases ≥1000		14,17	3	0.70 (0.53-0.93)	81.4	0.005	
Assessment of breastfeeding							
Prospective		18	1	0.54 (0.34-0.85)			0.43
Retrospective		14–17	5	0.70 (0.58–0.85)	78.0	0.001	
Study quality score							
0–3 stars			0				0.96
4–6		14,17,18	4	0.67 (0.52–0.87)	84.6	<0.0001	
7–9		15,16	2	0.69 (0.55–0.85)	0	0.90	
Adjustment for confounding factors							
Age	Yes	14–18	6	0.68 (0.57–0.82)	74.7	0.001	NC
	No		0				
Alcohol	Yes	15–17	3	0.61 (0.54–0.70)	0	0.45	0.35
	No	14, 18	3	0.72 (0.56–0.94)	73.5	0.02	
Smoking	Yes	14–18	6	0.68 (0.57–0.82)	74.7	0.001	NC
	No		0				
Body mass index	Yes	14–18	6	0.68 (0.57–0.82)	74.7	0.001	NC
	No		0				
Physical activity	Yes	14–17	5	0.70 (0.58–0.85)	78.0	0.001	0.43
	No	18	1	0.54 (0.34–0.85)			
Family history of diabetes	Yes	14, 15, 17	4	0.70 (0.56–0.89)	83.3	<0.001	0.58
	No	16, 18	2	0.64 (0.51–0.81)	0	0.40	
Income	Yes	16, 17	2	0.60 (0.53–0.69)	0	0.32	0.31
	No	14, 15, 18	4	0.73 (0.59–0.89)	63.0	0.04	
Education	Yes	15–17	3	0.61 (0.54–0.70)	0	0.45	0.35
	No	14, 18	3	0.72 (0.56–0.94)	73.5	0.02	
Parity	Yes	15, 16, 18	3	0.66 (0.54–0.80)	0	0.64	0.67
	No	14, 17	3	0.70 (0.53–0.93)	88.8	<0.0001	

n denotes the number of studies.
NC = not calculable.
[a] *p* for heterogeneity within each subgroup.
[b] *p* for heterogeneity between subgroups with meta-regression analysis.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Diabetes type 2	Jäger, 2014 Diabetologia Prospective study and meta-analysis[15]	To examine the association between breast-feeding and maternal risk of type 2 diabetes and to investigate whether this association is mediated by anthropometric and biochemical factors	*Inclusion criteria* - Prospective cohort study - Type 2 diabetes as outcome - Description of BF assessment - Presentation of RRs with 95% CI - Description of adjustment for potential confounders *Exclusion criteria* - Animal studies - Human studies that focused on children's health or other outcomes such as weight change, metabolic changes, cardiovascular diseases or GDM	NR (search completed on 27 March 2014) *Number of hits in original search* - PubMed and Web of Science, n=300 - Web of Science 'Times cited' function, n=8 *Number of included articles* n=3, including 4 prospective cohort studies	220,360 mothers, involving 8,064 incident cases of type 2 diabetes -USA (2 cohorts): 157,003 mothers, 6,277 cases -China: 62,095 mothers, 1,561 cases -Germany: 1,262 mothers, 226 cases	*Assessment* Self-reported BF Age at assessment: NR *Definition* - Self-reported total lifetime duration of BF for all pregnancies in months, n=2 - Self-reported BF duration per child in months, n=2

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment Self-reported diagnosis, n=4 (confirmed by treating physician in n=1) Follow-up ranged from 4.6 to 16 yrs *Definition* Self-reported type 2 diabetes	*BF(D) and maternal type 2 diabetes (adjusted for potential confounders)* HR $_{\text{BF vs. no BF}}$ (95% CI) = 0.95 (0.90-1.00) HR $_{\text{BFD >0 to 3 mo. vs. no BF}}$ (95% CI) = 0.97 (0.91-1.04) HR $_{\text{BFD >3 to 6 mo. vs. no BF}}$ (95% CI) = 1.00 (0.92-1.09) HR $_{\text{BFD >6 to 11 mo. vs. no BF}}$ (95% CI) = 0.89 (0.82-0.97) HR $_{\text{BFD >11 to 23 mo. vs. no BF}}$ (95% CI) = 0.88 (0.81-0.96) HR $_{\text{per additional year of BF}}$ (95% CI) = 0.93 (0.90-0.96) *BF(D) and maternal type 2 diabetes (adjusted for potential confounders + baseline BMI)* HR $_{\text{BF vs. no BF}}$ (95% CI) = 0.86 (0.71-1.02) HR $_{\text{BFD >0 to 3 mo. vs. no BF}}$ (95% CI) = 0.98 (0.92-1.05) HR $_{\text{BFD >3 to 6 mo. vs. no BF}}$ (95% CI) = 1.01 (0.93-1.10) HR $_{\text{BFD >6 to 11 mo. vs. no BF}}$ (95% CI) = 0.92 (0.85-1.00) HR $_{\text{BFD >11 to 23 mo. vs. no BF}}$ (95% CI) = 0.90 (0.83-0.99) HR $_{\text{per additional year of BF}}$ (95% CI) = 0.94 (0.91-0.97) Further adjustment for biomarkers is presented in table 4 (n=1)	Analyses were adjusted for potential confounders, which varied per included cohort Additional analyses were conducted adjusted for potential confounders plus baseline BMI	-Included cohorts were NHS I and II, Shanghai Women's Health Study and EPIC-Potsdam study. The EPIC Potsdam Study was described in the current article, next to the meta-analysis. The Shanghai Women's Health Study was only included in the association BFD >6 to 11 months vs. no BF. *Limitations (predefined quality criteria)* - Age at exposure assessment was not reported, but was likely many years after BF as lifetime lactation was assessed - Breastfeeding was self-reported irrespective of additional feeding, and there was not stratified as exclusive or non-exclusive - Outcome was assessed after exposure assessment, no information about blinding - Health outcome was self-reported and only confirmed by a physician in one cohort - Residual confounding cannot be excluded *Other limitations* -There was high heterogeneity between the included studies, which complicates drawing of general conclusions - Misclassification as false-negatives is a possibility - The Egger test provided evidence of publication bias
EPIC: European Prospective Investigation to Cancer and Nutrition; GDM: Gestational diabetes mellitus; NHS: Nurses' Health Study.			

[15] One of the included articles in this review were included in the report of RIVM (2007). Two of the included articles in this review were included in the review of Aune (2014).

Jäger, 2014

Table 4 HRs (95% CI) for type 2 diabetes by duration of breast-feeding with adjustment for biochemical mediators, EPIC-Potsdam study

	Ever breast-fed		Cumulative duration of breast-feeding					
	No	Yes	0	≤3 weeks	>3 weeks to <2 months	≥2 months to <6 months	≥6 months	Per additional 6 months of breast-feeding
n cases	49	177	49	31	38	66	42	226
Model I	1	0.77 (0.47, 1.25)	1	1.16 (0.62, 2.19)	0.77 (0.43, 1.41)	0.82 (0.47, 1.41)	0.47 (0.25, 0.89)	0.80 (0.61, 1.04)
Model I + HDL, LDL, triacylglycerols	1	0.88 (0.55, 1.42)	1	1.38 (0.71, 2.69)	0.93 (0.51, 1.67)	0.91 (0.53, 1.57)	0.55 (0.29, 1.02)	0.85 (0.66, 1.09)
Model I + CRP	1	0.73 (0.45, 1.18)	1	1.11 (0.59, 2.08)	0.72 (0.39, 1.32)	0.77 (0.45, 1.33)	0.47 (0.25, 0.88)	0.81 (0.62, 1.06)
Model I + fetuin-A, GGT	1	0.78 (0.48, 1.26)	1	1.24 (0.66, 2.33)	0.78 (0.43, 1.42)	0.83 (0.48, 1.42)	0.47 (0.24, 0.90)	0.81 (0.62, 1.06)
Model I + adiponectin	1	0.91 (0.57, 1.45)	1	1.64 (0.90, 3.00)	0.91 (0.51, 1.64)	0.93 (0.54, 1.59)	0.58 (0.31, 1.07)	0.84 (0.64, 1.10)
Model I + HDL, LDL, triacylglycerols + CRP + fetuin-A, GGT + adiponectin	1	0.95 (0.59, 1.53)	1	1.74 (0.91, 3.32)	1.00 (0.55, 1.83)	0.91 (0.53, 1.58)	0.62 (0.33, 1.16)	0.89 (0.68, 1.16)

GGT, γ-glutamyltransferase

Model I adjusted for age at baseline, marital status, education, occupation, smoking, sport, cycling, alcohol intake, coffee consumption, intake of red meat, intake of whole-grain bread, age at birth of last child, number of children, duration of oral contraceptive use, BMI at age of 25 years, BMI and waist circumference at baseline examination. n=1,262

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Epithelial ovarian cancer (EOC)	Luan, 2013 American Journal of Clinical Nutrition Systematic review and meta-analysis[16]	To summarize available evidence of the association between BF and BF duration and EOC risk from published CH and CC studies	*Inclusion criteria* - Studies published in English - CC or CH design - Investigate the association between ever BF or the total duration of BF and incidence EOC - Present HR, OR or RR with 95% CIs or data necessary to calculate these - When multiple publications of the same study were available, the publication with the largest number of cases and most-applicable information was included	From database initiation until December 31, 2012 *Number of hits in original search* - Total, n=6,892 - MEDLINE, n=6,888 - Reference lists, n=4 *Number of included articles* - Total: n=35 (from 1983-2012) - CC studies: n=30 - CH studies: n=5	14,465 EOC cases and 706,152 non-cases - CH studies: 2 USA, 2 Europe, 1 Japan - CCI studies: 12 USA, 3 China, 3 Japan, 2 Australia, 2 Sweden, 2 Italy, 1 Denmark, 1 Poland, 1 UK, 1 Mexico, 2 multiple countries	*Assessment* Self-administered questionnaires or by a trained interviewer Age at assessment was not reported *Definition* Ever BF and total duration of BF (for all children combined) CH studies: - longest total duration: 13mo->24mo - shortest total duration: never-<1mo CC studies: - longest total duration: 9mo->48mo - shortest total duration: never-<24mo

Health outcome assessment and definition	Results	Confounders	Remarks
Assessment Cancer registries or medical records Age at assessment was not reported *Definition* Occurrence of EOC determined as described above	*Association BF and EOC risk* SRR $_{\text{BF ever vs. never}}$ (95% CI) = 0.76 (0.69-0.83) (n=32) SRR $_{\text{BF longest vs. shortest}}$ (95% CI) = 0.65 (0.55-0.78) (n=26) SRR $_{\text{per 5 mo increase}}$ (95% CI)= 0.92 (0.90-0.95) (n=25): Several subgroup analyses and adjusted analyses including heterogeneity score are presented in tables 2, 3 and 4 below.	Study-specific adjusted RRs were used as measures for the association between studies. Adjustments varied between included studies. The meta-analysis was stratified for the following confounders: parity, BMI, OC use and smoking	*Limitations (predefined quality criteria)* - Time of assessing BF was not reported - Some recent CH studies provided detailed information of adjustment for confounders, whereas some early CC studies adjusted for fewer factors - Individual studies may have failed to control for potential confounders, which may have introduced bias in an unpredictable direction - Authors did not use the Newcastle-Ottawa Scale to assess the methodological quality of all included studies because quality scoring in a meta-analysis of observational studies is controversial, lacks demonstrated validity, and sometimes results may not be associated with quality. Instead, authors carried out numerous subgroup and sensitivity analyses *Other limitations* - As this was a meta-analysis of observational studies, it was prone to biases (e.g. recall and selection bias) inherent in the original studies - It is possible that the relations reported by CC studies may have been overstated as a result of recall or interviewer bias - Significant heterogeneity and a possible publication bias must be considered, however there was no indication of publication bias by using Egger's test, Begg's test or observation of funnel plots in any of the analyses
BMI: Body mass index; EOC: Epithelial ovarian cancer; Mo: months; OC: Oral contraceptive; UK: United Kingdom; USA: United States of America.			

Luan, 2013

[16] Nine of the included articles in this review were included in the report of RIVM (2007).

TABLE 2
Summary risk estimates of the association between breastfeeding and ovarian cancer risk

	Studies	Summary RR (95% CI)	*Q* statistic	I^2	P_h[1]	P_h[2]
	n			%		
Overall	32	0.76 (0.69–0.83)	69.40	55.3	<0.001	—
Subgroup analyses						
Study design						0.090
Cohort studies	5	0.88 (0.78, 0.99)	0.73	0	0.947	
Case-control studies	27	0.74 (0.67, 0.82)	62.36	58.3	<0.001	
Exposure assessment						0.065
Trained interviewer	15	0.68 (0.57, 0.80)	51.59	72.9	<0.001	
Self-administered questionnaire	12	0.82 (0.75, 0.90)	7.06	0	0.794	
Type of control subjects						0.158
Population based	16	0.73 (0.68, 0.78)	22.91	34.5	0.086	
Hospital based	10	0.78 (0.60, 1.02)	31.01	71.0	<0.001	
Study population						0.862
Asians	7	0.69 (0.53, 0.89)	3.99	0	0.678	
Americans	13	0.71 (0.63, 0.81)	35.90	66.6	<0.001	
Europeans	8	0.85 (0.69, 1.06)	19.75	64.6	0.006	
Cancer grading						0.645
Invasive	5	0.62 (0.53, 0.72)	6.14	34.9	0.189	
Borderline	4	0.57 (0.44, 0.74)	2.53	0	0.470	
Cancer histotype						0.267
Serous	7	0.82 (0.68, 0.99)	13.91	56.9	0.031	
Mucinous	6	0.80 (0.64, 1.00)	7.10	29.6	0.213	
Endometrioid	3	0.65 (0.47, 0.89)	2.10	5.0	0.349	
Clear cell	2	0.67 (0.39, 1.15)	0.92	0	0.336	
Adjustment for confounders						
Parity						0.285
Yes	22	0.78 (0.71, 0.85)	42.23	50.3	0.004	
No	10	0.70 (0.57, 0.87)	18.55	51.5	0.029	
BMI						0.803
Yes	5	0.79 (0.69, 0.91)	4.43	9.7	0.351	
No	27	0.75 (0.68, 0.83)	64.71	59.8	<0.001	
OC[3] use						0.782
Yes	17	0.77 (0.70, 0.84)	32.56	50.9	0.008	
No	15	0.87 (0.69, 1.09)	34.97	60.6	0.001	
Smoking						0.505
Yes	7	0.71 (0.57, 0.88)	15.32	60.8	0.018	
No	25	0.77 (0.70, 0.85)	54.00	55.6	<0.001	

[1] *P* value for heterogeneity within each subgroup.
[2] *P* value for heterogeneity between subgroups with meta-regression analysis.
[3] OC, oral contraceptive.

