Supplementary Materials

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Record of database search strategies - run 13/6/17

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)

Table S1. Ovid MEDLINE search strategy

#	Searches	Results
1	Infant, Premature/ OR Infants, Extremely premature/ OR Infant, Low birth weight/ OR Infant, Very Low Birth Weight/ OR Intensive care units, Neonatal/ OR Intensive care, Neonatal/ OR Premature birth/	83735
2	(((low birthweight OR low birth weight OR VLBW OR ELBW OR Prematur* OR Preterm OR Pre-term) adj2 (Infant* OR Neonat* OR newborn* OR new-born* OR baby* OR babies)) OR neonatal intensive care OR NICU).tw,kw.	73321
3	or/1-2	111350
4	Milk, Human/ OR Breast feeding/ OR Milk banks/ OR Breast milk expression/	46962
5	((breastmilk OR (human OR breast OR mother* OR maternal OR express* OR donor* OR donated OR bank*)) adj3 milk*).tw,kw.	23289
6	(breastfeed* OR breastfed OR ((breast OR HM) adj (fed OR feed*))).tw,kw.	36982
7	((EHM OR MOM OR PDM) and milk).tw,kw.	45
8	Enteral Nutrition/	18724
9	(Enteral* adj1 (nutrition* OR support OR feed*)).tw,kw.	12409
10	or/4-9	90007
11	infant, premature, diseases/	19459
12	((prematur* OR preterm OR pre-term) adj2 disease*).tw,kw.	3129
13	Enterocolitis, Necrotizing/	2706
14	(Necroti?ing enterocolitis OR NEC).tw,kw.	8044
15	Bronchopulmonary dysplasia/ OR Respiratory Distress Syndrome, Newborn/	15536
16	(Bronchopulmonary dysplasia OR broncho-pulmonary dysplasia OR BPD OR lung disease* OR lung disorder* OR immature lung* OR respiratory distress).tw,kw.	92321
17	"retinopathy of prematurity"/	5206
18	("Retinopathy of prematurity" OR ROP).tw,kw.	6468
19	exp Sepsis/ OR exp Infection/	726204
20	(sepsis OR sepses OR septic OR septic?emi* OR infect* OR bacteria* OR bacter?emi* OR microorganism* OR micro-organism* OR blood poisoning* OR pyoh?emi* OR py?emi*).tw,kw.	2051314
21	Child development/ OR Brain/ OR Intelligence/ OR Cognition/ OR Executive function/ OR Motor skills/ OR Motor activity/	669535
22	Intelligence tests/ OR Neuropsychological tests/	95266
23	((infan* OR child*) adj2 development*).tw,kw.	26347
24	((brain OR neurologic* OR cognitive* OR intellectual* OR motor OR psychomotor) adj2 development*).tw,kw.	37412
25	(neurodevelopment* OR neuro-development* OR neurocognitive* OR neuro-cognitive OR neurobehavio?r* OR neuro-behavio?r* OR neuropsycholog* OR neuro-psycholog* OR cognition OR intelligence OR executive function).tw,kw.	166261
26	or/11-25	3318491
27	3 and 10 and 26	2994
28	exp animals/ not (exp animals/ and humans/)	4417385

29	27 not 28	2945
30	limit 29 to english language	2677
31	limit 30 to yr="1990 -Current"	2441

PubMed (non-indexed subset only)

N=373

((((“low birthweight”[tiab] OR “low birth weight”[tiab] OR VLBW[tiab] OR ELBW[tiab] OR Prematur*[tiab] OR Preterm[tiab] OR “Pre-term”[tiab]) AND (Infant*[tiab] OR Neonat*[tiab] OR newborn*[tiab] OR “new-born*”[tiab] OR baby*[tiab] OR babies[tiab])) OR “neonatal intensive care”[tiab] OR NICU[tiab]) AND (((breastmilk[tiab] OR (human[tiab] OR breast[tiab] OR mother*[tiab] OR maternal[tiab] OR express*[tiab] OR donor*[tiab] OR donated[tiab] OR bank*[tiab])) AND milk*[tiab]) OR (breastfeed*[tiab] OR breastfed[tiab] OR ((breast[tiab] OR HM[tiab]) AND (fed[tiab] OR feed*[tiab]))) OR ((EHM[tiab] OR MOM[tiab] OR PDM[tiab]) AND milk[tiab]) OR (Enteral*[tiab] AND (nutrition*[tiab] OR support[tiab] OR feed*[tiab]))) AND (((prematur*[tiab] OR preterm[tiab] OR “pre-term” [tiab]) AND disease*[tiab]) OR “Necrotising enterocolitis”[tiab] OR “Necrotizing enterocolitis”[tiab] OR NEC[tiab] OR “Bronchopulmonary dysplasia”[tiab] OR “broncho-pulmonary dysplasia”[tiab] OR BPD[tiab] OR “lung disease*”[tiab] OR “lung disorder*”[tiab] OR “immature lung*”[tiab] OR “respiratory distress”[tiab] OR "Retinopathy of prematurity"[tiab] OR ROP[tiab] OR sepsis[tiab] OR sepses[tiab] OR septic[tiab] OR septicemi* [tiab] OR septicaemi*[tiab] OR infect*[tiab] OR bacteria*[tiab] OR bacteremi*[tiab] OR bacteraemi*[tiab] OR microorganism*[tiab] OR “micro-organism*”[tiab] OR “blood poisoning*”[tiab] OR pyohemi*[tiab] OR pyohaemi*[tiab] OR pyemi*[tiab] OR pyaemi*[tiab] OR ((brain[tiab] OR neurologic*[tiab] OR cognitive*[tiab] OR intellectual*[tiab] OR motor[tiab] OR psychomotor[tiab]) AND development*[tiab]) OR ((infan*[tiab] OR child*[tiab]) AND development*[tiab]) OR neurodevelopment*[tiab] OR “neuro-development*”[tiab] OR neurocognitive*[tiab] OR “neuro-cognitive”[tiab] OR neurobehavior*[tiab] OR neurobehaviour*[tiab] OR “neuro-behavior*”[tiab] OR “neuro-behaviour*”[tiab] OR neuropsycholog*[tiab] OR “neuro-psycholog*”[tiab] OR cognition[tiab] OR intelligence[tiab] OR “executive function”[tiab]) AND English[la] AND 1990:2017[dp]) NOT Medline[sb]

