WHO recommendations for care of the preterm or low-birth-weight infant

Web Supplement. Evidence base

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Contents

Note: The labelling convention in this document (e.g. “GRADE Table A.1a”) aligns with the evidence and recommendations in the guideline.

The full guideline document is available at https://apps.who.int/iris/bitstream/handle/10665/363697/9789240058262-eng.pdf

Abbreviations

BSID	Bayley Scales of Infant and Toddler Development	MDI	Mental Development Index (BSID-II)
CI	confidence interval	MMN	multiple micronutrient
CPAP	continuous positive airway pressure	OR	odds ratio
EBF	exclusive breastfeeding	PDI	Psychomotor Development Index (BSID-II)
GRADE	Grading of Recommendations Assessment, Development and Evaluation	PMA	postmenstrual age
IQR	interquartile range	RCT	randomized controlled trial
IU	international units	RR	relative risk
KMC	kangaroo mother care	SD	standard deviation
LBW	low birth weight	SMD	standardized mean difference
MD	mean difference	WHO	World Health Organization

A. Preventive and promotive care

A.1. Kangaroo mother care (KMC)

GRADE Table A.1a: Comparison 1 – KMC versus conventional newborn care

Source: Sivanandan S, Sankar MJ. Kangaroo mother care for preterm or low birth weight infants: a systematic review and meta-analysis. medRxiv. 2022:2022.09.14.22279053. doi:10.1101/2022.09.14.22279053.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Conventional newborn care	KMC		Risk with conventional newborn care	Risk difference with KMC
Mortality at latest follow-up – at discharge, at 40 weeks postmenstrual age or at 28 days of age											
10 505 (12 RCTs)	not serious[a]	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	140/4951 (2.8%)	105/5554 (1.9%)	**RR 0.68** (0.53 to 0.86)	28 per 1000	**9 fewer per 1000** (from 13 fewer to 4 fewer)
Mortality by 6 months of age											
8031 (4 RCTs)	not serious[b]	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	199/3862 (5.2%)	161/4169 (3.9%)	**RR 0.75** (0.62 to 0.92)	52 per 1000	**13 fewer per 1000** (from 20 fewer to 4 fewer)
Severe infection or sepsis by discharge or 40 weeks postmenstrual age (PMA) or 28 days of age											
9847 (9 RCTs)	serious[c]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	998/4632 (21.5%)	968/5215 (18.6%)	**RR 0.85** (0.79 to 0.92)	215 per 1000	**32 fewer per 1000** (from 45 fewer to 17 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Conventional newborn care	KMC		Risk with conventional newborn care	Risk difference with KMC
Hypothermia by discharge or 40 weeks PMA or 28 days of age											
1169 (11 RCTs)	not serious[d]	serious[e]	not serious	not serious	none	⨁⨁⨁◯ Moderate	149/580 (25.7%)	48/589 (8.1%)	**RR 0.32** (0.19 to 0.53)	257 per 1000	**175 fewer per 1000** (from 208 fewer to 121 fewer)
Weight gain at latest follow-up (g/day)											
1198 (11 RCTs)	serious[f]	serious[e]	not serious	not serious	none	⨁⨁◯◯ Low	575	623	-	The mean weight gain at latest follow-up was **0** g/day	MD **4.08 higher** (2.3 higher to 5.86 higher)
Exclusive breastfeeding by discharge or 40 to 41 weeks PMA or 28 days of age											
9983 (9 RCTs)	very serious[g]	serious[e]	not serious	not serious	none	⨁◯◯◯ Very low	2554/4675 (54.6%)	4305/5308 (81.1%)	**RR 1.48** (1.44 to 1.52)	546 per 1000	**262 more per 1000** (from 240 more to 284 more)
Exclusive breastfeeding at 1 to 3 months											
8139 (7 RCTs)	very serious[g]	serious[e]	not serious	serious[h]	none	⨁◯◯◯ Very low	1323/3847 (34.4%)	2504/4292 (58.3%)	**RR 1.39** (0.99 to 1.97)	344 per 1000	**134 more per 1000** (from 3 fewer to 334 more)
Griffith quotient for psychomotor development (all subscales) at follow-up (12 months corrected age)											
579 (1 RCT)	serious[i]	not serious	not serious	very serious[h,j]	none	⨁◯◯◯ Very low	271	308	-	The mean Griffith quotient at 12 months' corrected age was **0**	MD **1.05 higher** (0.75 lower to 2.85 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Conventional newborn care	KMC		Risk with conventional newborn care	Risk difference with KMC
Neurodevelopment at 12 months assessed with BSID-III											
516 (1 RCT)	serious[k]	not serious	not serious	very serious[h,j]	none	⨁◯◯◯ Very low	258	258	-	The mean neurodevelopmental outcome was 101.98 (SD 11.6)	MD **0.21 higher** (1.84 lower to 2.27 higher)