Luan, 2013

TABLE 3
Summary risk estimates of the association between the total duration of breastfeeding and ovarian cancer risk: longest compared with shortest durations[1]

	Studies	Summary RR (95% CI)	*Q* statistic	I^2	P_h[2]	P_h[3]
	n			%		
Overall	26	0.65 (0.55, 0.78)	70.26	64.4	<0.001	—
Subgroup analyses						
Study design						0.511
Cohort studies	3	0.80 (0.66, 0.98)	1.69	0	0.429	
Case-control studies	23	0.63 (0.52, 0.78)	67.25	67.3	<0.001	
Exposure assessment						0.790
Trained interviewer	14	0.61 (0.49, 0.76)	49.54	73.8	<0.001	
Self-administered questionnaire	9	0.75 (0.63, 0.88)	9.33	14.3	0.315	
Type of control subjects						0.185
Population based	14	0.57 (0.45, 0.71)	27.98	53.5	0.009	
Hospital based	8	0.81 (0.53, 1.21)	31.11	77.5	<0.001	
Study population						0.365
Asians	3	0.66 (0.43, 1.00)	1.36	0	0.505	
Americans	11	0.55 (0.43, 0.71)	25.93	61.4	0.004	
Europeans	9	0.81 (0.59, 1.10)	27.46	70.9	0.001	
Cancer grading						0.291
Invasive	4	0.55 (0.36, 0.84)	7.95	62.3	0.047	
Borderline	5	0.41 (0.28, 0.60)	1.67	0	0.797	
Cancer histotype						0.258
Serous	6	0.75 (0.59, 0.96)	1.78	0	0.879	
Mucinous	4	0.61 (0.19, 1.94)	12.04	75.1	0.007	
Endometrioid	3	0.59 (0.35, 0.98)	2.64	24.4	0.267	
Clear cell	1	0.24 (0.06, 0.97)	NA	NA	NA	
Adjustment for confounders						
Parity						0.318
Yes	21	0.68 (0.59, 0.82)	50.60	60.5	<0.001	
No	5	0.53 (0.30, 0.94)	17.53	77.2	0.002	
BMI						0.406
Yes	5	0.81 (0.67, 0.98)	3.44	0	0.486	
No	21	0.63 (0.50, 0.78)	64.46	69.0	<0.001	
OC use						0.428
Yes	16	0.62 (0.50, 0.77)	48.25	68.9	<0.001	
No	10	0.73 (0.53, 1.00)	22.00	59.1	0.009	
Smoking						0.521
Yes	6	0.58 (0.40, 0.85)	11.15	55.1	0.049	
No	20	0.67 (0.55, 0.83)	59.07	67.8	<0.001	

[1] NA, not available; OC, oral contraceptive.
[2] *P* value for heterogeneity within each subgroup.
[3] *P* value for heterogeneity between subgroups with meta-regression analysis.

Luan, 2013

TABLE 4
Summary risk estimates of the association between the total duration of breastfeeding and ovarian cancer risk: a dose-response analysis (per 5-mo increase)[1]

	Studies	Summary RR (95% CI)	*Q* statistic	I^2	P_h[2]	P_h[3]
	n			%		
Overall	25	0.92 (0.90, 0.95)	74.12	67.6	<0.001	—
Subgroup analyses						
Study design						0.686
Cohort studies	3	0.95 (0.90, 0.99)	2.57	22.1	0.277	
Case-control studies	22	0.92 (0.90, 0.95)	71.35	70.6	<0.001	
Exposure assessment						0.160
Trained interviewer	13	0.90 (0.85, 0.95)	55.21	78.3	<0.001	
Self-administered questionnaire	9	0.94 (0.92, 0.96)	9.77	18.1	0.281	
Type of control subjects						
Population based	14	0.57 (0.45, 0.71)	27.98	53.5	0.009	
Hospital based	8	0.81 (0.53, 1.21)	31.11	77.5	<0.001	
Study population						0.925
Asians	3	0.89 (0.77, 1.04)	6.45	69.0	0.040	
Americans	10	0.89 (0.85, 0.93)	27.48	67.3	0.001	
Europeans	9	0.96 (0.90, 1.01)	24.07	66.8	0.002	
Cancer grading						0.770
Invasive	4	0.88 (0.84, 0.92)	4.99	39.9	0.172	
Borderline	5	0.89 (0.82, 0.96)	11.43	65.0	0.022	
Cancer histotype						0.074
Serous	6	0.94 (0.90, 0.98)	2.17	0	0.824	
Mucinous	4	0.84 (0.72, 0.99)	8.46	64.6	0.037	
Endometrioid	3	0.86 (0.79, 0.95)	2.63	24.0	0.268	
Clear cell	1	0.62 (0.41, 0.94)	NA	NA	NA	
Adjustment for confounders						
Parity						0.169
Yes	21	0.93 (0.91, 0.96)	55.55	64.0	<0.001	
No	4	0.86 (0.82, 0.90)	4.93	39.2	0.177	
BMI						0.438
Yes	5	0.89 (0.82, 0.97)	10.79	62.9	0.029	
No	20	0.93 (0.90, 0.96)	63.04	69.9	<0.001	
OC use						0.219
Yes	16	0.91 (0.88, 0.94)	46.58	67.8	<0.001	
No	9	0.95 (0.90, 1.00)	22.37	64.2	0.004	
Smoking						0.521
Yes	6	0.93 (0.89, 0.98)	12.85	61.1	0.025	
No	19	0.92 (0.88, 0.96)	61.15	70.6	<0.001	

[1] NA, not available; OC, oral contraceptive.
[2] *P* value for heterogeneity within each subgroup.
[3] *P* value for heterogeneity between subgroups with meta-regression analysis.

Health outcome	Author, year, journal, type of study	Study objective	Inclusion and exclusion criteria	Search period, number of included studies, designs of included studies	Included study populations	Exposure assessment and definition
Breast cancer	Yang, 2008 Journal of Women's Health Systematic review[17]	To explore whether a consensus about the relationship between BF and breast cancer has emerged in the years following the conclusion of the Lipworth review by presenting the results of a systematic review of primary research papers published between 1999 and 2007	*Inclusion criteria* - Human studies - No language restrictions *Exclusion criteria* - Editorials, letters, case reports, guidelines, comments, reviews, and meta-analyses - Studies that did not assess the relationship between BF and breast cancer - Studies of breast cancer diagnosed while women were lactating - Studies in special populations, such as those that included only BRCA 1/2 carriers, and studies of ductal carcinoma in situ rather than invasive breast cancer - Studies with sample size <20	January 1, 1999 and December 31, 2007 *Number of hits in original search* PubMed: n=714 *Number of included articles* - Total: n=31 - CC studies: n=30 - CH study: n=1	Most of the studies included both premenopausal and postmenopausal women, except for 1 study of premenopausal women only *Countries* 18 countries: Brazil, China, Colombia, Egypt, Germany, Iceland, Indonesia, Israel, Italy, Malaysia, Mexico, Nigeria, Pakistan, South Africa, South Korea, Sweden, Turkey, and the USA	*Exposure assessment* NR *Exposure definition* NR

Health outcome assessment and definition	Results	Confounders	Remarks, limitations
Health outcome assessment NR *Health outcome definition* NR	*Ever BF and risk of breast cancer* 11 of the 27 studies found a significant protective association between ever BF (vs. never) and risk of breast cancer. 10 of the 24 studies in parous women only found a significant protective association between ever BF (vs. never) and risk of breast cancer. - The papers included in this systematic review did not yield consistent findings about the association between ever vs. never breastfeeding and odds of developing breast cancer. *Duration of BF and risk of breast cancer* 13 of the 24 studies found a significant protective association of some amount of extended duration of BF on breast cancer, but because ranges of durations assessed were not consistent, it is difficult to compare studies. - About half of the papers included in this systematic review found that some duration of cumulative breastfeeding was significantly protective against breast cancer. *Menopausal status and breast cancer* - 4 of the 8 studies that stratified for menopausal status found no significant effect of a history of BF on breast cancer risk in either premenopausal or postmenopausal women - 2 of the 8 studies that stratified for menopausal status found BF to be protective against breast cancer in both menopausal and postmenopausal women (although for one of these studies, protection was only found in women with >5 cumulative years of breastfeeding) - 1 of the 8 studies that stratified for menopausal status found BF conferred significant protection against	Menstrual history, reproductive history, reproductive system diseases, endocrine diseases, other health issues, and medication are potential confounders (supplementary table 2). However, only a few studies included in this systematic review adjusted for any of these variables in their analysis. For example, only 8 out of 31 studies adjusted for age at menarche, 5 adjusted for BMI, and 2 adjusted for using oral contraceptives	*Limitations (predefined quality criteria)* - Time of assessing BF data not reported - Clear definition of BF not reported - Not reported whether assessment of outcome was after assessment of exposure - Clear definition of health outcome not reported - Not all included studies corrected for confounders

[17] Five of the included articles in this review were included in the report of RIVM (2007).

	breast cancer only among postmenopausal women - 1 of the 8 studies that stratified for menopausal status found significant protection against breast cancer only among premenopausal women		
BMI: Body mass index; BRCA: Breast Cancer; USA: United States of America			

Yang, 2008

TABLE 2. CAUSES OF FEWER NUMBERS OF LIFETIME OVULATORY MENSTRUAL CYCLES

Menstrual history	Late menses
	Early menopause
Reproductive history	Pregnancy
	Lactation
	Hysterectomy/oophorectomy
Reproductive system diseases	Polycystic ovarian syndrome
	Ovarian tumor
	Endometriosis
Endocrine diseases	Thyroid disease
	Cushing's disease
	Pituitary tumors
	Hypothalamic disorders
	Other endocrine disorders
Other health issues	Low or high body mass index (BMI)
	Low or high percent body far
	Stress
	Other cancers
	Genetic disease (such as Turner's syndrome and Kallmann syndrome)
	Overall health status
Medications	Oral contraceptive pills
	Antidepressants
	Antipsychotics
	Opiates, cocaine
	Antihypertensives

B-II Primary articles with health outcomes related to the mother

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Benign breast disease – Fibroadenoma	Bernardi, 2012 Journal of Obstetrics and Gynaecology Italy Case-control study 2008	To investigate the relation between BBD and BF	*Setting* Department of Surgery and Clinic of Obstetrics and Gynecology, AOU 'SM della Misericordia', Udine, Italy *Study population* - Cases: women aged < 40y, who presented to the Senology Outpatients Facility of the Department of Surgery during 2008 with a histological diagnosis of BBD or a confirmed BI-RADS 1-2 (at least twice) - Controls: random group of women who delivered in the Clinic of Obstetrics and Gynecology during 2008 *Sample size* - Total: n=203 - Cases: n=105 - Controls: n=98	*Age at enrolment* Mean age Cases: 31.5years Controls: 32.3years *Age at assessment of outcome* Mean age Cases: 31.5years Controls: 32.3years	*Exposure assessment* Collected by a telephone interview, at routine visits, or consulting clinical files among cases and controls *Exposure definition* BF: NR BF duration: cumulative BF and BF per child, divided into 2 subgroups using the 3rd quartile as a cut-off: cumulative breastfeeding duration: < and > 20 mo; breastfeeding duration per child: < and > 13 mo	*Health outcome assessment* Collected by a telephone interview, at routine visits, or consulting clinical files among cases *Health outcome definition* - BBDs defined as previously reported in Guray and Sahin 2006 BBDs categories: 1) Fibroadenoma 2) Fibrocystic changes 3) Isolated mastalgia 4) Intraductal papilloma 5) Inflammatory breast disorder 6) Other BBDs

Results	Confounders	Remarks, limitations
BFD and ≥2 locations of fibroadenoma OR (95% CI) / aOR (95% CI) Per month BFD: 1.05 (1.00-1.08; P <0.05) / 1.01 (0.99-1.09; P =0.056) Per month BFD/child: 1.07 (1.01-1.16; P <0.05 / 1.06 (1.00-1.17; P <0.05) - Comparison of nullipara with pregnant women who cumulatively BF more or less than 20 mo., and who BF more or less than 13 mo./child and the presence of fibroadenoma, fibrocystic changes, inflammatory breast disorders and >2 locations of fibroadenoma's can be found in table III - There was a non-significant difference in BFD between cases and controls, but there was a non-significant longer BFD in women who suffered from inflammatory breast disorders (See figure 1)	Age, parity, BMI, hormonal contraception usage and menarche	*Limitations (predefined quality criteria)* - Time of assessing BF not reported - Clear definition of BF not reported - Assessment of exposure and health outcome were done simultaneously. Not reported whether assessment of exposure and outcome were blind *Other limitations* - NR
BBD: benign breast disease ; BI-RADS: Breast Imaging Report and Database System; BMI: body mass index		

Bernardi, 2012

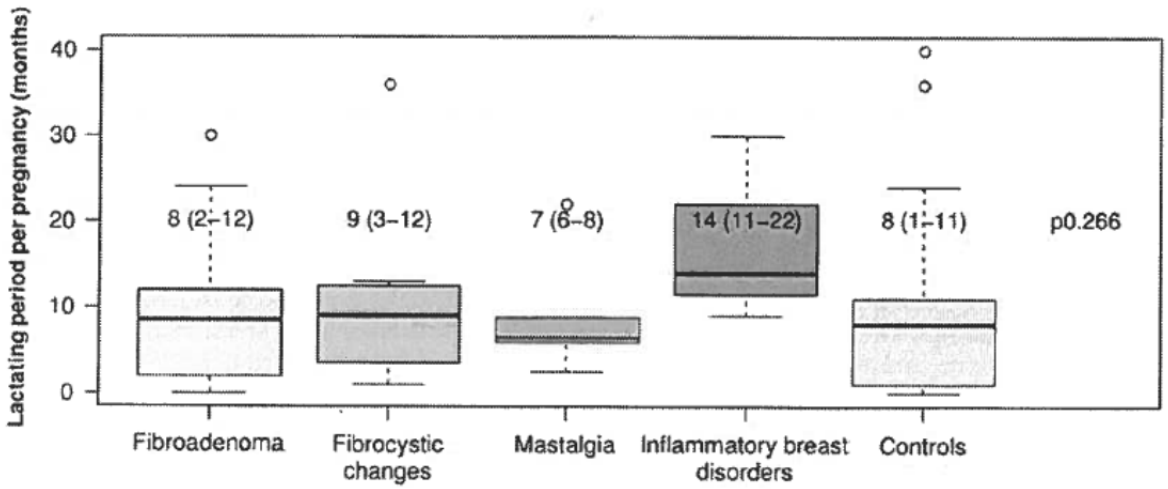


Figure 1. Comparison of breast-feeding duration among BBDs and controls (median, interquartile range and Kruskal–Wallis test).

Bernardi, 2012

Table III. Comparison of nullipara with pregnant women who cumulatively breast-fed more or less than 20 months, and who breast-fed more or less than 13 months/child.

		Breast-feeding					
	Nullipara	<20 months	>20 months	*p* value	<13 months	>13 months	*p* value
Age (years)*	29.5 ± 6.2	35.1 ± 3.8	36.1 ± 4.3	<0.05	35.7 ± 3.0	34 ± 6.53	<0.05
Gynaecological age (years)*	16.1 ± 6.4	22.3 ± 4.1	23.2 ± 4.1	<0.05	22.8 ± 3.5	21.1 ± 6.07	<0.05
BMI (kg/m²)*	20.8 ± 2.7	22.1 ± 4.7	21.0 ± 1.9	0.279	22.1 ± 4.5	20.7 ± 1.9	0.248
Breast size*	2.6 ± 0.8	3.1 ± 1.4	2.5 ± 0.4	0.230	2.9 ± 1.3	4.0 ± 1.4	0.139
Fibroadenoma†	59% (40/68)	46% (13/28)	56% (5/9)	0.540	53% (16/30)	29% (2/7)	0.300
Fibrocystic changes†	19% (13/68)	21% (6/28)	11% (1/9)	0.790	20% (6/30)	14% (1/7)	0.941
Inflammatory breast disorders†	3% (2/68)	3.6% (1/28)	22% (2/9)	<0.05	3% (1/30)	29% (2/7)	<0.05
Lesion number (>2)†,‡	15% (6/40)	0% (0/13)	80% (4/5)	<0.05	13% (2/16)	100% (2/2)	<0.05

Data are presented as: *mean ± SD and as †prevalences (with absolute values). Significance is calculated with χ^2-test or one-way ANOVA. ‡Only fibroadenomas.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Fragility fracture	Bjørnerem, 2011 J Bone Miner Res Norway Prospective population based cohort study Data from surveys conducted between 1974, 1979-1980, 1986-1987, 1994-1995, 2001 and 2007-2008	To investigate the effect of parity and BF on risk for hip, wrist and non-vertebral fragility fractures (hip wrist, or proximal humerus)	*Setting* All eligible inhabitants in Tromsø, Norway *Study population* Women ≥50 years participating in the Tromsø Study, who had data on parity, were postmenopausal at 1994-1995 (baseline), and had data on given BF. Excluded were premenopausal women who reported a menstrual period within the last year. *Sample size* 3,748 women Follow up: median 14.5 years	*Age at enrolment* 63.3 years (range 50 to 94years) *Age at assessment of outcome* NR	*Exposure assessment* Assessed by two self-administered questionnaires at baseline *Exposure definition* Definition BF not stated, duration of BF was defined as 0 months, 1-9 months, 10-19 months and ≥20 months	*Health outcome assessment* X-ray archives of the University Hospital of North Norway in Tromsø *Health outcome definition* Fracture at the hip, wrist or proximal humerus.