CINAHL (EBSCOhost)

Table S2. CINAHL search strategy

#	Query	Limiters/Expanders	Results
S1	(MH "Infant, Premature") OR (MH "Infant, Low Birth Weight") OR (MH "Infant, Very Low Birth Weight")	Search modes - Boolean/Phrase	17,057
S2	(MH "Childbirth, Premature")	Search modes - Boolean/Phrase	5,058
S3	(MH "Intensive Care, Neonatal") OR (MH "Intensive Care Units, Neonatal")	Search modes - Boolean/Phrase	10,284
S4	TI ((((“low birthweight” OR “low birth weight” OR VLBW OR ELBW OR Prematur* OR Preterm OR “Pre-term”) N1 (Infant* OR Neonat* OR newborn* OR “new-born*” OR baby* OR babies)) OR “neonatal intensive care” OR NICU)) OR AB ((((“low birthweight” OR “low birth weight” OR VLBW OR ELBW OR Prematur* OR Preterm OR “Pre-term”) N1 (Infant* OR Neonat* OR newborn* OR “new-born*” OR baby* OR babies)) OR “neonatal intensive care” OR NICU))	Search modes - Boolean/Phrase	17,903
S5	S1 OR S2 OR S4	Search modes - Boolean/Phrase	28,457
S6	(MH "Milk, Human") OR (MH "Donor Milk")	Search modes - Boolean/Phrase	3,094
S7	(MH "Milk Banks")	Search modes - Boolean/Phrase	289
S8	(MH "Breast Pumps")	Search modes - Boolean/Phrase	289
S9	(MH "Breast Feeding") OR (MH "Milk Expression")	Search modes - Boolean/Phrase	13,429
S10	TI ((((breastmilk OR (human OR breast OR mother* OR maternal OR express* OR donor* OR donated OR bank*)) N2 milk*) OR (breastfeed* OR breastfed OR ((breast OR HM) N0 (fed OR feed*))) OR ((EHM OR MOM OR PDM) AND milk) OR (Enteral* N0 (nutrition* OR support OR feed*)))) OR AB ((((breastmilk OR (human OR breast OR mother* OR maternal OR express* OR donor* OR donated OR bank*)) N2 milk*) OR (breastfeed* OR breastfed OR ((breast OR HM) N0 (fed OR feed*))) OR ((EHM OR MOM OR PDM) AND milk) OR (Enteral* N0 (nutrition* OR support OR feed*))))	Search modes - Boolean/Phrase	16,416
S11	(MH "Enteral Nutrition")	Search modes - Boolean/Phrase	5,571
S12	S6 OR S7 OR S8 OR S9 OR S10 OR S11	Search modes - Boolean/Phrase	25,094
S13	(MH "Infant, Newborn, Diseases") OR (MH "Bronchopulmonary Dysplasia") OR (MH "Enterocolitis, Necrotizing") OR (MH "Respiratory Distress Syndrome") OR (MH "Retinopathy of Prematurity") OR (MH "Neonatal Sepsis")	Search modes - Boolean/Phrase	6,483

#	Query	Limiters/Expanders	Results
S14	(MH "Infection+")	Search modes - Boolean/Phrase	90,193
S15	(MH "Child Development") OR (MH "Infant Development")	Search modes - Boolean/Phrase	14,958
S16	(MH "Brain")	Search modes - Boolean/Phrase	21,857
S17	(MH "Intelligence")	Search modes - Boolean/Phrase	2,999
S18	(MH "Cognition")	Search modes - Boolean/Phrase	23,286
S19	(MH "Executive Function")	Search modes - Boolean/Phrase	604
S20	(MH "Motor Skills") OR (MH "Psychomotor Performance")	Search modes - Boolean/Phrase	10,397
S21	(MH "Motor Activity")	Search modes - Boolean/Phrase	4,705
S22	(MH "Intelligence Tests")	Search modes - Boolean/Phrase	4,483
S23	(MH "Neuropsychological Tests")	Search modes - Boolean/Phrase	19,216
S24	TI ((((prematur* OR preterm OR "pre-term") N1 disease*) OR "Necrotising enterocolitis" OR "Necrotizing enterocolitis" OR NEC OR "Bronchopulmonary dysplasia" OR "broncho-pulmonary dysplasia" OR BPD OR "lung disease*" OR "lung disorder*" OR "immature lung*" OR "respiratory distress" OR "Retinopathy of prematurity" OR ROP OR sepsis OR sepses OR septic OR septicemi* OR septicaemi* OR infect* OR bacteria* OR bacteremi* OR bacteraemi* OR microorganism* OR "micro-organism*" OR "blood poisoning*" OR pyohemi* OR pyohaemi* OR pyemi* OR pyaemi* OR ((brain OR neurologic* OR cognitive* OR intellectual* OR motor OR psychomotor) N1 development*) OR ((infan* OR child*) N1 development*) OR neurodevelopment* OR "neuro-development*" OR neurocognitive* OR "neuro-cognitive" OR neurobehavior* OR neurobehaviour* OR "neuro-behavior*" OR "neuro-behaviour*" OR neuropsycholog* OR "neuro-psycholog*" OR cognition OR intelligence OR "executive function")) OR AB ((((prematur* OR preterm OR "pre-term") N1 disease*) OR "Necrotising enterocolitis" OR "Necrotizing enterocolitis" OR NEC OR "Bronchopulmonary dysplasia" OR "broncho-pulmonary dysplasia" OR BPD OR "lung disease*" OR "lung disorder*" OR "immature lung*" OR "respiratory distress" OR "Retinopathy of prematurity" OR ROP OR sepsis OR sepses OR septic OR septicemi* OR septicaemi* OR infect* OR bacteria* OR bacteremi* OR bacteraemi* OR microorganism* OR "micro-organism*" OR "blood poisoning*" OR pyohemi* OR pyohaemi* OR pyemi* OR pyaemi* OR ((brain OR	Search modes - Boolean/Phrase	177,981