BSID-III: Bayley Scales of Infant Development, third edition; CI: confidence interval; MD: mean difference; PMA: postmenstrual age; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation

Explanations

[a] Not downgraded: risk of bias (risk of performance bias due to lack of masking to intervention, some unclear risk of allocation concealment, some risk of attrition bias due to incomplete outcome data; however, mortality being a "hard" outcome and the relatively low weights of biased studies, therefore not downgraded for either performance or outcome assessment bias)

[b] Not downgraded: risk of bias (risk of performance bias due to lack of masking to intervention, some unclear risk of allocation concealment; however, mortality being a "hard" outcome and relatively low weights of biased studies, therefore not downgraded for biases)

[c] Downgraded by one level: risk of bias (moderate or severe risk of bias due to lack of masking to intervention and outcomes and unclear allocation concealment; although culture-positive sepsis is a "hard" outcome, risk of bias was downgraded due to heavily weighted studies with unclear case definitions and sepsis diagnosis methodology)

[d] Not downgraded: risk of bias (high risk of outcome ascertainment bias due to lack of masking to intervention and outcomes; however, temperature measurement was considered a "hard" outcome and more than half of the studies had low risk of bias, therefore not downgraded for risk of bias)

[e] Downgraded by one level: inconsistency (substantial heterogeneity $I^2 > 50\%$)

[f] Downgraded by one level: risk of bias (high risk of outcome ascertainment bias due to lack of masking to intervention and outcomes; however, weight gain is considered a "hard" outcome. Studies with risk of allocation concealment bias accounted for 64% of weight, therefore the evidence was downgraded)

[g] Downgraded by two levels: very serious risk of bias (high risk of outcome ascertainment bias due to lack of masking to the intervention and the outcome is not a "hard" outcome, allocation concealment was unclear in six studies that accounted for 82% of weight)

[h] Downgraded by one level: imprecision (95% CIs overlap, indicating no effect [i.e. CI includes RR of 1.0])

[i] Downgraded by one level: risk of bias (1 study with moderate risk of bias [unclear allocation concealment; lack of blinding of participants/parents/clinical team and outcome assessors; the follow-up rate at 12–18 months was 80%])

[j] Downgraded by one level: imprecision (single study)

[k] Downgraded by one level: low risk of bias (developmental outcomes were ascertained in the study clinic by trained psychologists, who were unaware of the group allocation)

GRADE Table A.1b: Comparison 2 – KMC initiated early versus later

Source: Sivanandan S, Sankar MJ. Kangaroo mother care for preterm or low birth weight infants: a systematic review and meta-analysis. medRxiv. 2022:2022.09.14.22279053. doi:10.1101/2022.09.14.22279053.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Late initiated KMC	Early initiated KMC		Risk with late initiated KMC	Risk difference with early initiated KMC
Mortality by 28 days of age											
3533 (3 RCTs)	not serious[a]	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	284/1762 (16.1%)	222/1771 (12.5%)	**RR 0.78** (0.66 to 0.92)	161 per 1000	**35 fewer per 1000** (from 55 fewer to 13 fewer)
Sepsis by 28 days of age											
3415 (2 RCTs)	serious[b]	serious[c]	not serious	not serious	none	⨁⨁◯◯ Low	459/1843 (24.9%)	395/1851 (21.3%)	**RR 0.85** (0.76 to 0.96)	249 per 1000	**37 fewer per 1000** (from 60 fewer to 10 fewer)
Exclusive breastfeeding by discharge											
3464 (3 RCTs)	not serious[d]	serious[c]	not serious	not serious	none	⨁⨁⨁◯ Moderate	1188/1728 (68.8%)	1333/1736 (76.8%)	**RR 1.12** (1.07 to 1.16)	688 per 1000	**83 more per 1000** (from 48 more to 110 more)
Exclusive breastfeeding by 28 days of age											
2841 (3 RCTs)	not serious[d]	serious[c]	not serious	not serious[e]	none	⨁⨁⨁◯ Moderate	1187/1388 (85.5%)	1257/1453 (86.5%)	**RR 1.01** (0.98 to 1.04)	855 per 1000	**9 more per 1000** (from 17 fewer to 34 more)
Hypothermia by discharge or by 28 days of age											
3513 (3 RCTs)	not serious[f]	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	193/1772 (10.9%)	144/1781 (8.1%)	**RR 0.74** (0.61 to 0.90)	109 per 1000	**28 fewer per 1000** (from 42 fewer to 11 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Late initiated KMC	Early initiated KMC		Risk with late initiated KMC	Risk difference with early initiated KMC
Weight gain (g/day) by latest follow-up (28 days)											
204 (1 RCT)	serious[g]	not serious	not serious	serious[h]	none	⨁⨁◯◯ Low	101	103	-	The mean weight gain at 28 days follow-up was **0** g/day	MD **2.2 lower** (5.26 lower to 0.86 higher)