Results	Confounders	Remarks, limitations
Hip fracture (fully adjusted analysis) $HR_{BF\ vs.\ no\ BF}$ (95% CI): 0.50 (0.32, 0.78) (n=3216) $HR_{BFD\ 1\text{-}9\ mo.\ vs.\ no\ BF}$ (95% CI): 0.51 (0.31, 0.83) (n=1466) $HR_{BFD\ 10\text{-}19\ mo.\ vs.\ no\ BF}$ (95% CI): 0.49 (0.30, 0.80) (n=1295) $HR_{BFD\ ≥20\ mo.\ vs.\ no\ BF}$ (95% CI): 0.50 (0.31, 0.81) (n=1355) P for trend: 0.15 *Fragility fracture (fully adjusted analysis)* $HR_{BF\ vs.\ no\ BF}$ (95% CI): 0.73 (0.54, 0.99) (n=3216) $HR_{BFD\ 1\text{-}9\ mo.\ vs.\ no\ BF}$ (95% CI): 0.71 (0.52, 0.98) (n=1466) $HR_{BFD\ 10\text{-}19\ mo.\ vs.\ no\ BF}$ (95% CI): 0.72 (0.53, 0.99) (n=1295) $HR_{BFD\ ≥20\ mo.\ vs.\ no\ BF}$ (95% CI): 0.76 (0.56, 1.05) (n=1355) NS No significant association between BF or BFD and wrist fracture was found. Results of less adjusted analyses can be found in Table 3.	Controlled for age, BMI, height, current smoking, alcohol use, HRT use, physical activity, a history of diabetes, previous hip or wrist fracture and length of education	*Limitations (predefined quality criteria)* - BF data were recalled many years after birth of the child as included women were aged ≥50 years - No clear definition of BF was provided. Duration of BF was specified - Assessment of BF was done before the disease outcome was known . Blinding not reported *Other limitations* - because most parous women breastfed after birth, the group of parous women who did not breast-feed was small
BMI: Body mass index; HR: Hazard ratio; Mo.: Months; NS: Not significant		

Bjørnerem, 2011

Breastfeeding versus non-breastfeeding women	*n*	Fracture	Rate	HR (95% CI)[a] *n* = 3748	HR (95% CI)[b] *n* = 3734	HR (95% CI)[c] *n* = 3216
		Hip,		**0.62 (0.40–0.96)**	**0.63 (0.41–0.97)**	**0.50 (0.32–0.78)**
		Wrist		1.02 (0.69–1.53)	1.01 (0.68–1.52)	1.06 (0.68–1.66)
		Fragility[d]		0.80 (0.60–1.06)	0.80 (0.60–1.05)	**0.73 (0.54–0.99)**
Breastfeeding duration		Hip				
0	184	22	9.7	1	1	1
1–9	1282	99	6.1	0.69 (0.43–1.09)	0.67 (0.42–1.06)	**0.51 (0.31–0.83)**
10–19	1111	93	6.7	**0.62 (0.39–0.99)**	**0.61 (0.38–0.97)**	**0.49 (0.30–0.80)**
≥20	1171	121	8.7	**0.57 (0.36–0.90)**	**0.61 (0.39–0.97)**	**0.50 (0.31–0.81)**
All/*p* trend	3748	335	7.3	**0.03**	0.13	0.15
		Wrist				
0	184	25	11.3	1	1	1
1–9	1282	174	11.4	1.04 (0.68–1.58)	1.00 (0.66–1.53)	1.08 (0.68–1.73)
10–19	1111	160	12.1	1.08 (0.71–1.64)	1.05 (0.69–1.60)	1.05 (0.66–1.69)
≥20	1171	150	11.3	0.96 (0.63–1.47)	0.99 (0.65–1.51)	1.04 (0.65–1.66)
All/*p* trend	3748	509	11.6	0.62	0.95	0.83
		Fragility[c]				
0	184	52	25.3	1	1	1
1–9	1282	275	18.7	0.80 (0.59–1.07)	0.78 (0.58–1.05)	**0.71 (0.52–0.98)**
10–19	1111	263	20.7	0.82 (0.61–1.10)	0.80 (0.59–1.07)	**0.72 (0.53–0.99)**
≥20	1171	294	23.4	0.79 (0.58–1.06)	0.81 (0.60–1.09)	0.76 (0.56–1.05)
All/*p* trend	3748	884	21.1	0.38	0.76	0.75

Statistical significant models are bold.
[a]Hazard ratio (HR) adjusted for age.
[b]HR adjusted for age and body mass index (BMI).
[c]HR adjusted for age, height, BMI, smoking, alcohol use, physical activity, history of diabetes and previous wrist or hip fracture, use of hormone replacement therapy, and length of education.
[d]Fragility fractures; hip, wrist or proximal humerus.

Table 3. Risk for hip, wrist, and any non-vertebral fragility fracture for breastfeeding versus non-breastfeeding women, and risk for fracture by total duration of breastfeeding (months)

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
BMI	Bobrow, 2013 International Journal of Obesity UK Cross-sectional study 1996 – 2001	To assess the association between women's childbearing and BF history, and their BMI in later life in a large population of postmenopausal women, taking into account the effects of potential confounding factors	*Setting* Population-based study of UK women *Study population* Postmenopausal women aged 50 – 64 years who participated in the Million Women Study and who reported their height, weight, reproductive histories and other relevant factors *Sample size* n=740,628	*Age at enrolment* 50 – 64 years *Age at assessment of outcome* - 50 – 64 years - Mean age ± SD: 57.5 ± 4 years	*Exposure assessment* Study questionnaire at recruitment. Questions on BF were added to the baseline questionnaire after the first 9% were recruited *Exposure definition* - Women were asked to report, for each birth, if they had BF and if so, the duration of BF in months. This information was used to define $BF_{\text{ever vs never}}$, and total BFD (summation over all children of reported BFD in months) - Total BFD was categorized as BF_{never}, $BF_{<6\text{ mo.}}$, $BF_{6-9\text{ mo.}}$, or $BF_{\geq 10\text{ mo.}}$ - No questions were asked about EBF	*Health outcome assessment* - Study questionnaire at recruitment which asked about height, weight, reproductive history, socioeconomic and lifestyle factors, and other personal characteristics. *Health outcome definition* BMI: weight (kg)/height $(m)^2$

Results	Confounders	Remarks, limitations
BMI and total BFD Total BFD (mean in months) / Regression coefficient / CI No BF / Reference / Reference <6 mo. (2.3) / -0.24 / -0.21 to -0.26 6-9 mo. (7.3) / -0.36 / -0.32 to -0.40 ≥10 mo. (18.5) / -0.53 / -0.50 to -0.57 Change in mean BMI per 6 mo. BF[a] / -0.13 / -0.11 to -0.13 [a] trend fitted through category mid-points and multiplied as appropriate - For unadjusted and partially aORs see table 2. For BMI among postmenopausal women by selected characteristics see figure 5.	Age, region, parity, socioeconomic group, smoking, and physical activity	- The reduction in BMI associated with just 6 months BF in UK women could importantly reduce their risk of obesity-related disease as they age - For a random sample of 2,800 women weight and height were measured by their general practitioners. This information was used to compare BMIs calculated from self-reported data to BMIs calculated from measured data. *Limitations (predefined quality criteria)* - Time of assessing BF was >1 year - Assessment of exposure and outcome were done simultaneously. Blinding NR. questions on BF were added to the baseline questionnaire after the first 9% were recruited *Other limitations* - BF data was obtained by self-report and long-term recall is reliable - BMI was calculated using women's self-reported heights and weights and may be affected by random and systematic measurement error. This is unlikely to be a material source of bias, because when comparing self-reported versus measured height and weight data a strong correlation was found between BMIs calculated from measured data and BMIs calculated from self-reported data (Spearman's correlation coefficient 0.95)
BMI: Body mass index; Mo.: Months; UK: United Kingdom		

Bobrow, 2013

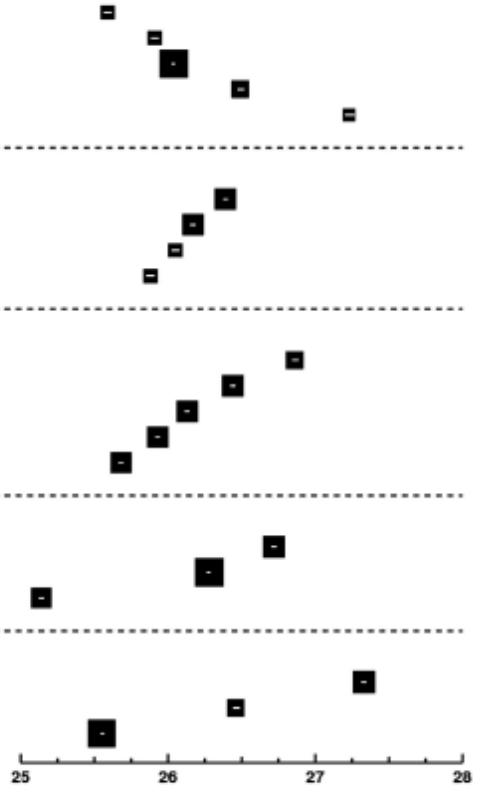
Table 2. Change in mean BMI (kg m $^{-2}$) among parous women by parity and total duration of breastfeeding in models variously standardised

	Number of women	*Unadjusted results*	*Model A—standardised by age and region only*	*Model A + additionally standardised by breastfeeding (when looking at parity), and for parity (when looking at breastfeeding)*	*Model A + additionally standardised by breastfeeding, parity, socioeconomic group, smoking and physical activity*
Parity (mean)					
1	100 639	Reference	Reference	Reference	Reference
2	310 841	−0.02 (−0.05 to 0.01)	−0.01 (−0.04 to 0.02)	0.11 (0.08 to 0.14)	0.13 (0.09 to 0.16)
3	159 100	0.45 (0.41 to 0.48)	0.45 (0.41 to 0.48)	0.63 (0.60 to 0.67)	0.58 (0.55 to 0.62)
⩾4 (4.4)	80 600	1.31 (1.27 to 1.36)	1.30 (1.26 to 1.34)	1.53 (1.49 to 1.58)	1.33 (1.28 to 1.37)
Total duration of breastfeeding (mean in months)					
Did not breastfeed	201 688	Reference	Reference	Reference	Reference
<6 months (2.3)	239 836	−0.27 (−0.24 to −0.30)	−0.26 (−0.24 to −0.29)	−0.32 (−0.29 to −0.35)	−0.24 (−0.21 to −0.26)
6–9 months (7.3)	82 198	−0.43 (−0.40 to −0.47)	−0.42 (−0.38 to −0.46)	−0.52 (−0.48 to −0.56)	−0.36 (−0.32 to −0.40)
⩾10 months (18.5)	127 458	−0.44 (−0.41 to −0.48)	−0.43 (−0.40 to −0.46)	−0.75 (−0.71 to −0.78)	−0.53 (−0.50 to −0.57)
Change in mean BMI per 6 months breastfeeding[a]		−0.12 (−0.11 to −0.13)	−0.11 (−0.10 to 0.12)	−0.17 (−0.16 to −0.18)	−0.13 (−0.11 to −0.13)

Abbreviation: BMI, body mass index. [a]Trend fitted through category mid-points and multiplied as appropriate.

Bobrow, 2013

Characteristics of women	Number of women	Standardised* mean BMI & 95% CI (kg/m²)
Parity		
0	89448	25.59 (25.56-25.62)
1	100639	25.91 (25.88-25.94)
2	310841	26.04 (26.02-26.05)
3	159100	26.49 (26.47-26.52)
≥4	80600	27.23 (27.20-27.27)
Total duration of breastfeeding		
0	291136	26.39 (26.37-26.41)
<6 months	239836	26.17 (26.15-26.19)
6 to 9 months	82198	26.05 (26.02-26.08)
≥10 months	127458	25.88 (25.85-25.91)
Socioeconomic group		
Lowest quintile (most deprived)	137389	26.86 (26.84-26.89)
	146603	26.44 (26.42-26.46)
Middle quintile	150713	26.13 (26.11-26.15)
	152622	25.93 (25.91-25.95)
Highest quintile (least deprived)	153301	25.68 (25.66-25.70)
Smoking status		
Past smoker	214953	26.72 (26.70-26.74)
Never smoked	386641	26.28 (26.26-26.29)
Current smoker	139034	25.14 (25.12-25.16)
Physical activity		
≤1 time per week	209706	27.33 (27.31-27.35)
2 to 3 times per week	111397	26.46 (26.44-26.49)
≥4 times per week	419525	25.55 (25.54-25.57)



* standardised by age, region, parity, total duration of breastfeeding, socioeconomic group, smoking status and physical activity, as appropriate.

Figure 5. Standardised* mean BMI (kg m^{-2}) among postmenopausal women by selected characteristics.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Postpartum fatigue	Callahan, 2006 Journal of Human Lactation France Prospective cohort study NR	To compare BF women with non-BF women to establish if there are any real differences in the experience of perceived fatigue during the postpartum period for these 2 groups	*Setting* Metropolitan, private hospital in Toulouse, Southern France *Study population* All women who were in the hospital to give birth on days when the interns were present, who gave either exclusive FF or EBF at baseline. Women who anticipated MBF at baseline were excluded *Sample size* n=247	*Age at enrolment* 20-43 years (mean ± SD: 29.96 ± 4.55) *Age at assessment of outcome* Same age, 12 weeks later	*Assessment* Assessment of BF on days 2, 3 or 4 (T1, baseline feeding choice), 6 weeks (T2) and 12 weeks (T3) postpartum. Women were requested to indicate if they were EBF, MBF or FF at T2 and T3 *Definition* - EBF: BF without any FF - Exclusive FF: NR - Quit BF: Those who switched from BF to FF at T2 or T3	*Assessment* Pichot Depression/Fatigue/Anxiety Scale (Pichot, 1984) at T1, T2 and T3 *Definition* Scores were calculated using a 5-point Likert-type scale ranging from *absent* (0 points) to *present and significant* (4 points) for each symptom associated with each subscale. Individual subscales are composed of 8 items: potential total score of 0-32 points for each. Only the fatigue portion of the scale was analysed

Results	Confounders	Remarks, limitations
BF and Pichot Fatigue Scores, descriptive statistics (BF, FF and those who switched from BF to FF) T1 Group | n | Median (mean) | IQR EBF | 128 | 7 (7.84) | 3-10 FF | 114 | 5 (7.10) | 2-10 Quit BF | - | | T2 Group | n | Median (mean) | IQR EBF | 68 | 4 (5.57) | 1-9 FF | 78 | 4 (5.25) | 1-7 Quit BF | 19 | 4 (7.78) | 3-6 T3 Group | n | Median (mean) | IQR EBF | 25 | 4 (4.76) | 2-6 FF | 41 | 3 (3.56) | 1-5 Quit BF | 23 | 2 (4.08) | 0-7 *BF and postpartum fatigue: Mann-Whitney analysis for the groups presented in the table above* $T1_{EBF\ vs.\ FF}$: U = 6,510, Z = -1.44; P = 0.14 (n=242) $T2_{EBF\ vs.\ FF}$: U = 2,637, Z = -1.34; P = 0.17 (n=146) $T2_{EBF\ vs.\ (FF + quit\ BF)}$: U = 3,280, Z = -0.05; P = 0.95 (n=165) $T3_{EBF\ vs.\ FF}$: U = 411, Z = -1.34; P = 0.17 (n=66) $T3_{EBF\ vs.\ (FF + quit\ BF)}$: U = 638, Z = -1.47; P = 0.13 (n=89)	None	- More BF women in the sample held higher level employment than did FF women. This difference is likely related to education level, which has been shown to have a positive impact on the choice to BF *Limitations (predefined quality criteria)* - Exclusiveness of BF was not defined - Assessment of exposure and outcome were at the same time points, it is not reported whether this was blind - No correction for relevant confounders *Other limitations* - Return rates of questionnaires were low for T2 (67%) and T3 (36%). It could be that women who did not return the questionnaire had higher levels of fatigue. However, equal numbers of women responded in each group suggesting nog effect due to feeding choice - Given that the women responded only three times during the postpartum period, they were not asked about feeding styles or average number of feedings per day
Vs.: Versus		