#	Query	Limiters/Expanders	Results
	neurologic* OR cognitive* OR intellectual* OR motor OR psychomotor) N1 development*) OR ((infan* OR child*) N1 development*) OR neurodevelopment* OR "neuro-development*" OR neurocognitive* OR "neuro-cognitive" OR neurobehavior* OR neurobehaviour* OR "neuro-behavior*" OR "neuro-behaviour*" OR neuropsycholog* OR "neuro-psycholog*" OR cognition OR intelligence OR "executive function"))		
S25	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24	Search modes - Boolean/Phrase	291,095
S26	S5 AND S12 AND S25	Search modes - Boolean/Phrase	880
S27	S5 AND S12 AND S25	Narrow by Language: - english Search modes - Boolean/Phrase	858
S28	S5 AND S12 AND S25	Limiters - Published Date: 19900101-20171231 Narrow by Language: - english Search modes - Boolean/Phrase	694

Scopus

N=2773

TITLE-ABS-KEY((((("low birthweight" OR "low birth weight" OR VLBW OR ELBW OR Prematur* OR Preterm OR "Pre-term") W/1 (Infant* OR Neonat* OR newborn* OR "new-born*" OR baby* OR babies)) OR "neonatal intensive care" OR NICU) AND (((breastmilk OR (human OR breast OR mother* OR maternal OR express* OR donor* OR donated OR bank*)) W/2 milk*) OR (breastfeed* OR breastfed OR ((breast OR HM) W/0 (fed OR feed*))) OR ((EHM OR MOM OR PDM) AND milk) OR (Enteral* W/0 (nutrition* OR support OR feed*))) AND (((prematur* OR preterm OR "pre-term") W/1 disease*) OR "Necrotising enterocolitis" OR "Necrotizing enterocolitis" OR NEC OR "Bronchopulmonary dysplasia" OR "broncho-pulmonary dysplasia" OR BPD OR "lung disease*" OR "lung disorder*" OR "immature lung*" OR "respiratory distress" OR "Retinopathy of prematurity" OR ROP OR sepsis OR sepses OR septic OR septicemi* OR septicaemi* OR infect* OR bacteria* OR bacteremi* OR bacteraemi* OR microorganism* OR "micro-organism*" OR "blood poisoning*" OR pyohemi* OR pyohaemi* OR pyemi* OR pyaemi* OR ((brain OR neurologic* OR cognitive* OR intellectual* OR motor OR psychomotor) W/1 development*) OR ((infan* OR child*) W/1 development*) OR neurodevelopment* OR "neuro-development*" OR neurocognitive* OR "neuro-cognitive" OR neurobehavior* OR neurobehaviour* OR "neuro-behavior*" OR "neuro-behaviour*" OR neuropsycholog* OR "neuro-psycholog*" OR cognition OR intelligence OR "executive function")) AND (LIMIT-TO (DOCTYPE,"ar") OR LIMIT-TO (DOCTYPE,"re") OR LIMIT-TO (DOCTYPE,"ip")) AND (LIMIT-TO (LANGUAGE,"English")) AND (EXCLUDE (PUBYEAR,1989) OR EXCLUDE (PUBYEAR,1988) OR EXCLUDE (PUBYEAR,1987) OR EXCLUDE (PUBYEAR,1986) OR EXCLUDE (PUBYEAR,1985) OR EXCLUDE (PUBYEAR,1984) OR EXCLUDE (PUBYEAR,1983) OR EXCLUDE (PUBYEAR,1982) OR EXCLUDE (PUBYEAR,1981) OR EXCLUDE (PUBYEAR,1980) OR EXCLUDE (PUBYEAR,1979) OR EXCLUDE (PUBYEAR,1978) OR EXCLUDE (PUBYEAR,1977) OR EXCLUDE (PUBYEAR,1976) OR EXCLUDE (PUBYEAR,1975) OR EXCLUDE (PUBYEAR,1974) OR EXCLUDE (PUBYEAR,1973) OR EXCLUDE (PUBYEAR,1972) OR EXCLUDE (PUBYEAR,1971) OR EXCLUDE (PUBYEAR,1970) OR EXCLUDE (PUBYEAR,1969) OR EXCLUDE (PUBYEAR,1968) OR EXCLUDE (PUBYEAR,1967) OR EXCLUDE (PUBYEAR,1966) OR EXCLUDE (PUBYEAR,1965) OR EXCLUDE (PUBYEAR,1964) OR EXCLUDE (PUBYEAR,1963) OR EXCLUDE (PUBYEAR,1959) OR EXCLUDE (PUBYEAR,1957) OR EXCLUDE (PUBYEAR,1954) OR EXCLUDE (PUBYEAR,1948) OR EXCLUDE (PUBYEAR,1946) OR EXCLUDE (PUBYEAR,1939))

Cochrane Central Register of Controlled Trials (Issue 5 of 12, May 2017)

N=311

((("low birthweight" OR "low birth weight" OR VLBW OR ELBW OR Prematur* OR Preterm OR "Pre-term") NEAR/1 (Infant* OR Neonat* OR newborn* OR "new-born*" OR baby* OR babies)) OR "neonatal intensive care" OR NICU) AND (((breastmilk OR (human OR breast OR mother* OR maternal OR express* OR donor* OR donated OR bank*)) NEAR/2 milk*) OR (breastfeed* OR breastfed OR ((breast OR HM) NEAR/0 (fed OR feed*))) OR ((EHM OR MOM OR PDM) AND milk) OR (Enteral* NEAR/0 (nutrition* OR support OR feed*))) AND (((prematur* OR preterm OR "pre-term") NEAR/1 disease*) OR "Necrotising enterocolitis" OR "Necrotizing enterocolitis" OR NEC OR "Bronchopulmonary dysplasia" OR "broncho-pulmonary dysplasia" OR BPD OR "lung disease*" OR "lung disorder*" OR "immature lung*" OR "respiratory distress" OR "Retinopathy of prematurity" OR ROP OR sepsis OR sepses OR septic OR septicemi* OR septicaemi* OR infect* OR bacteria* OR bacteremi* OR bacteraemi* OR microorganism* OR "micro-organism*" OR "blood poisoning*" OR pyohemi* OR pyohaemi* OR pyemi* OR pyaemi* OR ((brain OR neurologic* OR cognitive* OR intellectual* OR motor OR psychomotor) NEAR/1 development*) OR ((infan* OR child*) NEAR/1 development*) OR neurodevelopment* OR "neuro-development*" OR neurocognitive* OR "neuro-cognitive" OR neurobehavior* OR neurobehaviour* OR "neuro-behavior*" OR "neuro-behaviour*" OR neuropsycholog* OR "neuro-psycholog*" OR cognition OR intelligence OR "executive function")

