

Supplementary Materials

Table S1. PRISMA Checklist.

Section/Topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1-2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	2
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	3-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	3-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	3-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	3-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	3-10

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	3-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not applicable

Table S2. Trial bias assessment according to Cochrane Collaboration.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
Cristofalo 2013	Low	Low	Low	Unclear	Low	Low	Low
O'Connor 2016	Low	Low	Not Applicable	Unclear	Low	Low	Low
Sullivan 2010	Low	Low	Not Applicable	Unclear	Low	Low	Low
Schanler 2005	Low	Low	Unclear	Unclear	Low	Low	Low
Manzoni 2013	Low	Low	Not Applicable	Unclear	Low	Low	Low
Corpeleijn 2016	Low	Low	Low	Unclear	Low	Low	Low

Table S3. Observational Studies bias assessment according to New Castle-Ottawa scale.

Study ID	Selection			Comparability		Outcome		
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of the cohort on the basis of the design of analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up cohorts
Bishop 2010	*A	*A	*A	B	A*	*A	A*	B
Zamkir 2018	*A	*A	*A	B	A*	*A	A*	B
Spiegler 2016	*A	*A	*A	B	A*	*A	A*	B
Corpeleijn in 2012	*A	*A	*A	B	A*	*A	A*	B
Berkhout 2018	*A	*A	*A	B	A*	*A	A*	B
Chowing 2016	*A	*A	*A	B	A*	*A	A*	B
Manzoni 2013	*A	*A	*A	B	A*	*A	A*	B

Colaizy 2012	*A	*A	*A	B	A*	*A	A*	B
Kreissl 2017	*A	*A	*A	B	A*	*A	A*	B
Jacobi Pollistok 2016	*A	*A	*A	B	A*	*A	A*	B
Paker 2012	*A	*A	*A	B	A*	*A	A*	B
Vohr 2007	*A	*A	*A	B	A*	*A	A*	B
Huston 2018	*A	*A	*A	B	A*	*A	A*	B
Giuliani 2012	*A	*A	*A	B	A*	*A	A*	B
Ginovart 2016	*A	*A	*A	B	A*	*A	A*	B
Tanaka 2009	*A	*A	*A	B	A*	*A	A*	B
Furman 2003	*A	*A	*A	B	A*	*A	A*	B
Madore2 017	*A	*A	*A	B	A*	*A	A*	B
Herrman 2014	*A	*A	*A	B	A*	*A	A*	B
Sisk 2007	*A	*A	*A	B	A*	*A	A*	B
Sisk 2016	*A	*A	*A	B	A*	*A	A*	B
Manea 2018	*A	*A	*A	B	A*	*A	A*	B
Chowing 2016	*A	*A	*A	B	A*	*A	A*	B
Maayan- Metzger 2012	*A	*A	*A	B	A*	*A	A*	B
Assad 2016	*A	*A	*A	B	A*	*A	A*	B
Giuliani 2012	*A	*A	*A	B	A*	*A	A*	B

Table S4. Nutritional Pattern of Interventional Studies.

Author, year	Country	Study Population	Intervention	Control
Cristofalo 2013	USA and Austria	VLBW	Donor milk fortifier (20 kcal/oz Prolacta Bioscience, Monrovia)	Preterm Formula (24 kcal/oz)
O'Connor 2016	Canada	VLBW	Donor milk fortifier (Mother's milk bank of Ohio and NorthernStar Mother's milk bank with fortifier (Similac Humal Milk Fortifier or Enfamil Human Milk fortifier)	Preterm Formula (Similac Special Care (Abbot) Enfamil Premature (Mead Johnson Nutritional) 20-20 Kcal/oz 3 gr protein/100
Sullivan 2010	USA and Austria	VLBW	Donor milk fortifier (Proact+H2MF, Prolacta Bioscience)	Preterm Formula
Schanler 2005	USA	VLBW	Mother Milk or Donor milk (Mother milk bank, Presbyterian/-St Luke Medical center, Denver and Lactation Center WakeMed, Raleigh) and Mother milk fortifier (Enfamil Human Milk Fortifier Mead Johnson Nutritional)	Preterm Formula Enfamil Preamture Formula (100 kj/oz)
Manzoni 2013	Italy	VLBW	Human milk (mother and donor)	Preterm formula
Corpeleijn 2016	The Netherlands	VLBW	Donor Milk (Dutch Human Milk Bank)	Preterm formula (Nenatal Start Nutricia Advanced Medical Nutrition) or Hero Premature (Hero)

Table S5. Nutritional Pattern of Observational Studies.