CI: confidence interval; KMC: kangaroo mother care; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Not downgraded: risk of bias (not masked to the intervention, mortality was considered a "hard" outcome so the evidence was not downgraded)

[b] Downgraded by one level: risk of bias (not masked to the intervention, risk of performance bias by the clinical team and researchers in a subjective outcome such as clinical sepsis or possible serious bacterial infection cannot be ruled out)

[c] Downgraded by one level: inconsistency in effect estimates (moderate or high heterogeneity; $I^2 > 50\%$)

[d] Not downgraded: risk of bias (in three studies, participants and clinical team were masked. Assessment of exclusive or any breastfeeding is prone to bias; however, the outcome assessment was carried out by an independent team not involved in the intervention; risk of performance bias in breastfeeding outcomes was considered low so the evidence was not downgraded)

[e] Not downgraded: imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit)

[f] Not downgraded: risk of bias (all studies were at low risk of bias – although not masked to the intervention, measurement of temperature was considered to be less prone to outcome assessment bias)

[g] Downgraded by one level: risk of bias (a single study was prematurely terminated at 75% enrolment). Not downgraded for lack of masking of caregivers or outcome assessors because weight measurement is an objective outcome

[h] Downgraded by one level: imprecision (95% CI overlaps no effect [i.e. CI includes RR of 1.0])

A.2. Mother's own milk

GRADE Table A.2: Comparison – Any formula milk versus mother's own milk

Source: Strobel NA, Adams C, McAullay DR, Edmond KM. Mother's own milk compared with formula milk for feeding preterm or low birth weight infants: systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092D.

Certainty assessment							Summary of findings				
							No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Any human milk	Any non-human milk		Risk with any human milk	Risk difference with any non-human milk
Mortality by latest follow-up (mean: 116 days)											
9673 (5 observational studies)	serious[a]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	137/2420 (5.7%)	719/7253 (9.9%)	**OR 1.26** (0.91 to 1.76)	57 per 1000	**14 more per 1000** (from 5 fewer to 39 more)
Necrotizing enterocolitis by latest follow-up (mean: 44 days)											
3013 (15 observational studies)	serious[a]	not serious	not serious	not serious	strong association	⨁⨁◯◯ Low	90/1501 (6.0%)	163/1512 (10.8%)	OR 2.99 (1.75 to 5.11)	60 per 1000	**100 more per 1000** (from 40 more to 186 more)
Sepsis or severe infection by latest follow-up (mean: 31 days)											
2562 (15 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⨁◯◯◯ Very low	311/1197 (26.0%)	434/1365 (31.8%)	OR 1.52 (0.98 to 2.37)	258 per 1000	**88 more per 1000** (from 4 fewer to 195 more)
Child cognitive development; assessed with validated child development assessment at follow-up (range: 91–416 weeks)											
1560 (8 observational studies)	serious[c]	serious[d]	not serious	not serious	none	⨁◯◯◯ Very low	776	784	-	-	SMD **1.3 SD lower** (3.53 lower to 0.93 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Any human milk	Any non-human milk		Risk with any human milk	Risk difference with any non-human milk
Child language development; assessed with validated child development assessment at follow-up (range: 39–104 weeks)											
587 (3 observational studies)	serious[c]	not serious	not serious	serious[e]	none	⨁◯◯◯ Very low	209	378	-	-	SMD **0.02 SD higher** (0.39 lower to 0.43 higher)
Weight-for-age z score (WAZ) change by discharge (mean: 52 days)											
74 130 (4 observational studies)	serious[c]	not serious	serious[f]	not serious	none	⨁◯◯◯ Very low	9730	64 400	-	The mean WAZ score (change from birth to discharge) ranged from **-1.31 to -0.5** points	MD **0.14 points higher** (0.76 lower to 1.05 higher)
WAZ score at latest follow-up (range: 39–416 weeks)											
271 (3 observational studies)	serious[c]	not serious	not serious	serious[e]	none	⨁◯◯◯ Very low	104	167	-	The mean WAZ score ranged from **-1.31 to -0.5** points	MD **0.14 points higher** (0.76 lower to 1.05 higher)
Length (cm) at latest follow-up (mean: 58 days)											
1048 (9 observational studies)	serious[c]	serious[g]	not serious	serious[e]	none	⨁◯◯◯ Very low	418	630	-	The mean length at latest follow-up ranged from **43.6 to 50.0** cm	MD **0.33 cm more** (0.4 less to 1.05 more)
Length or height for-age z score (LAZ/HAZ) at latest follow-up (range: 39–416 weeks)											
271 (3 observational studies)	serious[c]	not serious	not serious	serious[f]	none	⨁◯◯◯ Very low	104	167	-	The mean LAZ/HAZ score ranged from **-0.9.3 to -0.05** points	MD **0.06 points higher** (0.81 lower to 0.92 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Any human milk	Any non-human milk		Risk with any human milk	Risk difference with any non-human milk
Head circumference (cm) at latest follow-up (mean: 45 days)											
1550 (9 observational studies)	serious[c]	serious[h]	not serious	not serious	none	⨁◯◯◯ Very low	792	758	-	The mean head circumference ranged from **30.9 to 34.5** cm	MD **0.26 cm higher** (0.35 lower to 0.87 higher)