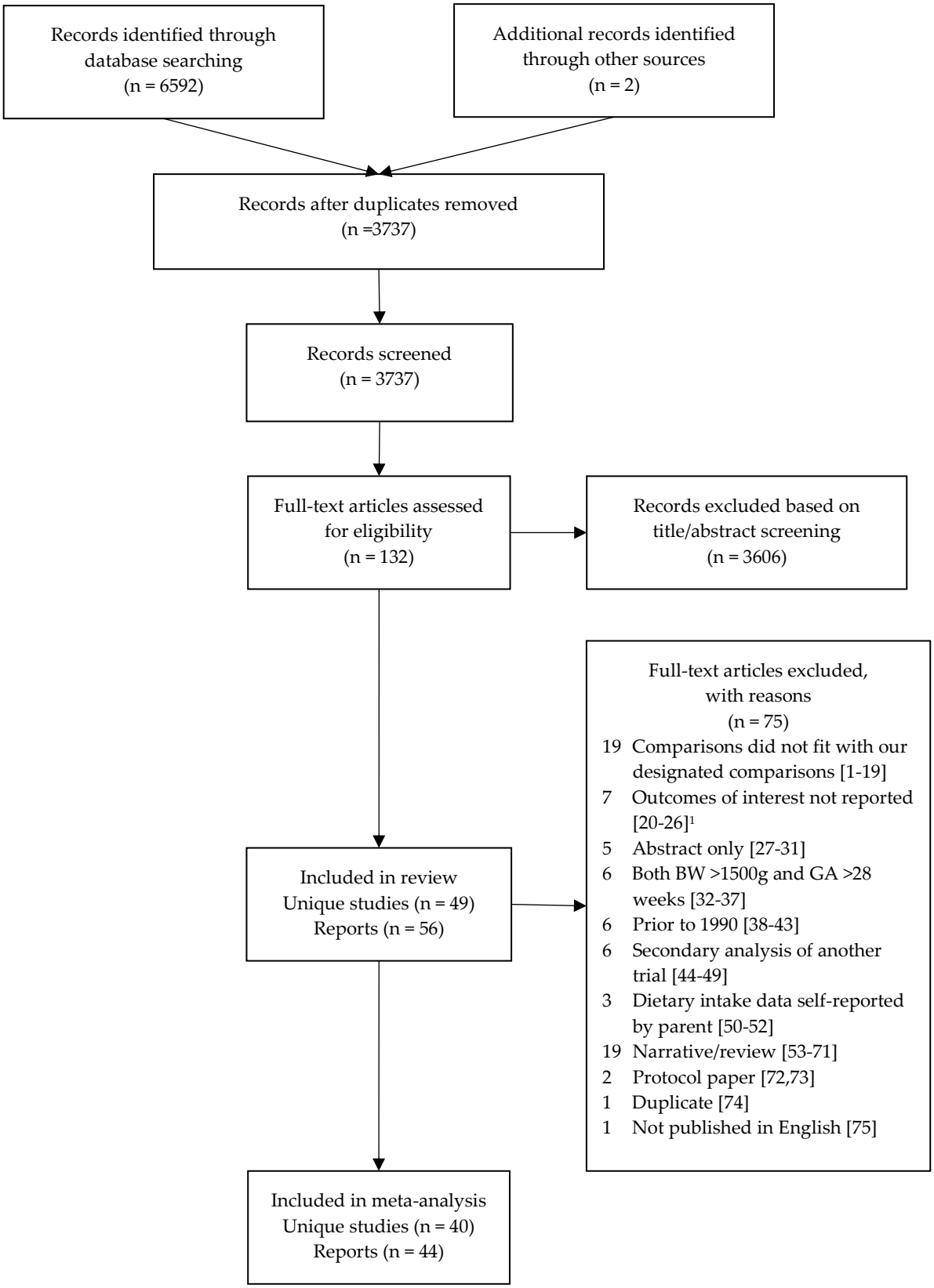

Figure S1. PRISMA diagram - selection of studies

[1] This includes one study which reported combined outcomes of interest [21]