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Obesity	Cohen, 2009 Journal of Women's Health USA Cross-sectional study March 2002-December 2006	To describe associations among parity, breastfeeding, and adult obesity in black and white women in the south-eastern United States	*Setting* 48 CHCs in the states of Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia *Study population* Women aged 40-79yrs, who speak English, have not undergone treatment for cancer (excluding non-melanoma skin cancer) within the past year, and who self-reported their race as either white or black *Sample size* n=31,184 (7,986 white and 23,198 black)	*Age at enrolment* Average: early 50s (range 40-79 yrs) *Age at assessment of outcome* Same as enrolment (cross-sectional design)	*Assessment* Comprehensive in-person interviews *Definition* BF: NR BF duration: total months of BF (counting all pregnancies) - Continuously - Categorized as: none, 1-3, 4-6, 7-12, and >12 mo.	*Assessment* Comprehensive in-person interviews *Definition* - BMI: self-reported weight in kg, divided by the square of self-reported height in meters and treated continuously - Obesity: obese as BMI ≥30 kg/m^2 and non-obese as BMI <30 kg/m^2 - Adult weight change: self-reported weight at the time of interview, minus the self-reported weight at age 21

Results	Confounders	Remarks, limitations
BF (total mo.) and BMI or adult weight change All women / White women / Black women β ± SE, P BMI: -0.003 ± 0.003, 0.26 / -0.02 ± 0.007, 0.008 / 0.0002 ± 0.003, 0.94 Weight change: 0.009 ± 0.09, 0.92 / -0.22 ± 0.17, 0.20 / 0.17 ± 0.10, 0.11 *BF and obesity (nulliparous women excluded)* BF (mo.): All women OR (95% CI) / White women OR (95% CI) / Black women OR (95% CI) None: 1.00 Ref / 1.00 Ref / 1.00 Ref 1-3: 1.02 0.93-1.12 / 0.95 0.80-1.13 / 1.07 0.96-1.20 4-6: 0.97 0.86-1.09 / 1.05 0.84-1.31 / 0.95 0.83-1.09 7-12: 1.05 0.94-1.18 / 1.07 0.86-1.32 / 1.07 0.93-1.23 >12: 0.91 0.82-1.00 / 0.68 0.56-0.82 / 1.04 0.93-1.17 *BF and obesity: additional analysis to evaluate residual confounding in white women* - Stratified for education and income: odds of obesity reduced in all education and income categories (data not shown) - Stratified by 10-year age categories, >12 mo. BF vs. none: 0.58 (0.42–0.79) for women of ages 40-49; 0.58 (0.41-0.82) for ages 50-59; 0.99 (0.63-1.56) for ages 60-69; and 0.51 (0.33-1.32) for ages 70-79.	Parity, age, BMI at age 21, education, household income, menopausal status, marital status, current occupational status, smoking status, alcohol consumption, fruit and vegetable consumption, total MET-hrs=day of physical activity, depression based on CESD, use of oral contraceptives, and age of menarche	*Limitations (predefined quality criteria)* - BF was assessed many years after birth (range 40-79 years) - BF was not defined - Exposure and outcome assessment were done simultaneously, no information about blinding *Other limitations* - Included population is not the general population due to recruitment of participants within the CHCs: overrepresentation of people of low SES and African-American race - Only self-reported measures of weight and height
BMI: Body mass index; CHC: Community Health Centre; Kg: Kilograms; Mo. Months; SES: Socio-economic status; USA: United States of America		

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Postpartum body weight	Dujmović, 2014 Collegium Antropologicum Croatia Prospective cohort study January 2009 – January 2010	To investigate how weight retention of women living in Primorsko-Goranska Country in Croatia, was affected by type of feeding, time since parturition, gestational weight gain, total energy intake, and energy intake derived from fat	*Setting* Primorsko-Goranska Country in Croatia *Study population* Postpartum lactating and non-lactating women who gave birth to healthy full term infants with a birth weight >2500 g, with time elapsed since parturition of 1 month (± 1 week) during 2009. Exclude: women suffering from any metabolic disorders, with complication in birth, those who gave birth by Caesarean section, and those which had history of early pregnancy loss *Sample size* n=159	*Age at enrolment* Mean age ± SD: 30.69 ± 5.05 years *Age at assessment of outcome* NR, but follow-up for 6 months	*Exposure assessment* Assessed at 3 waves: 1 month ± 1 week, 3 months ± 1 week, and 6 months ± 1 week postpartum. At each visit women were asked about their lactating status *Exposure definition* - WHO classification for full BF, mixed feeding, and FF - Lactating = Full BF and mixed feeding - Non-lactating = FF	*Health outcome assessment* Assessed at 3 waves: 1 month ± 1 week, 3 months ± 1 week, and 6 months ± 1 week postpartum. In each wave, a trained researcher took weight measurements with their own scale in the mothers' households. Data on gestational weight gain and pre-pregnancy body weight were taken from the pregnancy card at first visit. Women's height was self-reported at each visit. *Health outcome definition* - BMI was calculated as weight/height^2 - Postpartum weight retention = postpartum weight at each measurement wave minus pre-pregnancy weight -Inadequate gestational weight gain = gained less than the IOM recommendations* - appropriate gestational weight gain: gained within the IOM recommendations* - Excessive gestational weight gain = gained more than the IOM recommendations* *Recommended weight gain according to the recommendations of the IOM

Results	Confounders	Remarks, limitations
BF and BMI, weight retention and % of pre-pregnancy weight (unadjusted) Time since parturition / P in group dimension 1 mo. / 3 mo. / 6 mo. / 1 mo. / 3 mo. / 6 mo. BMI - Lactating: 25.39 (3.95) / 25.23 (4.24) / 23.43 (4.52) / 0.250 / 0.048 / 0.040 - Non-lactating: 27.02 (6.31) / 26.56 (4.18) / 24.96 (4.82) Weight retention - Lactating: 6.91 (4.85) / 8.48 (5.05) / 1.33 (5.45) / 0.721 / 0.001 / 0.001 - Non-lactating: 7.77 (6.61) / 4.28 (4.04) / 4.10 (4.93) % of pre-pregnancy weight - Lactating: 110.79 (7.39) / 109.92 (7.47) / 101.95 (8.21) / 0.721 / 0.009 / 0.014 - Non-lactating: 113.37 (8.17) / 106.69 (8.08) / 105.01 (7.39) - Results of weight retention in lactating and non-lactating women in relation to the fulfilment of recommendation of gestation weight gain can be found in figure 2 *BF and weight retention; regression analysis* (adjusted) Type of feeding, coding / Regression coefficient / SE / P Lactating = 1 / -0.281 / 0.040 / <0.001	Time since parturition, gestational weight gain, average energy intake, average energy from fat, protein and carbohydrate	*Limitations (predefined quality criteria)* - BFD not reported - Assessment of exposure and health outcome were done simultaneously. Not reported whether assessment of exposure and outcome were blind - Only corrected for confounders in regression model. *Other limitations* - Women's height was self-reported at each visit - The majority of the women were primiparous, which is to be expected, because these women have more interest to participate in this kind of study. However, primiparity is highly correlated with postpartum weight retention, so this could be a source of bias - Data were combined of fully BF and mixed BF women into 1 category for type of feeding. This strategy did not allow looking into the importance of EBF on weight change

Non-lactating = 2						
BMI: Body mass index; G.: Gram; IOM: Institute of Medicine; Mo.: Months; WHO: World Health Organization.						

Dujmović, 2014

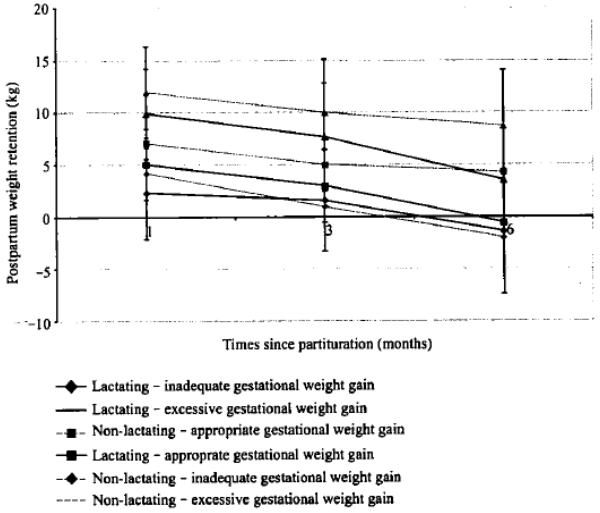


Fig. 2. Postpartum weight retention in relation to recommendations for gestational weight gain in lactating (N=83) and non-lactating (N=76) women during six months postpartum.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Age-related macular degeneration	Erke, 2013 British Journal of Ophthalmology Norway Cross-sectional study 2007-2008	To explore the sex disparity in risk factors by examining the association between female hormones, reproductive history and late AMD in older women	*Setting* The Tromsø Study *Study population* Women aged 65-87 years, participating in the Tromsø Study. Excluded were those with late AMD, extreme values for BFD and nulliparous women. *Sample size* n=1,057	*Age at enrolment* NR, but between 65-87 years *Age at assessment of outcome* NR, but between 65-87 years	*Assessment* Self-reported questionnaires *Definition* NR Duration of BF: mo. of BF in total divided by number of children Additional 3 dichotomous variables: - BF all children ≥3 mo. vs. not - BF all children ≥4 mo. vs. not - BF all children ≥6 mo. vs. not	*Assessment* Digital renal photography, graded for presence of macular drusen, drusen size and late AMD features. Most severe feature present within 3 mm from the fovea determined the predominant phenotype. *Definition* Photography graded for AMD based on ICS.

Results	Confounders	Remarks, limitations
BF and late AMD *a*OR $_{\text{total BF per 3 mo.}}$ (95% CI) = 0.84 (0.73-0.97; P = 0.02) aOR $_{\text{per mo. BF per child}}$ (95% CI) = 0.80 (0.68-0.94; P = 0.01) aOR $_{\text{total BFD ≥3 mo. vs. not BFD ≥3 mo.}}$ (95% CI) = 0.37 (0.16-0.85; P = 0.02) aOR $_{\text{total BFD ≥4 mo. vs. not BFD ≥4 mo.}}$ (95% CI) = 0.24 (0.09-0.62; P <0.01) aOR $_{\text{total BFD ≥6 mo. vs. not BFD ≥6 mo.}}$ (95% CI) = 0.09 (0.02-0.44; P <0.01)	Age, smoking, systolic blood pressure, BMI, total cholesterol, cardiovascular disease, number of children given birth to, age at first childbirth, physical activity	*Limitations (predefined quality criteria)* - BF data were recalled many years after birth of the child as included women were aged ≥65 years - No clear definition of BF was provided. - Assessment of BF and health outcome were done simultaneously. Blinding not reported *Other limitations* - No data on family history and genetic profiling - Low number of late AMD cases
AMD: Age-related macular degeneration; ICS: International classification system; Mo.: Months		

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Alzheimer's disease	Fox, 2013 Journal of Alzheimer's Disease UK Case-control study 2011-2012	To demonstrate how BF history affects women's risk of AD	*Setting* Nursing homes, churches, retirement community centers, the Alzheimer's Society and retired employee community *Study population* British female Alzheimer's disease patients and controls >70 years. Excluded were those with non-Alzheimer's type dementia or any possible external injury to the brain, nulliparas *Sample size* Cases: n = 40 Controls: n = 41	*Age at enrolment* Cases: 86 year Controls: 80 year *Age at assessment of outcome* Cases: 86 year Controls: 80 year	*Assessment* Information on probands' BF history came directly from probands, and was often confirmed or independently remembered by probands' spouces and/or children. Husbands were retrospectively asked on BF duration history. *Definition* NR	*Assessment* CDR scale by a researcher. CDR consist of a 60-90 minute interview conducted in two parts, one with the proband and the other with an informant (her relative or carer). CDR composite scores were computed (CDR-SOB) *Definition* Cases: CDR-SOB > 0 Controls: CDR-SOB = 0

Results	Confounders	Remarks, limitations
Total BF history and AD risk: HR $_{\text{exp(1)-fold higher value of BFSUM}}$ = 0.78 (P < 0.01) *BF-to-pregnancy ratio and AD risk* HR $_{\text{exp(1)-fold higher value of BFSUM/PMONTHS}}$ = 0.77 (P = 0.022) (figure 1) *BF and AD risk* HR $_{\text{BF vs. no BF}}$ = 0.36 (P = 0.017) (figure 2)	Age at interview and exponentiated age	Total duration of pregnancies during an individual's lifetime was calculated to include miscarriages and abortions. *Limitations (predefined quality criteria)* - BF data was assessed 35-50 years after birth - no definition of BF or clear statements about the duration of BF was provided - assessment of BF was done after the disease outcome was known (not blind). Health outcome not blind assessed *Other limitations* - only White British women are considered in this study
AD: Alzheimer's disease; AD risk: time between age 50 and a transition from CDR-SOB = 0 to 0.5 occurring, until age at interview; BFSUM: total sum of months spent BF; BFSUM/PMONTHS: ratio between BFSUM and total sum of months spent pregnant; CDR: clinical dementia rating; CDR-SOB: clinical dementia rating-sum of boxes; HR: hazard ratio; UK: United Kingdom		

Fox, 2013

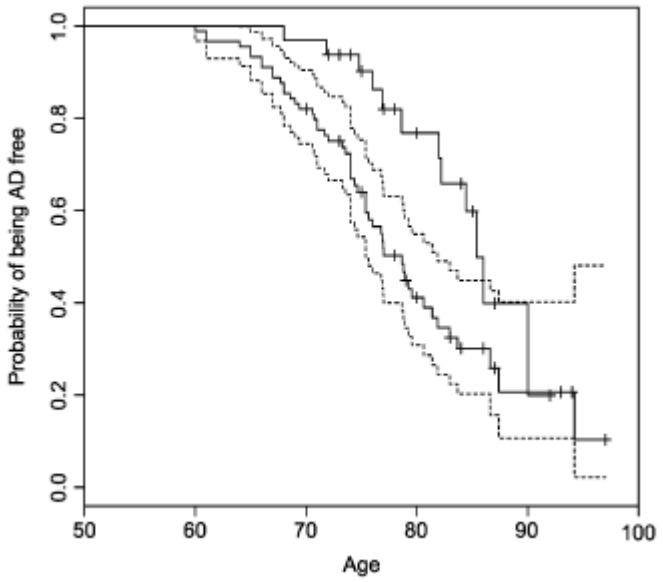


Figure 1. Women with higher BF-to-pregnancy ratio have lower AD risk. For each value of age, the plot reports the probability of being event-free for women with BFSUM/PMONTHS lower than the sample median (lower curve) and for women with BFSUM/PMONTHS above the sample median (upper curve). Point-wise 95% confidence bands for the lower curve are also shown (dotted lines). Age at event refers to estimated age at shift from CDR-SOB = 0 to CDR-SOB > 0. This plot gives a visual sense of the magnitude of the effect.