Author, year	Country	Study Population	Group 1	Group 2	Group 3
Bishop 2010	USA	VLBW	Donor milk	Preterm formula	-
Zamkir 2018	Germany	VLBW	Human milk	Preterm formula	Mixed feeding
Spiegler 2016	Germany	VLBW	Human milk (mother and donor)	Preterm formula	Mixed feeding
Corpeleijin 2012	Netherlands	VLBW	Mother milk	Preterm formula	
Berkhout 2018	Netherlands and Belgium	Preterm	Human milk (mother and donor)	Preterm formula	Mixed feeding
Chowing 2016	USA	VLBW	< 50% Human Milk	>50% Human Milk	-
Manzoni 2013	Italy	VLBW	Human milk (mother and donor)	Preterm formula	-
Colaizy 2012	USA	VLBW	Donor Milk (different percentiles)	Preterm formula	-
Kreissl 2017	Austria	VLBW	Donor Milk	Preterm formula	-
Jacobi Pollistok 2016	USA	VLBW	Human Milk (different percentiles)	Preterm Formula	-
Paker 2012	USA	VLBW	>50% Human Milk	Preterm formula	-
Vohr 2007	USA	VLBW	Breast Milk	Preterm formula	-
Huston 2018	USA	ELBW	Human milk + fortifier	Preterm formula	-
			Human milk	Preterm formula	-
Ginovart 2016	Spain	VLBW	Human milk (mother and donor)	Preterm formula	-
Tanaka 2009	Japan	Premature	Breast Milk	Preterm Formula	-
Furman 2003	USA	VLBW	Breast Milk	Preterm formula	-
Madore 2017	USA	VLBW *etnia	Mothers own milk	Donor Breast milk	Preterm formula
Herrman 2014	USA	Preterm	Breast milk	Preterm formula	-
Sisk 2007	USA	VLBW	< 50% Human Milk	>50% Human Milk	-
Sisk 2016	USA	VLBW	< 50% Human Milk	>50% Human Milk	-
Manea 2018	Romani	VLBW	Human milk	Preterm formula	
Chowing 2016	USA	VLBW	>90% human milk	Preterm Formula	-
Maayan-Metzger 2012	Israel	Preterm	>80% human milk	Preterm Formula	
Assad 2016	USA	VLBW	Donor Milk	Preterm formula	-
Giuliani 2012	Italy	VLBW	Human milk (mother and donor)	Preterm formula	

Table S6. Characteristics of included studies.

Author, year	Human milk and/or breast feeding						Mixed feeding						Preterm formula					
	n	%male	Birth weight	Gestational age	NEC incidence		n	%male	Birth weight	Gestational age	NEC incidence		n	%male	Birth weight	Gestational age	NEC incidence	
					n	%					n	%					n	%
					Observational													
Verd 2015	148	58	800	26.4	23	15.4	-	-	-	-	-	-	53	50	830	27.4	11	20.7
Giuliani 2012	46	39.1	968	28.2	0	0	-	-	-	-	-	-	46	43.5	984	28.2	1	2.1
Tanaka 2009	10	50	1016	28.7	0	0	-	-	-	-	-	-	8	50	1188	30.7	0	0
Ginovart 2016	114	48	1078	29.14	11	9.6	-	-	-	-	-	-	72	46	1108	29.5	6	8.3
Huston 2018	94	-	1025	28.4	5	5.3	-	-	-	-	-	-	54	-	904	26.6	9	16.6
Berkhout 2018	631	52	920	26.9	37	5.8	127	52	920	26.9	11	-	103	52	920	26.9	11	10.7
Bishop 2010	152	56	1059	28.6	10	6.6	-	-	-	-	-	-	179	48	1056	28.5	12	6.7
Chowing 2016	71	-	1016	-	0	0	-	-	-	-	-	-	76	-	1015	-	8	10.5
Corpeleijn 2012	300	-	-	-	-	-	300	-	-	-	-	-	49	-	-	-	N.R. (*)	-
Spiegler 2016	223	53	1100	29.0	2	0.9	971	54	1050	-	26	-	239	53	1080	28.7	14	5.8
Manea 2016	18	-	-	-	1	5.6	-	-	-	-	-	-	16	-	-	-	2	12.5
Zamrik 2018	217	55	892	27	14	6.4	46	55	892	27	7	15.2	171	-	-	-	10	5.8
Assad 2016	87	60	-	-	-	-	-	-	-	-	-	-	30	30	-	-	-	-
Colacci 2017	39	-	783	26.0	4	10.2	-	-	-	-	-	-	46	-	770	26.0	5	10.8
Hair 2016	819	50.2	844	26.5	56	6.8	-	-	-	-	-	-	768	49.5	823	26.4	128	16.7
Herrman 2014	162	55	1361	29.6	7	4.3	-	-	-	-	-	-	443	51	1334	29.7	17	3.1