References - excluded studies

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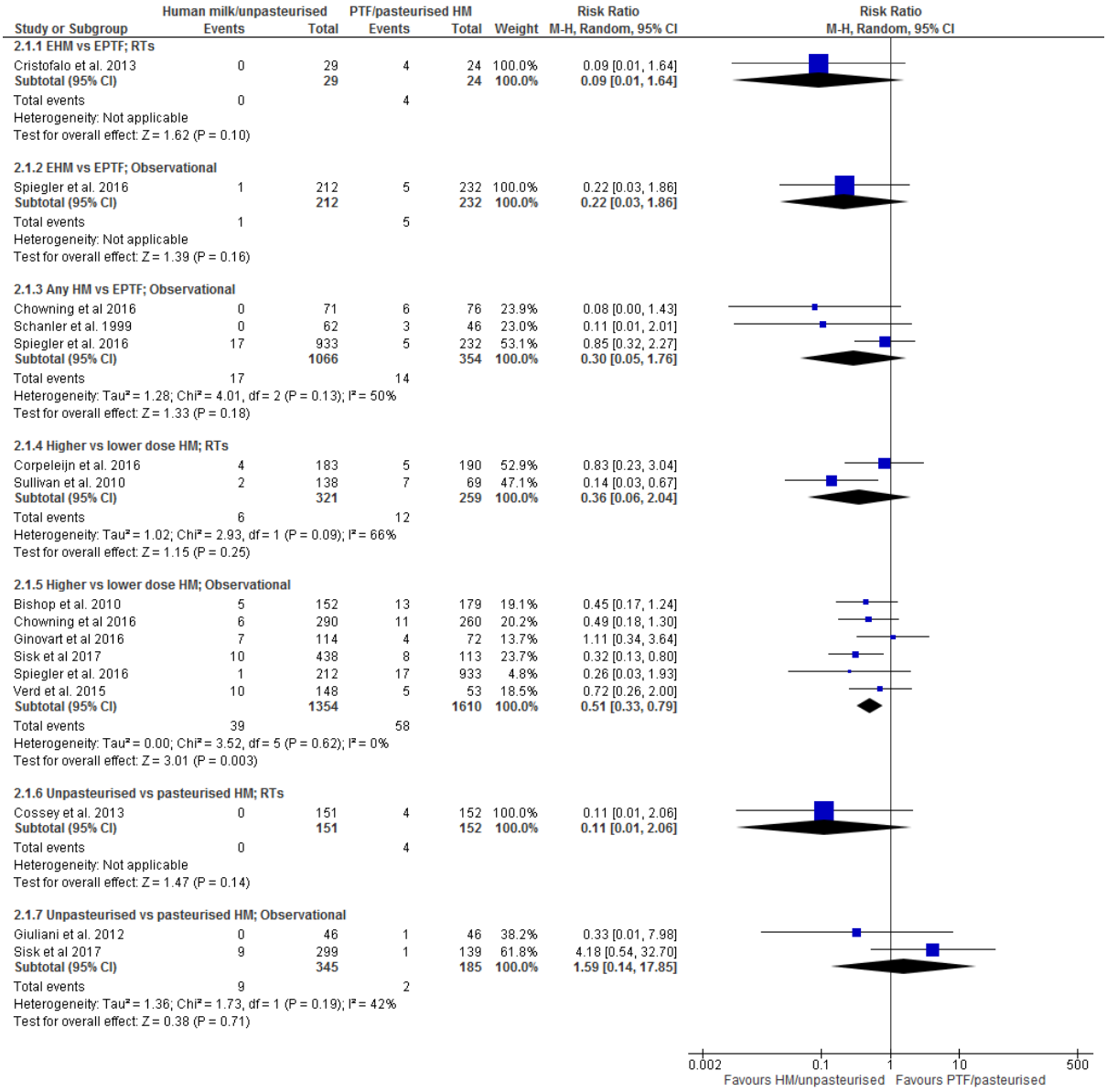


Figure S2. Forest plot of relative risk for the association of human milk and severe necrotising enterocolitis

Table S3. Any necrotising enterocolitis: summary of findings

Comparisons	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula/ pasteurised human milk	Risk with human milk/ unpasteurised human milk			
Necrotising enterocolitis - Exclusive human milk vs exclusive preterm formula; RTs	Study population		RR 0.17 (0.02 to 1.32)	53 (1 RCT)	⨁⨁⨀⨀ LOW [1]
	208 per 1,000	35 per 1,000 (4 to 275)			
Necrotising enterocolitis - Exclusive human milk vs exclusive preterm formula; Non-RT & Observational	Study population		RR 0.22 (0.09 to 0.54)	993 (3 observational studies)	⨁⨁⨁⨀ MODERATE
	55 per 1,000	12 per 1,000 (5 to 30)			
Necrotising enterocolitis - Any human milk vs exclusive preterm formula; Observational	Study population		RR 0.51 (0.35 to 0.76)	3783 (9 observational studies)	⨁⨁⨁⨀ MODERATE
	73 per 1,000	37 per 1,000 (26 to 56)			
Necrotising enterocolitis - Higher vs lower dose human milk intake; RTs	Study population		RR 0.54 (0.28 to 1.02)	1116 (4 RCTs)	⨁⨁⨁⨀ MODERATE [2 3]
	94 per 1,000	51 per 1,000 (26 to 96)			
Necrotising enterocolitis - Higher vs lower dose human milk intake; Observational	Study population		RR 0.53 (0.42 to 0.67)	8778 (22 observational studies)	⨁⨁⨁⨀ MODERATE
	80 per 1,000	42 per 1,000 (34 to 54)			
Necrotising enterocolitis - Unpasteurised vs pasteurised human milk (MOM or donor); RTs	Study population		RR 1.45 (0.64 to 3.30)	303 (1 RCT)	⨁⨁⨀⨀ LOW [4]
	59 per 1,000	86 per 1,000 (38 to 195)			
Necrotising enterocolitis - Unpasteurised vs pasteurised human milk (MOM or donor); Observational	Study population		RR 1.28 (0.68 to 2.43)	1894 (6 observational studies)	⨁⨀⨀⨀ VERY LOW [5]
	37 per 1,000	47 per 1,000 (25 to 90)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; RT: Randomised Trial

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: [1]1 study, wide CIs, small sample size; [2]Sullivan was not blinded, however, the outcome is objective and unlikely to be biased by this, hence not downgraded; [3]Moderate heterogeneity; [4]1 study, wide Cis; [5]Wide CIs

Table S4. Severe necrotising enterocolitis: summary of findings

Comparisons	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula/ pasteurised human milk	Risk with human milk/ unpasteurised human milk			
NEC surgery - EHM vs EPTF; RTs	Study population		RR 0.09 (0.01 to 1.64)	53 (1 RT)	⨁⨁◯◯ LOW [1]
	167 per 1,000	15 per 1,000 (2 to 273)			
NEC surgery - EHM vs EPTF; Observational	Study population		RR 0.22 (0.03 to 1.86)	444 (1 observational study)	⨁◯◯◯ VERY LOW [1]
	22 per 1,000	5 per 1,000 (1 to 40)			
NEC surgery - Any HM vs EPTF; Observational	Study population		RR 0.30 (0.05 to 1.76)	1420 (3 observational studies)	⨁◯◯◯ VERY LOW [2]
	40 per 1,000	12 per 1,000 (2 to 70)			
NEC surgery - Higher vs lower dose HM; RTs	Study population		RR 0.36 (0.06 to 2.04)	580 (2 RCTs)	⨁⨁◯◯ LOW [2 3]
	46 per 1,000	17 per 1,000 (3 to 95)			
NEC surgery - Higher vs lower dose HM; Observational	Study population		RR 0.51 (0.33 to 0.79)	2964 (6 observational studies)	⨁⨁⨁◯ MODERATE
	36 per 1,000	18 per 1,000 (12 to 28)			
NEC surgery - Unpasteurised vs pasteurised HM; RTs	Study population		RR 0.11 (0.01 to 2.06)	303 (1 RCT)	⨁⨁◯◯ LOW [1]
	26 per 1,000	3 per 1,000 (0 to 54)			
NEC surgery - Unpasteurised vs pasteurised HM; Observational	Study population		RR 1.59 (0.14 to 17.85)	530 (2 observational studies)	⨁◯◯◯ VERY LOW[3]
	11 per 1,000	17 per 1,000 (2 to 193)			
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;					
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes: [1]Single study, wide CIs; [2]Moderate heterogeneity; [3]Wide CI