Fox, 2013

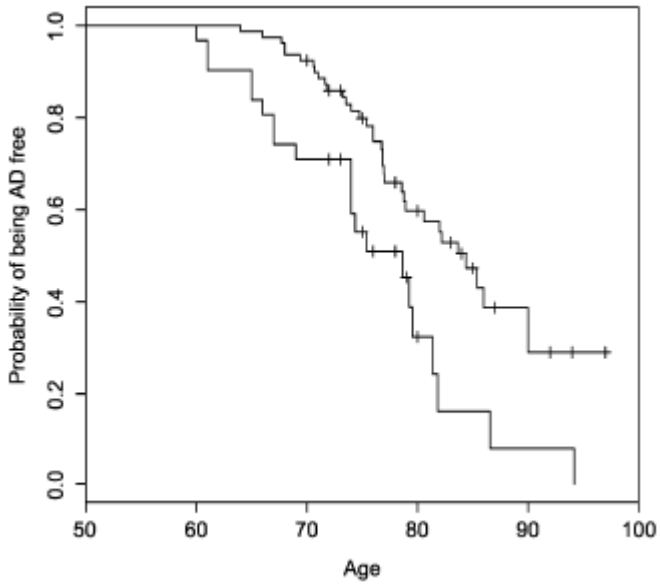


Figure 2. Parous women who BF have lower AD risk. For each value of age, the plot reports the probability of being event-free for parous women who did not BF (lower curve) and who did BF (upper curve). Age at event refers to estimated age at shift from CDR-SOB = 0 to CDR-SOB > 0.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Depressive symptomatology	Hahn-Holbrook, 2013 Archives of Women's Mental Health USA Prospective cohort study	To test whether early BF behaviours predicted reduced incidence of later depressive symptomatology in mothers	*Setting* Southern California *Study population* Pregnant women >18 years in the first trimester who had been enrolled in a larger study, English-speaking, non-smoking, have a singleton pregnancy, and no medical condition that could dysregulate neuroendocrine function *Sample size* n = 205	*Age at enrolment* Mean 29 years *Age at assessment of outcome* NR, but most depressive symptomatology was assessed in the first three months after birth	*Assessment* Asked at 3, 6, 12, 24 months postpartum by a trained interviewer *Definition* Any BF EBF: 100% of child's diet comprised breast milk Exclusive FF: 0% of child's diet comprised breast milk	*Assessment* Measured at 3, 6, 12, and 24 months, using 10-item EPDS *Definition* Depressive symptomatology: cut-off score ≥10 on EPDS

Results	Confounders	Remarks, limitations
Any BF at 3 mo. vs. no BF and depressive symptomatology - Depressive symptomatology at 3 months: p > 0.07 (not adjusted) - Absolute levels of depressive symptomatology at 24 months: Coeff=-0.10, SE=0.06, *t* ratio=-1.82, p=0.07 (not adjusted) Absolute levels of depression did not differ at 6 or 12 mo. as a function of BF at 3 mo. *EBF, FF and depressive symptomatology* - EBF vs. exclusive FF at 3 mo. did not predict depressive symptomatology at 3 mo.: p>0.8 (not adjusted) - EBF vs. exclusive FF at 3 mo. did not predict change in depressive symptomatology: p>0.2 (not adjusted) Covariates had no effect on the pattern of these results *High % of breast milk vs. low % of breast milk at 3 mo. and depressive symptomatology* - Change depressive symptomatology: Coeff= -0.02, SE=0.01, t ratio= -1.90, p=0.06 (not adjusted) - Change depressive symptomatology: Coeff= -0.02, SE=0.01, t ratio= -1.89, p=0.06 (fully adjusted) No difference in absolute levels of depressive symptomatology	Maternal age, income, education, marital status, parity, preterm birth, maternal employment, ethnicity and, social support.	- Continuous scores of depressive symptomatology are generally preferable in statistical modelling because they provide more variability. However, cut-off scores have been validated in identifying women with depression. -Data on BF frequency available *Limitations (predefined quality criteria)* - Assessment of BF and health outcome were done simultaneously. Blinding not reported *Other limitations* - Depressive symptomatology was assessed with self-report questionnaires - Women in this study were largely White, upper-middle class and married
EPDS: Edinburgh Postnatal Depression Scale; Mo.: Months; SE: Standard error; USA: United States of America		

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Weight retention	Krause, 2010 Public Health Nutrition USA Retrospective cohort 1996-2004	To determine the effect of BF on weight retention at 3 and 6 months postpartum	*Setting* The North Caroline Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) *Study population* Women participating in the WIC program and recertifying in the WIC programme at 3 and 6 months *Sample size* 3 mo. postpartum sample: n=14,330 6 mo. postpartum sample: n=4,922	*Age at enrolment* NR *Age at assessment of outcome* At 3 mo. postpartum: 23.5 years (SD 5.5 years) At 6 mo. postpartum: 25.2 years (SD 5.6 years)	*Assessment* Questionnaire at 3 mo. and 6 mo. postpartum. Questions were about current BF, BF discontinuation and time of introducing FF *Definition* EBF: currently BF, had never discontinued BF and had never introduced FF. MBF: currently BF, but introduced FF. FF: stopped BF and introduced FF before time of visit.	*Assessment* Weight measured at WIC postpartum recertification visit. Pre-pregnancy weight was self-reported. *Definition* Weight retention: Subtracting self-reported pre-pregnancy weight from the measured postpartum weight

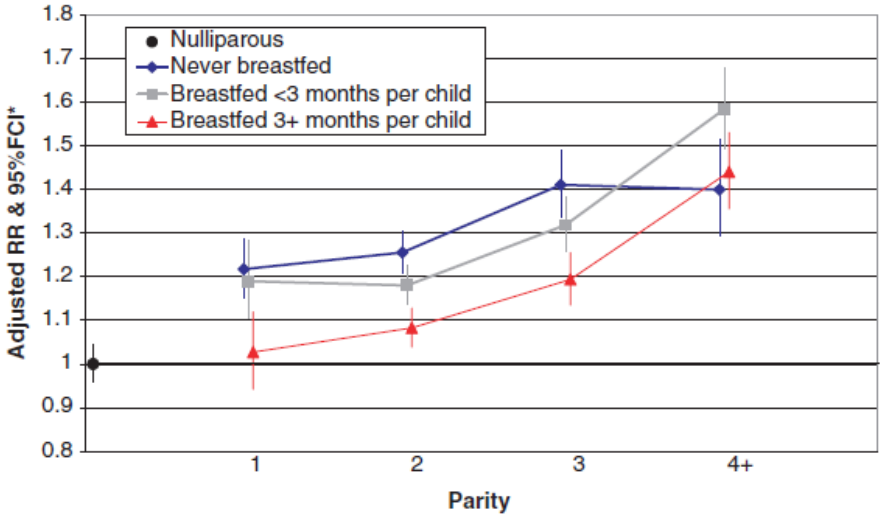
Results							Confounders	Remarks, limitations
BF and weight retention (r*eference =FF)*							Age, race, ethnicity, education, parity, gestational weight gain and pre-pregnancy weight.	*Limitations (predefined quality criteria)* - Assessment of BF and health outcome were done simultaneously. Blinding not reported- The data used in the present study were collected through the NC PNSS *Other limitations* - WIC includes low-income pregnant women, non-BF postpartum women and BF women as well as their children up to the age of 5 years. - Rate of BF at 6 mo. postpartum appear higher because women who are FF may receive WIC benefits only up to 6 mo. postpartum (deadline approach) - Measures at 3 and 6 mo. were not collected serially from the same individuals, but from separate groups of women recertifying at each time point
	Weight retention at 3 mo. postpartum (kg; n=14,330)			**Weight retention at 6 mo. postpartum (kg; n=4,922)**				
BF	**Regression coefficient**	**SE**	**P**	**Regression coefficient**	**SE**	**P**		
MBF	0.18	0.14	0.21	-0.84	0.23	0.0002		
EBF	-0.33	0.19	0.09	-1.38	0.25	<0.0001		

Kg: Kilogram; Lbs: Pounds; Mo.: Months; SE: Standard error; USA: United States of America; WIC: Women, Infants, and Children;NC PNSS: North Caroline Pregnancy Nutrition Surveillance System

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Hospitalization for gallbladder disease	Liu, 2009 International Journal of Epidemiology England and Scotland Prospective cohort study 1996 – 2001 (mean follow-up: 6.1 years per women)	To study the effect of reproductive factors, such as BF, age at menarche, and age at menopause and the risk of hospital admission for gallbladder disease	*Setting* Million Women Study *Study population* Women mostly aged 50 – 64 years recruited through NHS breast screening centres in England and Scotland during 1996 – 2001. Exclude: cancer (except non-melanoma skin cancer, ICD-10 code C44), an admission for gallbladder disease before recruitment or if parity was unknown *Sample size* n=1,289,029	*Age at enrolment* 50 – 64 years. Mean age 56.0 years (SD 4.7) *Age at assessment of outcome* NR, but admissions occurred a mean of 3.4 years following recruitment	*Exposure assessment* Women completed a baseline questionnaire on entry. A question on the BFD for each birth was added to the baseline questionnaire after the first 9% were recruited *Exposure definition* NR Lifetime BFD was categorized in: - BF_{never} - BF_{ever} - $BF_{<6\ mo.,\ BF\ 6–11\ mo.}$ - $BF_{12+\ mo.}$ - $BF_{continuous\ variable}$	*Health outcome assessment* - Data from NHS HES, containing records of all NHS hospital admissions from April 1997 (England) and the Scottish Morbidity Records from January 1981 (Scotland) - Patients were followed through computerized databases of NHS hospital admissions, deaths and cancer registrations using their unique health care number (NHS number), date of birth and other identifying details *Health outcome definition* Hospital admission with either a primary diagnosis of cholelithiasis or cholecystitis (ICD-10 code K80 or K81) or a procedural code for an excision of the gallbladder (OPCS-4 code J18)

Results	Confounders	Remarks, limitations
BF in parous women only and hospitalization for gallbladder disease - $aRR_{BF\ vs.\ no\ BF}$ (95% CI) = 0.92 (0.90-0.96) - $aRR_{BFD\ <6\ mo.\ vs\ no\ BF}$ (95% CI) = 0.97 (0.93-1.00) - $aRR_{BFD\ 6\text{-}11\ mo.\ vs\ no\ BF}$ (95% CI) = 0.89 (0.85-0.94) - $aRR_{BFD\ \ 12+\ mo.\ vs\ no\ BF}$ (95% CI) = 0.85 (0.81-0.89) P for linear trend <0.0001 - For minimally aRR see table 3 - See figure 1 for the aRR of gallbladder disease according to BFD per child and in a woman's' parity *BFD and hospitalization for gallbladder disease* $aRR_{per\ year\ BF}$ (95% CI) = 0.93 (0.90-0.95) - When examining the effect of BF with additional adjustment for alcohol intake and other medical illnesses the calculated risks did not alter appreciably. Similarly stratifying the analyses by parity did not alter the results	Age at recruitment, region of recruitment, socioeconomic status, BMI, smoking, hysterectomy, use of oral contraceptives, hormone replacement therapy, and parity	The article also reports the aRR of cholecystectomy *Limitations (predefined quality criteria)* - Time of assessing BF was >1 year - No clear definition of BF was reported - Assessment of exposure and outcome were not blind; questions on BF were added to the baseline questionnaire after the first 9% were recruited *Other limitations* - Recall of BFD may be less precise and women were not asked for how long they exclusively breastfed - The findings from this study are limited to middle-aged women and hospitalizations for symptomatic gallbladder disease. However from a public health view point it is women of this age who are responsible for the greatest proportion of the burden of gallbladder disease and it is symptomatic gallbladder disease which results in hospitalization that is of clinical importance
BMI: body mass index; HES: Hospital episode statistics; ICD: International Classification of Diseases; mo.: months; NHS: National Health Service; OPCS: Office of Population Censuses and Surveys		

Liu, 2009



*To permit valid comparisons between each group the relative risks and their confidence intervals were treated as floating absolute risks and 95% floating confidence intervals. [26] This approach does not alter the value of the relative risk but reduces the variances attributed to them and allows valid comparisons to be made between any two groups and tests of trend. Floated relative risks adjusted for age, region, socioeconomic status, BMI, hysterectomy, oral contraceptive and HRT use.

Figure 1 Adjusted relative risk of gallbladder disease according to duration of breastfeeding per child and a woman's parity

Liu, 2009

Table 3 Adjusted relative risk for gallbladder disease according to breastfeeding in parous women only

	Cases/population	Minimally adjusted[a] RR	Fully adjusted[b] RR (95% CI)
All parous women	23 054/1 148 789	–	–
Breastfeeding			
No	6 073/292 675	1.00	1.00
Yes	11 736/615 773	0.91	0.92 (0.90–0.96)
By total duration (months)			
<6	6 549/322 897	0.96	0.97 (0.93–1.00)
6–11	2 605/142 768	0.87	0.89 (0.85–0.94)
12+	2 582/150 074	0.83	0.85 (0.81–0.89)
P-value (linear trend)			<0.0001

[a]Adjusted for age, region of recruitment.
[b]Adjusted for age, region of recruitment, socioeconomic status, smoking, BMI, hysterectomy, use of hormone replacement therapy and oral contraceptives, parity.
Numbers of cases and population do not sum to totals because of missing values and women who were not asked about breastfeeding at recruitment (see Methods section).

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Metabolic syndrome, elevated blood pressure, and abdominal obesity	Ram, 2008 American Journal of Obstetrics & Gynecology USA Cross-sectional study 1995-1997	To evaluate whether lactation duration is associated with lower prevalence of metabolic syndrome in midlife, parous women	*Setting* Community-based samples at 7 clinical sites (Caucasian and pre-specified non-Caucasian sample at each site) *Study population* Parous (at least 1 birth), midlife women: age 42-52 years, an intact uterus and at least 1 ovary, at least 1 menstrual cycle in the past 3 months, and not having taken any reproductive hormones for the last 3 months *Sample size* n=2,516	*Age at enrolment* Mean (SD) Absence of MetSyn: 46.5 (2.2) years Presence of MetSyn: 46.7 (2.1) years *Age at assessment of outcome* Same, only baseline measurements included in the analysis	*Assessment* Retrospective questions about number of pregnancies and lactation duration following each birth *Definition* NR Duration of BF: coded in months (BFD is zero for no BF and BFD <1 mo.). For women who BF longer than 1 year/pregnancy each lactation period was truncated at 1 year (because after 1 year the infant receives majority of its caloric needs from alternate sources) Analysis: lifetime BF in years	*Assessment* 12h fasting blood samples were collected, blood pressure, height, weight and waist and hip circumference were measured using standardized procedures *Definition* MetSyn: at least 3 of the following criteria: - Abdominal obesity (waist circumference >80cm for Chinese and Japanese, >88cm for Caucasians, African Americans and Hispanics; - Hypertriglyceridemia (fasting triglycerides ≥150 mg/dL); - Low HDL cholesterol (<50 mg/dL); - Elevated blood pressure (average systolic ≥130 mm Hg or average diastolic ≥85 mm Hg or antihypertensive medication; - Impaired fasting glucose (>110 mg/dL or <125 mg/dL.