CI: confidence interval; MD: mean difference; OR: odds ratio; RR: relative risk; SD: standard deviation; SMD: standardized mean difference

Explanations

[a] Downgraded by two levels: serious risk of bias (some studies did not account for confounding; it is possible that classification of intervention status could have been affected by knowledge of the outcome or risk of the outcome)

[b] Downgraded by one level: serious inconsistency (I^2 = 65%)

[c] Downgraded by two levels: serious risk of bias (no studies accounted for confounding)

[d] Downgraded by one level: serious inconsistency (high I^2 = 99%)

[e] Downgraded by one level: serious imprecision (small sample size)

[f] Downgraded by one level: serious indirectness (1 study contributes a large study population)

[g] Downgraded by one level: serious inconsistency (I^2 = 80%)

[h] Downgraded by one level: serious inconsistency (I^2 = 88%)

A.3. Donor human milk

GRADE Table A.3: Comparison: Infant formula versus donor human milk

Source: Quigley M, Embleton ND, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev. 2019;(7):CD002971. doi:10.1002/14651858.CD002971.pub5.

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Donor human milk	Infant formula	Relative risk (RR) (95% CI)	Risk with donor human milk	Risk difference with infant formula
Mortality by hospital discharge											
1527 (7 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	65/759 (8.6%)	72/768 (9.4%)	**RR 1.1** (0.8 to 1.5)	86 per 1000	**9 more per 1000** (from 17 fewer to 43 more)
Necrotizing enterocolitis by hospital discharge											
1675 (9 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	30/837 (3.6%)	57/838 (6.8%)	**RR 1.87** (1.23 to 2.85)	36 per 1000	**31 more per 1000** (from 8 more to 66 more)
Invasive infection by hospital discharge											
1025 (5 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	162/506 (32.0%)	155/519 (29.9%)	**RR 0.94** (0.79 to 1.12)	320 per 1000	**19 fewer per 1000** (from 67 fewer to 38 more)
Weight gain (g/kg per day) by hospital discharge											
1028 (9 RCTs)	not serious	serious[b]	not serious	not serious	none	⨁⨁⨁◯ Moderate	488	540	-	The mean weight gain ranged from **12.4 to 23.9** g/kg per day	MD **2.51 g/kg per day** more (1.93 more to 3.08 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Donor human milk	Infant formula		Risk with donor human milk	Risk difference with infant formula
Linear growth (mm/week); assessed with crown–heel length by hospital discharge											
820 (8 RCTs)	not serious	serious[b]	not serious	not serious	none	⨁⨁⨁◯ Moderate	418	402	-	The mean linear growth ranged from **6.4 to 12.0** mm/week	MD **1.21 mm/week higher** (0.77 higher to 1.65 higher)
Head growth (mm/week) by hospital discharge											
894 (8 RCTs)	not serious	serious[b]	not serious	not serious	none	⨁⨁⨁◯ Moderate	456	438	-	The mean head growth ranged from **6.8 to 9.4** mm/week	MD **0.85 mm/week higher** (0.47 higher to 1.23 higher)
Neurodevelopmental disability at 18 months of age											
400 (2 RCTs)	not serious	serious[b]	not serious	not serious	none	⨁⨁⨁◯ Moderate	15/206 (7.3%)	17/194 (8.8%)	**RR 1.21** (0.62 to 2.35)	73 per 1000	**15 more per 1000** (from 28 fewer to 98 more)