Table S5. Late onset sepsis: summary of findings

Comparisons	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula/ pasteurised human milk	Risk with human milk/ unpasteurised human milk			
Late onset sepsis - Exclusive human milk vs exclusive preterm formula: RT	Study population		RR 0.70 (0.47 to 1.03)	53 (1 RCT)	⨁⨁◯◯ LOW [1]
	792 per 1,000	554 per 1,000 (372 to 815)			
Late onset sepsis - Exclusive human milk vs exclusive preterm formula; Non-RT and Observational	Study population		RR 0.71 (0.49 to 1.05)	776 (3 observational studies)	⨁⨁◯◯ LOW
	174 per 1,000	123 per 1,000 (85 to 183)			
Late onset sepsis - Any human milk vs exclusive preterm formula; Observational	Study population		RR 0.95 (0.67 to 1.34)	2497 (8 observational studies)	⨁◯◯◯ VERY LOW [2,3]
	301 per 1,000	286 per 1,000 (202 to 404)			
Late onset sepsis - Higher vs lower dose human milk intake; RTs	Study population		RR 1.07 (0.89 to 1.28)	1186 (4 RCTs)	⨁⨁⨁◯ MODERATE [3]
	276 per 1,000	295 per 1,000 (245 to 353)			
Late onset sepsis - Higher vs lower dose human milk intake; Observational	Study population		RR 0.71 (0.56 to 0.90)	6521 (18 observational studies)	⨁◯◯◯ VERY LOW [2]
	230 per 1,000	163 per 1,000 (129 to 207)			
Late onset sepsis - Unpasteurised vs pasteurised human milk (MOM or donor); RT	Study population		RR 0.71 (0.43 to 1.18)	303 (1 RCT)	⨁⨁⨁◯ MODERATE [4]
	204 per 1,000	145 per 1,000 (88 to 241)			
Late onset sepsis - Unpasteurised vs pasteurised human milk (MOM or donor); Observational	Study population		RR 1.05 (0.86 to 1.27)	1875 (5 observational studies)	⨁◯◯◯ VERY LOW [5]
	258 per 1,000	271 per 1,000 (222 to 328)			
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;					
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes: [1]Only 1 study, wide CIs; [2]Substantial heterogeneity; [3]Wide CI; [4]1 study only; [5]Moderate heterogeneity

Table S6. Bronchopulmonary dysplasia: summary of findings

Comparisons	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula/ pasteurised human milk	Risk with human milk/ unpasteurised human milk			
Bronchopulmonary dysplasia - Exclusive human milk vs exclusive preterm formula: Observational	Study population		RR 0.94 (0.26 to 3.41)	706 (2 observational studies)	⨁⨀⨀⨀ VERY LOW [1,2]
	197 per 1,000	185 per 1,000 (51 to 672)			
Bronchopulmonary dysplasia - Any human milk vs exclusive preterm formula; Observational	Study population		RR 1.02 (0.83 to 1.27)	3703 (6 observational studies)	⨁⨀⨀⨀ VERY LOW [2,3]
	345 per 1,000	352 per 1,000 (286 to 438)			
Bronchopulmonary dysplasia - Higher vs lower dose human milk intake: RTs	Study population		RR 0.95 (0.73 to 1.25)	1075 (4 RCTs)	⨁⨁⨀⨀ LOW [2,3]
	263 per 1,000	250 per 1,000 (192 to 328)			
Bronchopulmonary dysplasia - Higher vs lower dose human milk intake; Observational	Study population		RR 0.84 (0.73 to 0.96)	7023 (18 observational studies)	⨁⨀⨀⨀ VERY LOW [3]
	305 per 1,000	256 per 1,000 (223 to 293)			
Bronchopulmonary dysplasia - Unpasteurised vs pasteurised human milk (MOM or donor); RTs	Study population		RR 0.69 (0.43 to 1.10)	303 (1 RCT)	⨁⨁⨀⨀ LOW [4]
	230 per 1,000	159 per 1,000 (99 to 253)			
Bronchopulmonary dysplasia - Unpasteurised vs pasteurised human milk (MOM or donor); Observational	Study population		RR 1.01 (0.72 to 1.43)	1644 (5 observational studies)	⨁⨀⨀⨀ VERY LOW [2]
	203 per 1,000	205 per 1,000 (146 to 290)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: [1]Substantial heterogeneity; [2]Wide CI; [3]Moderate heterogeneity; [4]Only 1 study, wide CI