Results	Confounders	Remarks, limitations
BF and MetSyn, elevated blood pressure and abdominal obesity BF history (ever vs. never) / Lifetime BFD (per year) aOR (95% CI) P aOR (95% CI) P MetSyn 0.77 (0.62-0.96) 0.02 0.88 (0.77-0.99) 0.03 Elevated blood pressure 0.83 (0.68-0.998) 0.048 0.90 (0.81-0.996) 0.043 Abdominal obesity 0.70 (0.58-0.86) <0.01 0.86 (0.78-0.96) <0.01 Unadjusted ORs were only presented for MetSyn: $OR_{BF\ ever\ vs.\ never}$ (95% CI) = 0.62 (0.51-0.96) $OR_{each\ year\ of\ lifetime\ BF}$ (95% CI) = 0.80 (0.72-0.91) *BFD and MetSyn; stratification by parity* Parity aOR 95% CI P Para 1 0.57 0.34-0.95 0.03 Para 2 0.69 0.47-0.998 0.048 Para 3 0.69 0.43-1.10 0.12 Para 4 1.31 0.68-2.54 0.41	Age, smoking history, parity, ethnicity, study site, socioeconomic status, physical activity, daily caloric intake and high school BMI	- ORs were also presented for BF or BFD, and impaired fasting glucose, low HDL or elevated triglycerides *Limitations (predefined quality criteria)* - BF was assessed 42-52 years after birth - Limited definition of BF - Outcome and exposure assessed at same time point, no information about blinding *Other limitations* - Lactation may protect against obesity, and this may be driving the association with MetSyn, which is difficult to evaluate in the current model because of collinearly with the outcome variable. However, in adjusted analysis BF was associated with several components of MetSyn in addition to abdominal obesity. Furthermore, when waist circumference was removed and re-entered into the multivariable model adjusted for current BMI, the association remained significant - Next to recall bias of BF data, also possible recall bias for BMI at completion of high school

BMI: Body mass index; HDL: High-density lipoprotein; MetSyn: Metabolic syndrome; USA: United States of America

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Postmenopausal osteoporosis	Schnatz, 2010 Menopause USA Cross-sectional study January 1, 2007-March 1, 2009	To examine the effects of age at first pregnancy and BF on the development of post-menopausal OPS, as well as the potential synergistic effect of BF on the development of OPS after menopause	*Setting* Four private radiology groups in Hartford, CT *Study population* Women presenting for a dual-energy x-ray absorptiometry (DXA), aged ≥49 years. Excluded were those who not signed a HIPAA release, did not learn about the study and not being available for follow-up. *Sample size* n=619	*Age at enrolment* ≥49 years, mean age 61.4 years *Age at assessment of outcome* Same, CS analysis	*Assessment* Telephone interview on BF history by a member of the research team *Definition* BF: EBF ≥1 month	*Assessment* DXA scan obtained from one of the four radiology sites *Definition* OPS: T score of -2.5 or lower Low bone mass (osteopenia): T score between -1.0 and -2.5

Results	Confounders	Remarks, limitations
BF in women who were ≥27y at first pregnancy and OPS Prevalence OPS $_{\text{BF vs. no BF}}$ = 4.6% vs. 25.4%; P <0.001 See *Figur*. *BF in women who were ≥22y at first pregnancy and OPS* Prevalence OPS $_{\text{BF vs. no BF}}$ = 7.1% vs. 20.6%; P <0.001 *BF and OPS* Prevalence OPS $_{\text{BF vs. no BF}}$ = 7.6% vs. 18.7%; P<0.001. See Figure 7. Prevalence OPS $_{\text{BF and ≥27y at first pregnancy vs. no BF and <27y at first pregnancy}}$ = 4.6% vs. 16.3%; P = 0.001	None	Because 99% of the PBM is achieved by age of 27 years, separated analysis were performed for this age group. *Limitations (predefined quality criteria)* - BF data were recalled many years after birth of the child as included women were aged ≥45 years - Limited definition of BF reported - Data presented in this table were not corrected for confounders *Other limitations* - Biased by participants' recall by retrospective collection of historical data - 94.5% of the participants were white: not generalizable to all racial or ethnic populations
CT: Connecticut; DXA: dual-energy x-ray absorptiometry; HIPAA: Health Insurance Portability and Accountability Act; OPS: osteoporosis; P1: age at first pregnancy		

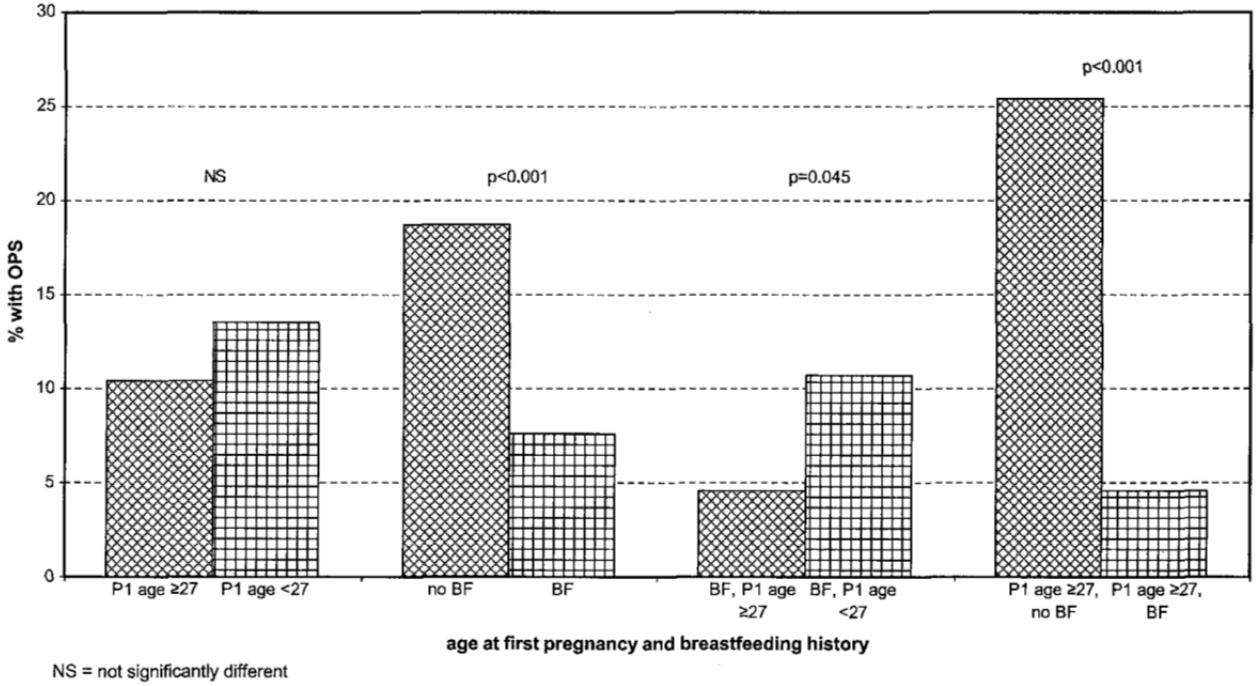


Figure 7. Prevalence of OPS as a function of P1 age and BF status.

Schnatz, 2010

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Cardiovascular disease, obesity, hypertension, diabetes	Schwarz, 2009 Obstetrics & gynecology USA Prospective cohort, including historical data 1994-2005	To examine dose-response relationships between the cumulative number of months women lactated and postmenopausal risk factors for cardiovascular disease	*Setting* Women's Health Initiative (WHI) study *Study population* Participants of the WHI, healthy postmenopausal women age 50-79 years on enrolment. Excluded were nulliparous. *Sample size* n = 139,681	*Age at enrolment* Median age: 63 years *Age at assessment of outcome* Prevalent cases: Median age 63 Incident cases: NR, but during the median follow-up of 7.9 years	*Assessment* Questionnaire at baseline clinic visit. *Definition* NR Cumulative lifetime duration of BF in months: - None or <1 month - 1-6 months - 7-12 months - 13-23 months - ≥24 months	*Assessment* Baseline questionnaire regarding medical history. Medication use was validated on enrolment by nurse examination of medication bottles, which participants were instructed to bring to the enrolment visit. Annual questionnaire to asses any hospitalization or any other outcomes. All incident cardiovascular diseases were validated by physician adjudication using standardized protocols. Height and weight were collected by study staff at baseline clinic visits. *Definition* CVD: Coronary heart disease, stroke, congestive heart failure, angina, peripheral vascular disease, carotid artery disease and coronary revascularization Prevalent cases: self-reported history of cardiovascular disease before enrolling in the WHI Incident cases: cardiovascular disease during follow-up Obesity: BMI calculated from height and weight. BMI ≥30 kg/m^2 Hypertension: self-reported history of treated hypertension or blood pressure measurements meeting criteria for hypertension. Diabetes: self-reported history of need to use a medication to control "sugar diabetes.

Results	Confounders	Remarks, limitations
BF and cardiovascular disease before enrolling in the WHI OR $_{\text{cumulative BFD >12mo. vs never BF}}$ (95% CI) = 0.91 (0.85-0.98; P = 0.008) *Prevalent CVD* / *Incident CVD* BFD (ref= never BF) — aOR (95% CI) 1-6 months: 1.03 (0.98-1.09) / 1.03 (0.98-1.08) 7-12 months: 0.95 (0.88-1.02) / 0.97 (0.90-1.04) 013-23 months: 0.93 (0.85-1.01) / 0.98 (0.91-1.05) 24+ months: 0.89 (0.80-0.98) / 0.93 (0.85-1.02) P for trend: 0.005 / 0.12 See table 1 for the unadjusted and party adjusted associations between duration of lactation and prevalent or incident CVD *BF by age groups and cardiovascular disease before enrolling in the WHI, prevalent cases* BFD (ref= never BF) — aOR (95% CI) BFD 7-12 mo.: 0.84 (0.71-0.99) / NS / NS BFD 13-23 mo.: 0.80 (0.65-0.97) / 0.85 (0.75-0.96) / NS BFD ≥24 mo.: 0.75 (0.58-0.96) / NS / NS *Women aged 50-59 y* / *Women aged 60-69 y* / *Women aged 70-79y*	Sociodemographic, family history and lifestyle variables (age, race, parity, age at menopause, education, income, family history of DM, myocardial infarction or stroke, physical activity, energy, cholesterol, fat, fiber and sodium intakes, tobacco history, hormone therapy use, aspirin use, multivitamin use) and BMI	- WIC began in 1994 and consisted of a set of clinical trials and an observational study focused on strategies for preventing chronic disease in postmenopausal women. - Association between duration of lactation and self-reported history of hyperlipidemia on enrolling in the Women's Health Initiative observational study and controlled trial was stated in the article *Limitations (predefined quality criteria)* - BF data were recalled on average 35 years after birth of the child - No clear definition of BF was provided. Duration of BF was specified - Assessment of BF and health outcome were done simultaneously. Blinding not reported *Other limitations* - All outcomes self-reported

BF by age groups and cardiovascular disease, incident cases (Cox modelling)*

	Women aged 50-59 y	*Women aged 60-69 y*	*Women aged 70-79y*
BFD (ref= never BF)		BMI adjusted HR (95% CI)	
BFD 7-12 mo.	0.80 (0.67-0.95)[1]	NS	NS
BFD 13-23 mo.	NS	NS	NS
BFD ≥24 mo.	0.68 (0.52- 0.89)[2]	NS	NS
P for trend	0.001		

**age on enrolment*

[1] Not adjusted HR = 0.79 (0.66, 0.94)

[2] Not adjusted HR = 0.66 (0.50, 0.86)

BF by parity and cardiovascular disease, incident cases (Cox modelling)

	One live birth	*Two live birth*	*Three live birth*
BF (ref= never BF)		Unadjusted HR (95% CI)	
BFD 7-12 mo.	0.72 (0.53-0.97)	NS	NS
BFD 13-23 mo.	NS	NS	NS
BFD ≥24 mo.	NS	0.58 (0.35-0.95)	0.78 (0.63-0.98)
P for trend	0.001		

BFD and obesity on enrolment in the WHI

BFD (ref=never BF)	aOR (95% CI)*	P
1-6 mo.	1.00 (0.96-1.03)	0.84
7-12 mo.	0.96 (0.91-1.00)	0.07
13-23 mo.	0.95 (0.90-1.00)	0.07
24+ mo.	1.02 (0.96-1.09)	0.56
P for trend	0.28	

*adjusted for all, except BMI .

Partial adjusted associations between BFD and obesity can be found in table 2.

BF and hypertension, diabetes

	Hypertension	*Diabetes*
BFD (ref= never BF)	aOR (95% CI)	
1-6 mo	0.95 (0.92-0.98)	0.91 (0.84-0.99)
7-12 mo.	0.88 (0.84-0.92)	0.87 (0.78-0.97)
13-23 mo.	0.89 (0.84-0.93)	0.75 (0.66-0.85)
24+ mo.	0.87 (0.82-0.92)	0.88 (0.76-1.01)
P for trend	<0.001	<0.001

Partly adjusted association between BFD and self-reported history of hypertension or diabetes can be found in table 3.

BMI: Body mass index; CVD: Cardiovascular disease; DM: Diabetes mellitus; HR: Hazard ratio; NS: Not significant; USA: United States of America; WHI: Women's Health Initiative; Y: Years.

Schwarz, 2009

Mo of Lactation	Prevalent CVD*	Incident CVD†
Univariable models		
Never	Referent	Referent
1–6	1.11 (1.06–1.15)	1.08 (1.03–1.13)
7–12	0.94 (0.88–0.99)	0.92 (0.86–0.98)
13–23	0.90 (0.85–0.96)	0.93 (0.86–1.00)
24+	0.99 (0.92–1.07)	0.96 (0.88–1.05)
P for trend	.007	.01
Adjusted for sociodemographic, family history, and lifestyle variables‡		
Never	Referent	Referent
1–6	1.03 (0.97–1.08)	1.03 (0.98–1.08)
7–12	0.94 (0.87–1.01)	0.97 (0.90–1.03)
13–23	0.92 (0.85–1.00)	0.98 (0.91–1.05)
24+	0.86 (0.89–0.98)	0.93 (0.85–1.02)
P for trend	.003	.10
Adjusted for above plus body mass index§		
Never	Referent	Referent
1–6	1.03 (0.98–1.09)	1.03 (0.98–1.08)
7–12	0.95 (0.88–1.02)	0.97 (0.90–1.04)
13–23	0.93 (0.85–1.01)	0.98 (0.91–1.05)
24+	0.89 (0.80–0.98)	0.93 (0.85–1.02)
P for trend	.005	.12

CVD, cardiovascular disease.
Data are odds ratio (95% confidence interval) unless otherwise specified.
* Cardiovascular disease on enrollment was identified by a self-reported history of myocardial infarction, angina, congestive heart failure, peripheral arterial disease, revascularization, or stroke.
† Incident cardiovascular disease (coronary heart disease, stroke, congestive heart failure, angina, peripheral vascular disease, carotid artery disease, and coronary revascularization) was validated by physician adjudication of medical records over 7.9 years of follow-up.
‡ Specifically, age, race, parity, age at menopause, education, income, family history (of diabetes mellitus, myocardial infarction, or stroke), physical activity, energy, cholesterol, fat, fiber, and sodium intakes, tobacco history, hormone therapy use, aspirin use, multivitamin use.
§ Adjusted for three categories of body mass index: less than 25, 25 to less than 30, and 30 or higher.

Table 1. Association between duration of lactation and cardiovascular disease among participants in the Women's health initiative observational study and controlled trial

Schwarz, 2009

Mo of Lactation	OR	95% CI	P	P Trend
Adjusted for age, parity, race, education, income, smoking				
Never	–	–	–	.001
1–6	0.97	0.94–1.00	.07	
7–12	0.92	0.89–0.96	<.001	
13–23	0.92	0.88–0.96	<.001	
24+	0.99	0.94–1.04	.69	
Adjusted for sociodemographic, family history, and lifestyle variables*				
Never	–	–	–	0.28
1–6	1.00	0.96–1.03	.84	
7–12	0.96	0.91–1.00	.07	
13–23	0.95	0.90–1.00	.07	
24+	1.02	0.96–1.09	.56	

OR, odds ratio; CI, confidence interval.

* Specifically, age, race, parity, age at menopause, education, income, family history (of diabetes mellitus, myocardial infarction, or stroke), physical activity, energy, cholesterol, fat, fiber, and sodium intakes, tobacco history, hormone therapy use, aspirin use, multivitamin use.