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit)

[b] Downgraded by one level: inconsistency in effect estimates (moderate or high heterogeneity; $I^2 > 50\%$)

A.4. Multicomponent fortification of human milk

GRADE Table A.4: Comparison – Multicomponent fortification versus unfortified breast-milk

Source: Brown JV, Lin L, Embleton ND, Harding JE, McGuire W. Multi-nutrient fortification of human milk for preterm infants. Cochrane Database Syst Rev. 2020;6(7):CD000343. doi:10.1002/14651858.CD000343.pub4.

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Unfortified breast-milk	Multicomponent fortification of human milk	Relative risk (RR) (95% CI)	Risk with unfortified breast-milk	Risk difference with multicomponent fortification of human milk
Mortality by hospital discharge											
375 (2 RCTs)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	9/185 (4.86%)	14/190 (7.37%)	**RR 2.33** (0.16 to 34.76)	0 per 1000	**2 fewer per 1000** (from 35 fewer to 0 fewer)
Necrotizing enterocolitis by hospital discharge											
1110 (13 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	14/546 (2.6%)	20/564 (3.5%)	**RR 1.37** (0.72 to 2.63)	26 per 1000	**9 more per 1000** (from 7 fewer to 42 more)
Weight gain (g/kg per day) by hospital discharge											
951 (14 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	467	484	-	The mean weight gain ranged from **7.90 to 19.90** g/kg per day	MD **1.76 g/kg per day more** (1.3 more to 2.22 more)
Length gain (cm/week) by hospital discharge											
741 (10 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	364	377	-	The mean length gain ranged from **0.70 to 0.96** cm/week	MD **0.11 cm/week more** (0.08 more to 0.15 more)

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Unfortified breast-milk	Multicomponent fortification of human milk	Relative risk (RR) (95% CI)	Risk with unfortified breast-milk	Risk difference with multicomponent fortification of human milk
Head growth (cm/week) by hospital discharge											
821 (11 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	404	417	-	The mean head growth ranged from **0.54 to 0.98** cm/week	MD **0.06 cm/week more** (0.03 more to 0.08 more)
Mental Development Index (MDI, BSID-II) at 18 months											
245 (1 RCT)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ Moderate	120	125	-	The mean mental development index was **103.8** units	MD **2.2 units more** (3.35 fewer to 7.75 more)
Psychomotor Development Index (PDI, BSID-II) at 18 months											
245 (1 RCT)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ Moderate	120	125	-	The mean psychomotor development index was **89.9** units	MD **2.4 units more** (1.9 fewer to 6.7 more)

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: high risk of bias (uncertainty about methods used to generate random sequence, conceal allocation and blind assessments); serious study limitations in most trials

[b] Downgraded by one level: inconsistency in effect estimates (moderate or high heterogeneity; $I^2 > 50\%$)

[c] Downgraded by one level: imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit)

A.5. Preterm formula

GRADE Table A.5: Comparison – Nutrient enriched (preterm) formula versus standard (term) formula

Source: Walsh V, Brown JVE, Askie LM, Embleton ND, McGuire W. Nutrient-enriched formula versus standard formula for preterm infants. Cochrane Database Syst Rev. 2019;(7):CD004204. doi:10.1002/14651858.CD004204.pub3.

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Standard formula	Nutrient-enriched formula	Relative risk (RR) (95% CI)	Risk with standard formula	Risk difference with nutrient-enriched formula
Mortality by hospital discharge											
424 (2 RCTs)	very serious[a,b]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	22/211 (10.4%)	25/213 (11.7%)	**RR 1.12** (0.65 to 1.93)	104 per 1000	**13 more per 1000** (from 36 fewer to 97 more)
Necrotizing enterocolitis by hospital discharge											
489 (3 RCTs)	very serious[a,b]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	27/241 (11.2%)	21/248 (8.5%)	**RR 0.72** (0.41 to 1.25)	112 per 1000	**31 fewer per 1000** (from 66 fewer to 28 more)
Weight gain (g/kg per day) by hospital discharge											
440 (6 RCTs)	serious[a]	serious[c]	not serious	not serious	none	⨁⨁◯◯ Low	220	220	-	The mean weight gain ranged from **3.6 to 15.9** g/kg per day	MD **2.43 g/kg per day higher** (1.6 higher to 3.26 higher)
Length gain (mm/week) by hospital discharge											
386 (5 RCTs)	serious[a]	serious[c]	not serious	not serious	none	⨁⨁◯◯ Low	189	197	-	The mean length gain ranged from **8.7 to 10.9** mm/week	MD **0.22 mm/week higher** (0.7 lower to 1.13 higher)