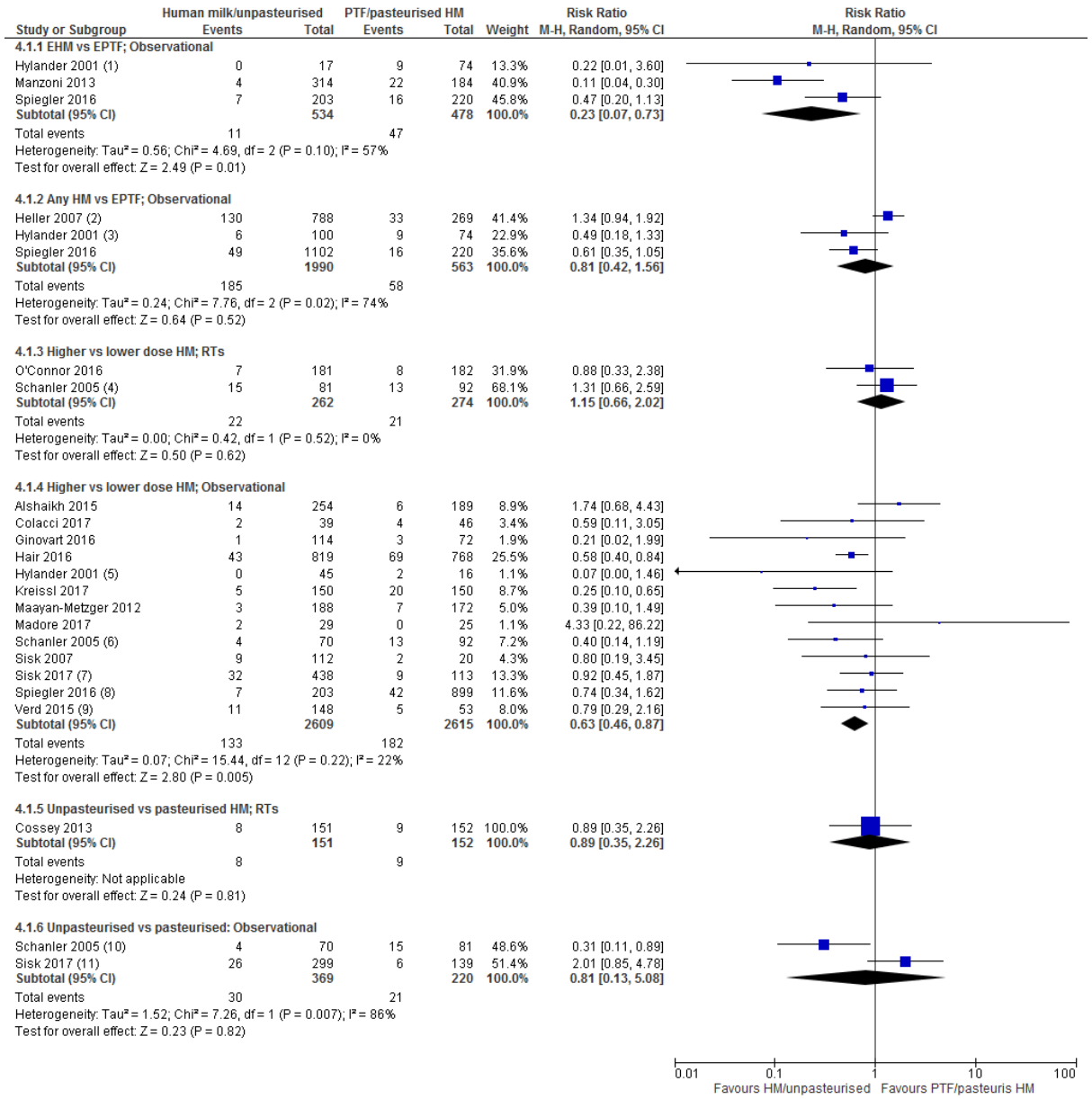
Table S7. Retinopathy of prematurity: summary of findings

Comparison	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula/ pasteurised human milk	Risk with human milk/ Unpasteurised human milk			
Retinopathy of prematurity - Exclusive human milk vs exclusive preterm formula; RTs	Study population		RR 1.32 (0.50 to 3.52)	53 (1 RCT)	⨁⨁⨀⨀ LOW [1]
	208 per 1,000	275 per 1,000 (104 to 733)			
Retinopathy of prematurity - Exclusive human milk vs exclusive preterm formula; Observational	Study population		RR 0.65 (0.31 to 1.34)	1256 (4 observational studies)	⨁⨀⨀⨀ VERY LOW [2,3]
	329 per 1,000	214 per 1,000 (102 to 441)			
Retinopathy of prematurity - Any human milk vs exclusive preterm formula; Observational	Study population		RR 1.08 (0.79 to 1.48)	3576 (6 observational studies)	⨁⨀⨀⨀ VERY LOW [2,3]
	286 per 1,000	309 per 1,000 (226 to 423)			
Retinopathy of prematurity - Higher vs lower dose human milk intake; RTs	Study population		RR 1.14 (0.86 to 1.50)	1071 (4 RCTs)	⨁⨁⨁⨀ MODERATE [3]
	119 per 1,000	136 per 1,000 (103 to 179)			
Retinopathy of prematurity - Higher vs lower dose human milk intake; Observational	Study population		RR 0.82 (0.70 to 0.96)	6302 (18 observational studies)	⨁⨀⨀⨀ VERY LOW [4]
	210 per 1,000	172 per 1,000 (147 to 202)			
Retinopathy of prematurity - Unpasteurised vs pasteurised human milk (MOM or donor); RTs	Study population		RR 0.89 (0.35 to 2.26)	303 (1 RCT)	⨁⨁⨀⨀ LOW [5]
	59 per 1,000	53 per 1,000 (21 to 134)			
Retinopathy of prematurity - Unpasteurised vs pasteurised human milk (MOM or donor); Observational	Study population		RR 0.89 (0.33 to 2.38)	681 (3 observational studies)	⨁⨀⨀⨀ VERY LOW [2,3]
	117 per 1,000	104 per 1,000 (38 to 277)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: [1]Wide CIs; only 1 study; small sample; [2]Substantial heterogeneity; [3]Wide CI; [4]Moderate heterogeneity; [5]Only 1 study, wide CIs.