Kreissll 2017	133	-	-	-	12	9.0	-	-	-	-	-	-	150	-	-	-	8	5.3	
Maayan- Metzger 2012	188	63.3	1304	30.5	0	0							172	50	1425	31	5	2.9	
RCT																			
Cristofalo 2013	29	41	996	27.7	1	3.4	-	-	-	-	-	-	24	46	983	27.5	5	20.8	
O'Connor 2016	181		968		7	3.8	-	-	-	-	-	-	182		973		12	6.6	
Sullivan 2010	141	40	906	26.5	8	5.7	-	-	-	-	-	-	69	52	922	27.3	11	15.9	
Schanler 2005	151	53	971	27.2	9	6.0	-	-	-	-	-	-	92	46	957	27.2	10	10.9	
Manzoni 2017	314	53	1125	29.4	20	6.4	-	-	-	-	-	-	184	54	1110	29.2	7	3.8	
Corpeleijn 2016	183	50.3	1065	28.3	17	9.3	-	-	-	-	-	-	190	54.7	1077	28.6	17	8.9	

* statistically significant difference between human milk and preterm formula.

Legend

Selection

1) Is the case definition adequate?

- a) yes, with independent validation *
- b) yes, eg record linkage or based on self reports
- c) no description

2) Representativeness of the cases

- a) consecutive or obviously representative series of cases *
- b) potential for selection biases or not stated

3) Selection of Controls

- a) community controls *
- b) hospital controls
- c) no description

4) Definition of Controls

- a) no history of disease (endpoint) ✱
- b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

- a) study controls for (Select the most important factor.) ✱
- b) study controls for any additional factor ✱

Exposure

1) **Assessment of Outcome**

For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to x-rays would be required.

- a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.) ✱ ☆
- b) Record linkage (e.g. identified through ICD codes on database records) ☆
- c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)
- d) No description.

2) **Was Follow-Up Long Enough for Outcomes to Occur**

- a) An acceptable length of time should be decided before quality assessment begins (e.g. 5 yrs. for exposure to breast implants) ✱