Table 2. Association between months of lactation and obesity on enrolling Women's Health Initiative observational study or controlled trials

Schwarz, 2009

Mo of Lactation	Hypertension	Diabetes	Hyperlipidemia
Adjusted for sociodemographic, family history, and lifestyle variables*			
Never	Referent	–	–
1–6	0.95 (0.92–0.98)	0.92 (0.85–0.99)	0.93 (0.89–0.97)
7–12	0.88 (0.84–0.91)	0.87 (0.78–0.97)	0.87 (0.82–0.93)
13–23	0.89 (0.84–0.93)	0.74 (0.65–0.84)	0.81 (0.76–0.87)
24+	0.87 (0.82–0.93)	0.89 (0.77–1.02)	0.80 (0.74–0.87)
P for trend	<.001	<.001	<.001
Adjusted for above plus body mass index†			
Never	Referent	–	–
1–6	0.95 (0.92–0.98)	0.91 (0.84–0.99)	0.93 (0.89–0.97)
7–12	0.88 (0.84–0.92)	0.87 (0.78–0.97)	0.88 (0.83–0.94)
13–23	0.89 (0.84–0.93)	0.75 (0.66–0.85)	0.81 (0.76–0.87)
24+	0.87 (0.82–0.92)	0.88 (0.76–1.01)	0.80 (0.73–0.87)
P for trend	<.001	<.001	<.001

Data are odds ratio (95% confidence interval) unless otherwise specified.
* Specifically, age, race, parity, age at menopause, education, income, family history (of diabetes mellitus, myocardial infarction, or stroke), physical activity, energy, cholesterol, fat, fiber, and sodium intakes, tobacco history, hormone therapy use, aspirin use, multivitamin use.
† Adjusted for three categories of body mass index: less than 25, 25 to less than 30, and 30 or higher.

Table 3. Association between duration of lactation and self-reported history of hypertension, diabetes, or hyperlipidemia on enrolling in the Women's Health Initiative observational study and controlled trials.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Myocardial infarction	Stuebe, 2009 American Journal of Obstetrics and Gynecology USA Prospective cohort study 1986 – 2002	To assess the relation between duration of lactation and maternal incident MI	*Setting* NHS (began in 1976) *Study population* Parous women aged 30 – 55 years from 11 states of the USA. Exclude: parous women who reported only stillbirths, a history of MI, angina, or coronary artery bypass graft before 1986 *Sample size* n=89,326	*Age at enrolment* 30 – 55 years *Age at assessment of outcome* 40 – 81 years	*Exposure assessment* BF history was assessed once in 1986 using a questionnaire. The total BFD for all pregnancies as a categorical variable was asked *Exposure definition* NR Lifetime BFD was categorized in: - None - 0 – 3 mo. - 3 – 6 mo. - 6 – 11 mo. - 11 – 23 mo. - >23 mo.	*Health outcome assessment* Biennially questionnaire, regarding medical diagnoses and health-related topics. Women who reported a non-fatal MI were asked to release medical records. *Health outcome definition* Confirmed cases met WHO criteria for MI: symptoms associated with diagnostic electrocardiographic changes or elevations in cardiac enzymes

Results	Confounders	Remarks, limitations
BFD and MI - aHR $_{\text{BFD >0-3 mo. vs. no BF}}$ (95% CI) = 1.01 (0.91-1.11) - aHR $_{\text{BFD >3-6 mo. vs. no BF}}$ (95% CI) = 1 (0.88-1.14) - aHR $_{\text{BFD >6-11 mo. vs. no BF}}$ (95% CI) = 1.02 (0.88-1.18) - aHR $_{\text{BFD >11-23 mo. vs. no BF}}$ (95% CI) = 0.93 (0.8-1.07) - aHR $_{\text{BFD >23 mo. vs. no BF}}$ (95% CI) = 0.77 (0.62-0.94) P for trend 0.02 - See table 2 for age, parity and stillbirth aHR - aHR $_{\text{BFD ≥12 mo. vs no BF}}$ (95% CI) = 0.87 (0.77-0.99) (adjusted for coronary and lifestyle-covariates) - Results of the association between BFD and incident MI, stratified by time since last birth among parous women can be found in table 3	Age, parity, history of stillbirth, BMI at age 18 years, birth weight of subject, parental history of MI before age 60 years, diet quintile, physical activity, smoking menopausal status, use of aspirin, alcohol multivitamins and postmenopausal hormones	*Limitations (predefined quality criteria)* - Time of assessing BF was >1 year - Clear definition of BF not reported - Physicians blinded to the participants' questionnaire reviewed records to confirm diagnosis. Not reported whether assessment of exposure was blind *Other limitations* - Misclassification is a potential concern, because lifetime BF was self-reported
BMI: body mass index; MI: myocardial infarction; mo.; months; NHS: Nurses' Health Study; USA: United States of America; WHO: World Health Organization		

Stuebe, 2009

TABLE 2
Incident MI and duration of lactation among parous women in the Nurses' Health Study: prospective analysis using cases from 1986 to 2002

Cumulative duration of lactation (mo)	None	> 0-3	> 3-6	> 6-11	> 11-23	> 23	*P* for trend
Cases, n	1037	627	304	224	241	107	
Person-years	494,667	306,669	161,586	132,492	164,746	90,805	
Age, parity, and stillbirth-adjusted HR (95% CI)	1.0 (ref)	0.90 (0.81-0.99)	0.91 (0.8-1.03)	0.88 (0.76-1.02)	0.77 (0.67-0.89)	0.63 (0.51-0.77)	< .0001
Multivariate-adjusted HR (95% CI)[a]	1.0 (ref)	1.01 (0.91-1.11)	1 (0.88-1.14)	1.02 (0.88-1.18)	0.93 (0.8-1.07)	0.77 (0.62-0.94)	.02

All models were adjusted for age, parity, and history of stillbirth.

[a] Hazard ratio and 95% confidence interval (CI) adjusted for age; parity; history of stillbirth; body mass index (BMI) at age 18 years; birthweight of subject; parental history of MI before age 60 years; diet quintile; physical activity; smoking; menopausal status; and use of aspirin, alcohol, multivitamins, and postmenopausal hormones.

Stuebe. Duration of lactation and incidence of MI. Am J Obstet Gynecol 2009.

Stuebe, 2009

TABLE 3
Incident MI and duration of lactation, stratified by time since last birth among parous women in the Nurses' Health Study: prospective analysis using cases from 1986 to 2002

Cumulative duration of lactation (mo)	None	> 0-3	> 3-6	> 6-11	> 11-23	> 23	*P* for trend
No birth in last 30 y							
No of cases	616	426	186	130	133	54	
Person-years	211,951	146,625	67,250	49,338	54,082	21,443	
Age, parity, and stillbirth-adjusted HR (95% CI)	1.0 (ref)	0.96 (0.85-1.09)	0.94 (0.79-1.11)	0.91 (0.75-1.1)	0.82 (0.68-0.99)	0.77 (0.58-1.02)	0.01
Multivariate-adjusted HR (95% CI)[a]	1.0 (ref)	1.04 (0.92-1.18)	1.02 (0.86-1.21)	1.02 (0.84-1.24)	0.95 (0.78-1.15)	0.90 (0.67-1.19)	0.33
Birth in last 30 y							
No of cases	421	201	118	94	108	53	
Person-years	282,716	160,044	94,336	83,155	110,663	69,362	
Age, parity and stillbirth-adjusted HR (95% CI)	1.0 (ref)	0.81 (0.69-0.96)	0.87 (0.71-1.07)	0.81 (0.65-1.02)	0.71 (0.57-0.88)	0.50 (0.37-0.67)	< .0001
Multivariate-adjusted HR (95% CI)[a]	1.0 (ref)	0.94 (0.79-1.12)	0.98 (0.8-1.21)	0.96 (0.76-1.21)	0.89 (0.71-1.1)	0.66 (0.49-0.89)	.02

All models were adjusted for age, parity, and history of stillbirth.

[a] Hazard ratio (HR) and 95% confidence interval (CI) adjusted for age; parity; history of stillbirth; body mass index (BMI) at age 18 years; birthweight of subject; parental history of MI before age 60 years; diet quintile; physical activity; smoking; menopausal status; and use of aspirin, alcohol, multivitamins, and postmenopausal hormones.

Stuebe. Duration of lactation and incidence of MI. Am J Obstet Gynecol 2009.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Premenopausal breast cancer	Stuebe, 2009 Archives of Internal Medicine USA Prospective cohort study, including historical data 1997-2005	To assess the relationship between BF intensity and incidence of premenopausal breast cancer.	*Setting* Participants part of the Nurses' Health Study II *Study population* Registered nurses who reported at least 1 pregnancy in 1997. Excluded were nulliparous or those with missing data on parity in 1997 or did not report BF history, postmenopausal women or whose menopausal status was unknown, those with prevalent breast cancer, carcinoma in situ or other malignant disease, missing year of first birth or missing height. *Sample size* n=60,075	*Age at enrolment* Between 25-42 years *Age at assessment of outcome* 46.2 years	*Assessment* Prospectively assessed in 1997, by a detailed questionnaire on BF and EBF for each of their first 4 children including timing of introducing FF and solid foods. *Definition* - EBF: combination of two questions "at what month did you start giving solid foods/FF at least once daily?" EBF duration = the earlier of these 2 time points. - BFD: all duration reported as categorical variables	*Assessment* Baseline and biennial follow-up questionnaires in which participants were asked whether they had been diagnosed as having breast cancer. For non-responders, the National Death Index was searched. *Definition* Self-reported breast cancer (confirmed in medical records in more than 99% of the cases)

Results	Confounders	Remarks, limitations
BF and BFD and incident premenopausal breast cancer Age-adjusted HR (95% CI) / Covariate-adjusted HR (95% CI) BF $_{never}$: 1 / 1 BF $_{ever}$: 0.87 (0.69-1.08) / 0.75 (0.56-1.00) BFD $_{<1\ mo.}$: 1.04 (0.71-1.51) / 0.93 (0.63-1.38) BFD $_{>1-3\ mo.}$: 0.80 (0.53-1.21) / 0.72 (0.46-1.11) BFD $_{>3-6\ mo.}$: 0.62 (0.43-0.91) / 0.54 (0.36-0.82) BFD $_{>6-12\ mo.}$: 0.91 (0.69-1.19) / 0.78 (0.56-1.08) BFD $>_{12-24\ mo.}$: 0.84 (0.65-1.10) / 0.71 (0.51-1.00) BFD $_{>24-36\ mo.}$: 1.07 (0.80-1.43) / 0.92 (0.64-1.32) BFD $_{>36\ mo.}$: 0.71 (0.50-1.01) / 0.63 (0.40-0.99) P for trend: 0.88 / 0.95 *EBF duration and incident premenopausal breast cancer* Age-adjusted HR (95% CI) / Covariate-adjusted HR (95% CI) BF, never EBF: 1 / 1 EBFD $_{>0-3\ mo.}$: 0.94 (0.70-1.28) / 0.94 (0.69-1.28) EBFD $_{>3-6\ mo.}$: 1.08 (0.82-1.42) / 1.08 (0.82-1.43) EBFD $_{>6-12\ mo.}$: 1.08 (0.86-1.37) / 1.07 (0.84-1.36) EBFD $>_{12-18\ mo.}$: 1.11 (0.83-1.48) / 1.09 (0.80-1.48)	Height, BMI, BMI at age 18 years, and year of first birth (continuous); family history of first- or second-degree relative with breast cancer, history of benign breast disease, and use of medications to suppress lactation (dichotomous); and birth weight of participant, age at menarche, parity, and age at first birth; physical activity; alcohol consumption; and oral contraceptive use (categorical)	Nurses's Health Study II (started in 1989) is a large prospective cohort including data on duration of exclusive lactation for each child as well hypertensive pregnancy complications and preterm birth *Limitations (predefined quality criteria)* - Recall of BF history was limited to two years by the biennial follow-up questionnaire - Assessment of BF was before after the disease outcome was known. Blinding not reported - Health outcome could have been more specified, but medical records were checked in almost all cases *Other limitations* - All participants in the study are registered nurses, and 94% Caucasian

EBFD >18	0.83 (0.53-1.29)	0.86 (0.54-1.39)		
P for trend	0.74	0.74		
See table 3 for the HR (95% CI) of BFD and incident premenopausal breast cancer among women with only 1 child. See table 6 for the HR (95% CI) of BFD and incident premenopausal breast cancer, stratified by family history of a first-degree relative with breast cancer.				
EBFD: Exclusive BF duration; BMI: Body mass index; HR: Hazard ratio; Mo.: Months.				

Stuebe, 2009

Table 3. Hazard Ratios (HRs) of Incident Premenopausal Breast Cancer by Duration of Lactation Among 10 164 Women With Only 1 Child in the Nurses' Health Study II From 1997 to 2005

Characteristic	Cases, No.[a]	Person-Years, No.	Age-Adjusted, HR (95% CI)	Covariate-Adjusted,[b] HR (95% CI)
Never breastfed	32	12 371	1 [Reference]	1 [Reference]
Ever breastfed	80	43 786	0.67 (0.44-1.03)	0.50 (0.28-0.91)
Duration of breastfeeding, mo				
<1	12	5216	0.95 (0.48-1.87)	0.74 (0.34-1.59)
1-2	10	4814	0.77 (0.37-1.58)	0.59 (0.26-1.35)
3-5	14	11 457	0.46 (0.24-0.88)	0.33 (0.16-0.71)
6-8	12	8161	0.61 (0.31-1.20)	0.43 (0.19-0.96)
9-11	13	5776	0.71 (0.37-1.37)	0.51 (0.23-1.13)
12-18	11	5428	0.72 (0.35-1.44)	0.53 (0.23-1.21)
≥19	8	2934	0.85 (0.38-1.88)	0.55 (0.22-1.40)
P value for trend			.49	.50

Abbreviation: CI, confidence interval.
[a] Incident cases of invasive breast cancer.
[b] The HR and 95% CI were adjusted for age, height, current body mass index (BMI), BMI at age 18 years, personal history of benign breast disease, first- or second-degree relative with a history of breast cancer, year of first birth, birth weight of participant, age at menarche, age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.

Stuebe, 2009

Table 6. Hazard Ratios (HRs) of Incident Premenopausal Breast Cancer by Duration of Lactation, Stratified by Family History of a First-Degree Relative with Breast Cancer, Among 60 075 Parous Women in the Nurses' Health Study II From 1997 to 2005[a]

	No Family History of Breast Cancer				With Family History of Breast Cancer			
Lactation History	Cases, No.[b]	Person-Years, No.	Age-Adjusted, HR (95% CI)	Covariate-Adjusted,[c] HR (95% CI)	Cases, No.[b]	Person-Years, No.	Age-Adjusted, HR (95% CI)	Covariate-Adjusted,[c] HR (95% CI)
Never	68	39 377	1 [Reference]	1 [Reference]	24	4965	1 [Reference]	1 [Reference]
Ever	429	278 545	0.97 (0.75-1.25)	0.89 (0.64-1.22)	87	34 670	0.55 (0.34-0.88)	0.41 (0.22-0.75)
Duration of breastfeeding, mo								
<1	33	17 780	1.16 (0.76-1.76)	1.08 (0.70-1.67)	6	2139	0.67 (0.26-1.70)	0.54 (0.21-1.43)
>1-3	24	18 305	0.85 (0.53-1.35)	0.82 (0.50-1.33)	6	1989	0.71 (0.28-1.80)	0.51 (0.19-1.36)
>3-6	33	30 109	0.71 (0.47-1.08)	0.66 (0.42-1.05)	5	3304	0.33 (0.12-0.88)	0.23 (0.08-0.66)
>6-12	96	62 313	0.96 (0.70-1.32)	0.90 (0.62-1.30)	25	7610	0.68 (0.37-1.23)	0.48 (0.24-0.98)
>12-24	119	77 511	0.96 (0.71-1.29)	0.88 (0.60-1.28)	23	10 035	0.51 (0.28-0.94)	0.35 (0.17-0.74)
>24-36	88	42 940	1.28 (0.93-1.77)	1.16 (0.77-1.75)	12	5582	0.49 (0.24-1.00)	0.33 (0.14-0.79)
>36	36	29 586	0.76 (0.50-1.14)	0.68 (0.41-1.12)	10	4011	0.53 (0.25-1.13)	0.42 (0.16-1.09)
P value for trend			.52	.73			.09	.16

[a] *P* value for interaction = .03.
[b] Incident cases of invasive breast cancer.
[c] The HR and 95% CI were adjusted for age, height, current body mass index (BMI), BMI at age 18 years, personal history of benign breast disease, year of first birth, birth weight of participant, age at menarche, parity and age at first birth, use of medications to suppress lactation, use of oral contraceptives, consumption of alcohol, and physical activity.