Footnotes
(1) Group '100% HM' compared with EPTF group
(2) Incidence calculated from odds ratio
(3) Groups 0-19%, 20-79%, 80-99% and 100% were collapsed for 'any human milk' and cf EPTF
(4) Groups 'PDM'(higher dose) cf group 'PTF as supplement to MOM" (lower dose)
(5) Group 0-19% (lower dose HM) compared with group 80 -99% and group 100% (higher dose HM)
(6) Group MOM (high dose) cf wtih group PTF (low dose). MOM group not randomised
(7) Groups '≥50% MOM' and '≥50% PDHM' combined for high dose and cf '≥50% EPTF'
(8) EHM = higher dose HM; mixed feeding = lower dose HM; grande 3/4
(9) Data derived from inverse of 'no ROP"; EHM = higher dose HM; mixed feeding = lower dose HM
(10) MOM non-randomised
(11) Group '≥50% MOM' cf '≥50% PDHM'

Figure S3. Forest plot of relative risk for the association between human milk and severe retinopathy of prematurity

Table S8. Severe retinopathy of prematurity: summary of findings

Comparisons	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula/ pasteurised human milk	Risk with human milk/ Unpasteurised human milk			
Severe ROP - EHM vs EPTF; Observational	Study population		RR 0.23 (0.07 to 0.73)	1012 (3 observational studies)	⨁⨁⨀⨀ LOW [1]
	98 per 1,000	23 per 1,000 (7 to 72)			
Severe ROP - Any HM vs EPTF; Observational	Study population		RR 0.81 (0.42 to 1.56)	2553 (3 observational studies)	⨁⨀⨀⨀ VERY LOW 1
	103 per 1,000	83 per 1,000 (43 to 161)			
Severe ROP - Higher vs lower dose HM; RTs	Study population		RR 1.15 (0.66 to 2.02)	536 (2 RCTs)	⨁⨁⨀⨀ LOW [2]
	77 per 1,000	88 per 1,000 (51 to 155)			
Severe ROP - Higher vs lower dose HM; Observational	Study population		RR 0.63 (0.46 to 0.87)	5224 (13 observational studies)	⨁⨁⨀⨀ LOW
	70 per 1,000	44 per 1,000 (32 to 61)			
Severe ROP - Unpasteurised vs pasteurised HM; RTs	Study population		RR 0.89 (0.35 to 2.26)	303 (1 RCT)	⨁⨁⨁⨁ HIGH
	59 per 1,000	53 per 1,000 (21 to 134)			
Severe ROP - Unpasteurised vs pasteurised: Observational	Study population		RR 0.81 (0.13 to 5.08)	589 (2 observational studies)	⨁⨀⨀⨀ VERY LOW [1]
	95 per 1,000	77 per 1,000 (12 to 485)			

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes: [1]Substantial heterogeneity; [2]Wide CIs, only 2 studies; [3]Cossey et al 2013 did not blind participants and personnel, however not downgraded for this as outcome is objective, outcome assessors were blinded, and bias is unlikely.

Table S9. Neurodevelopment: summary of findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula	Risk with human milk			
Neurodevelopment – Cognition <18 months: Any human milk vs exclusive preterm formula; Observational	The mean neurodevelopment – Cognition <18 months: Any human milk vs exclusive preterm formula; Observational was 0	MD 9 higher (1.42 higher to 16.58 higher)	-	39 (1 observational study)	⨁⊖⊖⊖ VERY LOW [1]
Neurodevelopment – Cognition 18 to <36 months: Any human milk vs exclusive preterm formula; observational	The mean neurodevelopment – Cognition 18 to <36 months: Any human milk vs exclusive preterm formula; observational was 0	MD 2.01 higher (1.35 lower to 5.36 higher)	-	1744 (3 observational studies)	⨁⊖⊖⊖ VERY LOW [2]
Neurodevelopment – Cognition <18 months: Higher vs lower dose human milk; Observational	The mean neurodevelopment – Cognition <18 months: Higher vs lower dose human milk; Observational was 0	MD 0.67 higher (2.68 lower to 4.03 higher)	-	684 (5 observational studies)	⨁⊖⊖⊖ VERY LOW [2]
Neurodevelopment – Cognition 18 to <36 months: Higher vs lower dose human milk; RT	The mean neurodevelopment – Cognition 18 to <36 months: Higher vs lower dose human milk; RT was 0	MD 1.6 lower (5.95 lower to 2.75 higher)	-	299 (1 RCT)	⨁⨁⨁⊖ MODERATE [3]
Neurodevelopment – Cognition 18 to 36 months: Higher vs lower dose human milk; observational	The mean neurodevelopment – Cognition 18 to 36 months: Higher vs lower dose human milk; observational was 0	MD 0.59 lower (3.41 lower to 2.24 higher)	-	722 (4 observational studies)	⨁⊖⊖⊖ VERY LOW [2]
Neurodevelopment – Cognition >3 years; Higher vs lower dose human milk; Observational	The mean neurodevelopment – Cognition >3 years; Higher vs lower dose human milk; Observational was 0	MD 6.4 higher (5.8 lower to 18.6 higher)	-	18 (1 observational study)	⨁⊖⊖⊖ VERY LOW [1]
Neurodevelopment – Motor 18 to <36 months: Any human milk vs exclusive preterm formula; Observational	The mean neurodevelopment – Motor 18 to <36 months: Any human milk vs exclusive preterm formula; Observational was 0	MD 0.8 lower (6.02 lower to 4.42 higher)	-	1744 (3 observational studies)	⨁⊖⊖⊖ VERY LOW [2 3]
Neurodevelopment – Motor 18 to <36 months: Higher vs lower dose human milk; RT	The mean neurodevelopment – Motor: Higher vs lower dose human milk; RT was 0	MD 2.2 lower (6.42 lower to 2.02 higher)	-	299 (1 RCT)	⨁⨁⨁⊖ MODERATE [1]
Neurodevelopment – Motor<18 months: Higher vs lower dose human milk; Observational	The mean neurodevelopment – Motor<18 months: Higher vs lower dose human milk; Observational was 0	MD 0.33 lower (4.8 lower to 4.14 higher)	-	684 (5 observational studies)	⨁⊖⊖⊖ VERY LOW [2 4]

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with preterm formula	Risk with human milk			
Neurodevelopment – Motor 18 to <36 months: Higher vs lower dose human milk; observational	The mean neurodevelopment – Motor 18 to <36 months: Higher vs lower dose human milk; observational was 0	MD 1.94 lower (4.78 lower to 0.9 higher)	-	722 (4 observational studies)	⨁⊖⊖⊖ VERY LOW [2]
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;					
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes: [1]Only 1 study; [2]Wide Cis; [3]Only 1 study, wide Cis; [4]Moderate heterogeneity