3) **Adequacy of Follow Up of Cohorts**

- a) This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome. ✱✱

Allocation of stars as per rating sheet

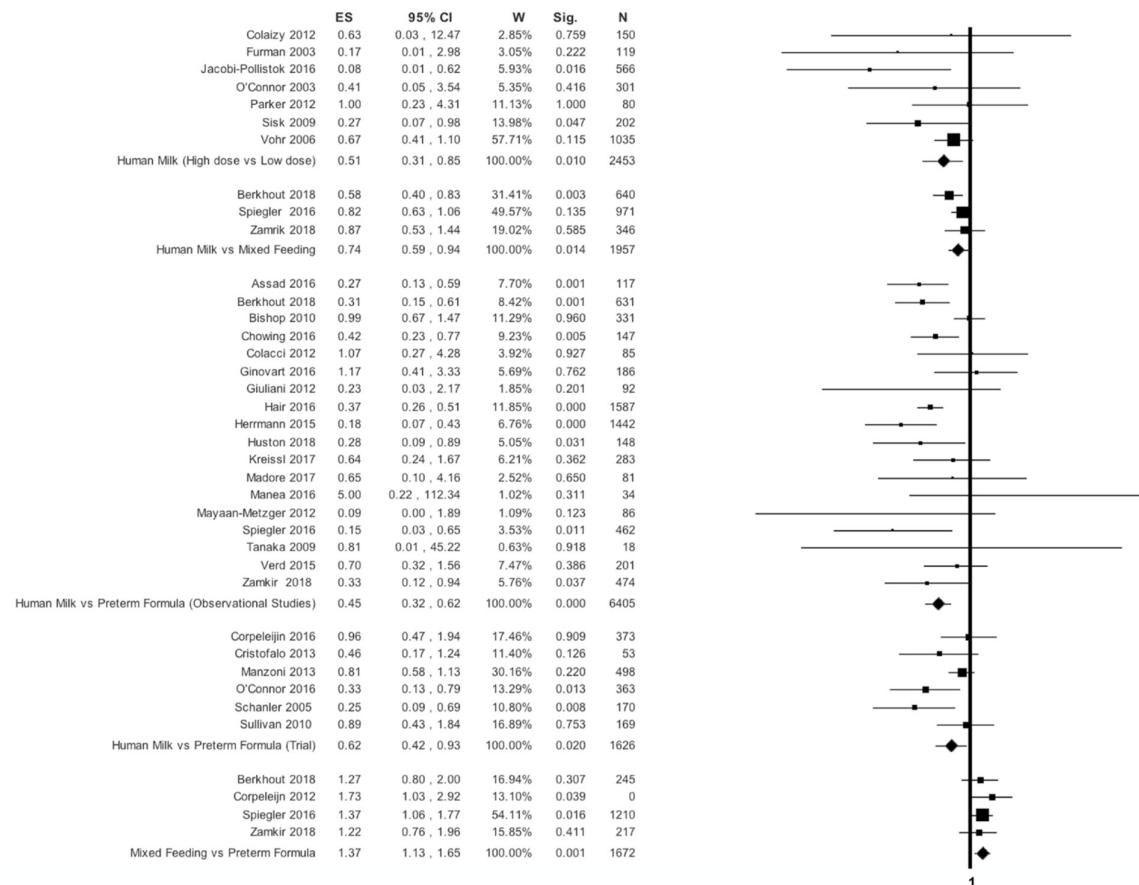


Figure S1. Meta-analysis: results from RCT and observational studies. Forest plot for selected outcomes.

Table S7. Human Milk Banks in the world

Nation	HMB	Nation	HMB
Afghanistan	0	Cyprus	0
Albania	0	Czechia	4
Algeria	0	Democratic People's Republic of Korea	0
Angola	0	Democratic Republic of the Congo	0
Antigua and Barbuda	0	Denmark	2
Argentina	5	Djibouti	0
Armenia	0	Dominican Republic	1
Australia	5	Ecuador	0
Austria	2	Egypt	0
Azerbaijan	0	El Salvador	0
Bahamas	0	Equatorial Guinea	0
Bahrain	0	Eritrea	0
Bangladesh	0	Estonia	1
Barbados	0	Ethiopia	0
Belarus	0	Fiji	0
Belgium	4	Finland	17
Belize	0	France	36
Benin	0	Gabon	0
Bhutan	0	Gambia	0
Bolivia (Plurinational State of)	1	Georgia	0
Bosnia and Herzegovina	0	Germany	20
Botswana	0	Ghana	0
Brazil	214	Greece	2
Brunei Darussalam	0	Grenada	0
Bulgaria	1	Guatemala	1
Burkina Faso	0	Guinea	0
Burundi	0	Guinea-Bissau	0
Cabo Verde	1	Guyana	0
Cambodia	0	Haiti	0
Cameroon	0	Honduras	0
Canada	4	Hungary	8
Central African Republic	0	Iceland	2
Chad	0	India	22
Chile	1	Indonesia	0
China	14	Iran (Islamic Republic of)	1
Colombia*	5	Iraq	0
Comoros	0	Ireland	1
Congo	0	Israel	1

Costa Rica	2	Italy	37
Côte d'Ivoire	0	Jamaica	1
Japan	1	Papua New Guinea	0
Jordan	0	Paraguay	1
Kazakhstan	0	Peru	1
Kenya	1	Philippines	0
Kingdom of Eswatini	0	Poland	11
Kiribati	0	Portugal	1
Kuwait	1	Qatar	0
Kyrgyzstan	0	Republic of Korea	1
Lao People's Democratic Republic	0	Republic of Moldova	0
Latvia	0	Romania	0
Lebanon	0	Russian Federation	2
Lesotho	0	Rwanda	0
Liberia	0	Saint Lucia	0
Lithuania	2	Saint Vincent and the Grenadines	0
Luxembourg	0	Samoa	0
Madagascar	0	Sao Tome and Principe	0
Malawi	0	Saudi Arabia	0
Malaysia	0	Senegal	0
Maldives	0	Serbia	3
Mali	0	Seychelles	0
Malta	1	Sierra Leone	0
Mauritania	0	Singapore	1
Mauritius	0	Slovakia	6
Mexico	8	Slovenia	1
Micronesia (Federated States of)	0	Solomon Islands	0
Mongolia	0	Somalia	0
Montenegro	0	South Africa	44
Morocco	0	South Sudan	0
Mozambique	1	Spain	15
Myanmar	0	Sri Lanka	0
Namibia	1	State of Libya	0
Nepal	1	Sudan	0
Netherlands	1	Suriname	0
New Zealand	1	Sweden	28
Nicaragua	3	Switzerland	7
Niger	0	Syrian Arab Republic	0
Nigeria	1	Tajikistan	0
Norway	12	Thailand	0
Pakistan	1	The former Yugoslav republic of Macedonia	0

Panama	1	Timor-Leste	0
Trinidad and Tobago	0	United States of America***	24
Tunisia	0	Uruguay	0
Turkey	0	Uzbekistan	0
Turkmenistan	0	Vanuatu	0
Uganda	0	Venezuela (Bolivarian Republic of)	10
Ukraine	1	Viet Nam	1
United Arab Emirates	0	Yemen	0
United Kingdom of Great Britain and Northern Ireland**	16	Zambia	0
United Republic of Tanzania	0	Zimbabwe	0