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Hypertension	Stuebe, 2011 American journal of Epidemiology USA Prospective cohort study, including historical data 1991-2005	To measure the association between duration and exclusivity of lactation and incident maternal hypertension	*Setting* Nurses' Health Study II *Study population* Participants of the study, since 1991. Excluded were nulliparous, those with a diagnosis of hypertension prior to 1991, or who reported in 1989 elevated blood pressure, antihypertensive medications. Also were excluded women with self-reported physician diagnosed diabetes, cardiovascular diseases, hyperlipidemia or cancer *Sample size* n=55,636	*Age at enrolment* Mean age between 35.1-37.3 years *Age at assessment of outcome* NR	*Assessment* Assessed in 1997, by a detailed questionnaire on BF for each of their first 4 children including timing of introducing FF and solid foods. Women with births after 1997 completed a similar questionnaire in 2003. *Definition* NR Duration categories: Total BF: Never, >0-3 months, >3-<6 months, 6-<9 months, 9-<12 months, ≥12 months EBF: Never BF, BF but never EBF, >0-3 months EBF, >3-<6 months EBF, ≥6 months EBF	*Assessment* Baseline and biennial follow-up questionnaires in which participants were asked whether they ever had a physician diagnosis of high blood pressure, excluding during pregnancy. *Definition* Self-reported hypertension

Results	Confounders	Remarks, limitations
BF and maternal hypertension *BF for the first child* / *Mean duration/child** BF (ref= BFD ≥12 mo.) — Adjusted HR (95% CI) *Never BF*: 1.22 (1.13-1.31) / *1.16 (1.07-1.26)* BFD >0-3 mo.: 1.24 (1.15-1.33) / *1.13 (1.05-1.22)* BFD >3-<6 mo.: 1.13 (1.05-1.22) / *1.13 (1.05-1.21)* BFD 6-<9 mo.: 1.09 (1.01-1.17) / *1.07 (0.99-1.15)* BFD 9-<12 mo.: 1.03 (0.96-1.11) / *1.08 (0.99-1.17)* P trend < 0.001 / P trend < 0.001 *additionally adjusted for parity. HR adjusted for age, or HR adjusted for age + IPW in table 2 and 3 *EBF and maternal hypertension* *EBF for the first child* / *Mean EBF duration/child** BF (ref= EBF duration ≥6 mo.) — Adjusted HR (95% CI) Never BF: 1.22 (1.13-1.31) / 1.12 (1.02-1.23) BF, never EBF: 1.07 (1.00-1.15) / 1.09 (1.00-1.19) EBF >0-3 months: 1.08 (0.99-1.18) / 1.07 (0.98-1.16) EBF >3-<6 months: 1.04 (0.96-1.13) / 1.04 (0.95-1.13) P trend < 0.001 / P trend = 0.01 *additionally adjusted for parity HR adjusted for age, or HR adjusted for age + IPW can be found in table 2 and 3	Age, IPW (Maternal BMI at age 18 years (linear and quadratic), year of first birth (linear and quadratic), self-reported history of preeclampsia, gestational hypertension, gestational diabetes, birth of an infant at <37 weeks' gestation, birth of an infant weighing <2,500 g, miscarriage or stillbirth at >12 weeks' gestation, smoking status, vigorous physical activity, alcohol consumption, DASH diet score quintile, family history of hypertension, current oral contraceptive use, current nonnarcotic analgesic use, self-reported race) and current BMI	Nurses's Health Study II (started in 1989) is a large prospective cohort including data on duration of exclusive lactation for each child as well hypertensive pregnancy complications and preterm birth. *Limitations (predefined quality criteria)* - Not clear when BF data was recalled, but for the majority of the participants after 10 years of birth - No clear definition of BF provided, but a distinction is made between EBF and total BF - Assessment of BF and health outcome were done simultaneously. Blinding not reported *Other limitations* - All participants in the study are registered nurses, and 94% Caucasian - Data on births before 1989 retrospective collected

Mean BFD per child and maternal hypertension, in women with first birth after 1989 (n=8,318) HR $_{\text{never BF vs. BFD ≥12 mo.}}$ (95% CI) = 1.22 (0.93-1.60) HR $_{\text{BFD >0-3 mo. vs. BFD ≥12 mo.}}$ (95% CI) = 1.22 (0.93-1.59)		
BMI: Body mass index; DASH: Dietary approaches to stop hypertension; G: Gram; HR: Hazard ratio; IPW: Inverse probability weight; Mo.: Months; USA: United States of America; Y: Years.		

Stuebe, 2011

Table 2. Association Between Duration of Breastfeeding for the First Child and Incident Hypertension Among 55,636 Parous Women in the Nurses' Health Study II, United States, 1991–2005[a]

Duration	No. of Cases	Person-Years	Age-adjusted Hazard Ratio[b]	95% CI	Age- and IPW-adjusted Hazard Ratio[c]	95% CI	Age-, IPW-,[c] and Current BMI-adjusted Hazard Ratio[d]	95% CI
Total breastfeeding								
Never	2,179	126,012	1.46	1.36, 1.57	1.27	1.18, 1.36	1.22	1.13, 1.31
>0–3 months	1,459	95,475	1.46	1.35, 1.57	1.29	1.20, 1.39	1.24	1.15, 1.33
>3–<6 months	1,639	125,370	1.28	1.19, 1.38	1.16	1.08, 1.25	1.13	1.05, 1.22
6–<9 months	1,356	111,970	1.17	1.08, 1.26	1.11	1.03, 1.19	1.09	1.01, 1.17
9–<12 months	1,014	89,853	1.07	0.99, 1.17	1.03	0.95, 1.11	1.03	0.96, 1.11
≥12 months	1,214	112,200	1.00	Referent	1.00	Referent	1.00	Referent
P_{trend}			<0.001		<0.001		<0.001	
Exclusive breastfeeding								
Never breastfed	2,179	126,012	1.45	1.34, 1.56	1.29	1.20, 1.39	1.22	1.13, 1.31
Breastfed, never exclusively	2,801	198,791	1.32	1.23, 1.42	1.11	1.03, 1.19	1.07	1.00, 1.15
>0–3 months exclusively	1,491	118,373	1.19	1.10, 1.29	1.08	0.99, 1.18	1.08	0.99, 1.18
>3–<6 months exclusively	1,319	118,717	1.08	1.00, 1.17	1.03	0.95, 1.12	1.04	0.96, 1.13
≥6 months exclusively	1,054	97,390	1.00	Referent	1.00	Referent	1.00	Referent
P_{trend}			<0.001		<0.001		<0.001	

Abbreviations: BMI, body mass index; CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; IPW, inverse probability weight.
[a] Inverse probability weight-adjusted Cox proportional hazards regression models were used.
[b] Adjusted for participant's age and follow-up time in months.
[c] Inverse probability weights derived from multinomial logistic regression model for probability of each breastfeeding duration category as a function of maternal BMI at age 18 years (linear and quadratic), year of first birth (linear and quadratic), self-reported history of preeclampsia, gestational hypertension, gestational diabetes, birth of an infant at <37 weeks' gestation, birth of an infant weighing <2,500 g, miscarriage or stillbirth at >12 weeks' gestation, smoking status, vigorous physical activity, alcohol consumption, DASH diet score quintile, family history of hypertension, current oral contraceptive use, current nonnarcotic analgesic use, and self-reported race.
[d] BMI during follow-up modeled by using a 3-knot quadratic spline.

Stuebe, 2011

	No. of Cases	Person-Years	Age-adjusted Hazard Ratio[b]	95% CI	Age- and Covariate-adjusted Hazard Ratio[c]	95% CI	Age-, Covariate-, and Current BMI-adjusted Hazard Ratio[d]	95% CI	Age-, Covariate-, Current BMI-, and Parity-adjusted Hazard Ratio	95% CI
Mean total duration/ child										
Never breastfed	1,522	89,026	1.48	1.38, 1.60	1.22	1.13, 1.32	1.20	1.10, 1.29	1.16	1.07, 1.26
>0–3 months	1,893	127,191	1.43	1.33, 1.54	1.21	1.12, 1.30	1.14	1.06, 1.23	1.13	1.05, 1.22
>3–<6 months	1,930	143,362	1.32	1.23, 1.42	1.19	1.11, 1.28	1.14	1.06, 1.22	1.13	1.05, 1.21
6–<9 months	1,525	125,810	1.17	1.08, 1.26	1.09	1.02, 1.18	1.07	0.99, 1.15	1.07	0.99, 1.15
9–<12 months	1,049	87,155	1.14	1.05, 1.24	1.07	0.99, 1.17	1.07	0.99, 1.16	1.08	0.99, 1.17
≥12 months	1,282	119,499	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
P_{trend}			<0.001		<0.001		<0.001		<0.001	
Mean exclusive duration/child										
Never breastfed	1,522	89,026	1.45	1.32, 1.58	1.16	1.05, 1.27	1.14	1.04, 1.26	1.12	1.02, 1.23
Breastfed, never exclusively	2,337	162,909	1.34	1.23, 1.46	1.14	1.04, 1.24	1.10	1.01, 1.20	1.09	1.00, 1.19
>0–3 months	2,288	172,266	1.24	1.13, 1.35	1.08	0.99, 1.18	1.06	0.97, 1.15	1.07	0.98, 1.16
>3–<6 months	1,914	164,355	1.10	1.01, 1.20	1.04	0.95, 1.13	1.03	0.95, 1.13	1.04	0.95, 1.13
≥6 months	707	65,167	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
P_{trend}			<0.001		<0.001		0.001		0.01	

Abbreviations: BMI, body mass index; CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension.
[a] Multivariable Cox proportional hazards regression models were used.
[b] Adjusted for participant's age and follow-up time in months.
[c] Covariate-adjusted models include maternal BMI at age 18 years (linear and quadratic), year of first birth (linear and quadratic), self-reported history of preeclampsia, gestational hypertension, gestational diabetes, birth of an infant at <37 weeks' gestation, birth of an infant weighing <2,500 g, miscarriage or stillbirth at >12 weeks' gestation, smoking status, vigorous physical activity, alcohol consumption, DASH diet score quintile, family history of hypertension, current oral contraceptive use, current nonnarcotic analgesic use, and self-reported race.
[d] BMI during follow-up modeled by using a 3-knot quadratic spline.

Table 3. Association between mean duration of total and exclusive BF per child and incident hypertension among 59852 parous women in the Nurses' Health Study II, USA, 1991-2005[a]

Health outcome	Author, year, journal, country, study design, study period	Study objective	Setting, study population, sample size	Age at enrolment, age at assessment of outcome	Exposure assessment and definition	Health outcome assessment and definition
Weight gain, obesity	Wiklund, 2011 Public Health Nutrition Finland Cross-sectional study 2007-2008	To investigate the long-term effects of duration of postpartum lactation on maternal body composition and risk for cardio-metabolic disorders in later life.	*Setting* Study part of the Calex-family study *Study population* Women who gave birth from the city of Jyväskylä and surroundings in Central Finland. Excluded were those who had gestational diabetes of hypertension, were currently pregnancy or reported being pregnant within 5 years before the present measurements. Exclude were also those who reported twin pregnancies, or did not have body composition data. *Sample size* n=198	*Age at enrolment* Mean age 48y (range 36-60y) *Age at assessment of outcome* Mean age 48y (range 36-60y)	*Assessment* Self-administered questionnaire *Definition* Average duration of BF= total mo. of BF / number of biological children. SDB: <6 mo. BF MDB: 6-10 mo. BF LDB: >10 mo. BF	*Assessment* Body height (cm)n and weight (kg) were measured using standardized protocols. *Definition* BMI = kg/m^2

Results	Confounders	Remarks, limitations
BF and weight gain 16–20 years after the last parturition SDB (14.0 kg, SD 9.1) vs. MDB (8.3 kg, SD 6.5): P=0.001 SDB (14.0 kg, SD 9.1) vs. LDB (7.6 kg, SD 6.6): P<0.001 See figure 2 *BF and BMI 16–20 years after the last parturition* SDB (27.3 kg/m^2, SD 5.5) vs. MDB (24.4 kg/m^2, SD 3.7): P<0.001 SDB (27.3 kg/m^2, SD 5.5) vs. LDB (24.6 kg/m^2, SD 3.3): P=0.001 MDB (24.4 kg/m^2, SD 3.7) vs. LDB (24.6 kg/m^2, SD 3.3): P=0.847 *EBF and total duration of BF and weight gain, generalized estimating equations model* EBF: R^2=-0.06, P<0.024 Total duration of BF: R^2=-0.20, P<0.001	Adjusted for relevant factors: pre-pregnancy weight and BMI, age at first pregnancy, smoking, menopause status, level of education, previous and current participation in leisure-time physical activity, current dietary energy intake, number of biological children, and duration of exclusive and total breast-feeding months.	- 7% of the SDB and 3% of the LDB mothers reported that they had never given EBF - Presented health outcomes in the article: Risk factors for cardio-metabolic disorders (serum glucose concentrations, insulin concentrations, insulin resistance, index blood pressure) in later life, body composition and weight gain between pregnancies - Detailed and accurate data on weight change during each pregnancy could be extracted from maternal tracking records. *Limitations (predefined quality criteria)* - BF data were recalled many years after birth of the child - The assessment of BF and health outcome was done simultaneously . Blinding not reported
BMI: Body mass index; Cm: Centirmetre; Kg: Kilogram; LDB: Long duration of BF; MDB: Medium duration of BF; SDB: Short duration of BF; Vs.: Versus; Y: Years.		

Wiklund, 2011

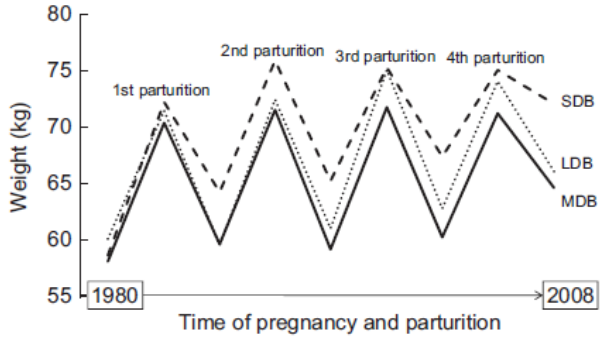


Fig. 2 ANOVA was used to compare weight change among the breast-feeding groups during the reproductive years. Body weight was similar among the groups at the beginning of the first pregnancy. After the first and each consecutive parturition, the SDB mothers retained significantly more body weight compared with MDB and LDB mothers (all $P < 0.001$). Number of women in each group: at first pregnancy, SDB (*n* 38), MDB (*n* 44) and LDB (*n* 44); at second pregnancy, SDB (*n* 33), MDB (*n* 41) and LDB (*n* 42); at third pregnancy, SDB (*n* 14), MDB (*n* 26) and LDB (*n* 30); at fourth preganancy, SDB (*n* 5), MDB (*n* 8) and LDB (*n* 15); and in year 2008, SDB (*n* 38), MDB (*n* 44) and LDB (*n* 39). SDB, short duration of breast-feeding; MDB, medium duration of breast-feeding; LDB, long duration of breast-feeding. Women (mean age 48, range 36–60 years) from the city of Jyväskylä and surroundings in Central Finland, 2007–2008

RIVM

Committed to health and sustainability