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Standard formula	Nutrient-enriched formula	Relative risk (RR) (95% CI)	Risk with standard formula	Risk difference with nutrient-enriched formula
Head circumference gain (mm/week) by hospital discharge											
399 (5 RCTs)	serious[a]	serious[c]	not serious	not serious	none	⨁⨁◯◯ Low	200	199	-	The mean head circumference gain ranged from **6.4 to 9.7** mm/week	MD **1.04 mm/week higher** (0.18 higher to 1.89 higher)
Mental Development Index (MDI, BSID-II) at 18 months											
310 (2 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	154	156	-	The mean MDI at 18 months ranged from **92.6 to 103.5** units	MD **2.81 units higher** (1.44 lower to 7.06 higher)
Psychomotor Development Index (PDI, BSID-II) at 18 months											
310 (2 RCTs)	serious[a]	serious[c]	not serious	not serious	none	⨁⨁◯◯ Low	154	156	-	The mean PDI at 18 months ranged from **84.2 to 92.5** units	MD **6.56 units more** (2.87 more to 10.26 more)

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: risk of bias (uncertainty about methods used to generate random sequence, conceal allocation and mask assessments in trials)

[b] Downgraded by one level: risk of bias (post hoc exclusions in two trials)

[c] Downgraded by one level: inconsistency (moderate to high heterogeneity)

A.6. Early initiation of enteral feeding

GRADE Table A.6: Comparison – Early versus delayed initiation of enteral feeding

Source: Chitale R, Ferguson K, Talej M, Yang WC, He S, Edmond KM, et al. Early enteral feeding for preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092E.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Delayed feeding	Early feeding		Risk with delayed feeding	Risk difference with early feeding
Mortality at latest follow-up (by hospital discharge or 28 days)											
1292 (12 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	65/631 (10.3%)	44/661 (6.7%)	**RR 0.69** (0.48 to 0.99)	103 per 1000	**32 fewer per 1000** (from 54 fewer to 1 fewer)
Necrotizing enterocolitis by hospital discharge											
1484 (13 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	61/727 (8.4%)	66/757 (8.7%)	**RR 1.05** (0.75 to 1.46)	84 per 1000	**4 more per 1000** (from 21 fewer to 39 more)
Sepsis by hospital discharge											
626 (5 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	101/312 (32.4%)	85/314 (27.1%)	**RR 0.90** (0.54 to 1.52)	324 per 1000	**32 fewer per 1000** (from 149 fewer to 168 more)
Intraventricular haemorrhage by hospital discharge											
84 (1 RCT)	serious[a]	serious[c]	not serious	serious[d]	none	⨁◯◯◯ Very low	11/43 (25.6%)	5/41 (12.2%)	**RR 0.48** (0.18 to 1.25)	256 per 1000	**133 fewer per 1000** (from 210 fewer to 64 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Delayed feeding	Early feeding		Risk with delayed feeding	Risk difference with early feeding
Time to regain birth weight (days)											
569 (7 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	282	287	-	The mean time to regain birthweight ranged from **11.7 to 24.4** days	MD **0.26 days more** (0.63 fewer to 1.15 more)
Weight (g) at latest follow-up (6–12 weeks chronological age)											
142 (3 RCTs)	serious[a]	not serious	not serious	serious[e]	none	⨁⨁◯◯ Low	67	75	-	The mean weight ranged from **1338 to 2990** g	MD **49.02 g lower** (149.65 lower to 51.61 higher)
Weight gain (g) from enrolment to 30 days follow-up											
40 (1 RCT)	serious[a]	serious[c]	not serious	serious[e]	none	⨁◯◯◯ Very low	21	19	-	The mean weight gain was **213** g	MD **51 g more** (32.4 more to 69.6 more)
Length (cm) at latest follow-up (at 32 weeks chronological age)											
82 (2 RCTs)	serious[a]	not serious	not serious	serious[e]	none	⨁⨁◯◯ Low	36	46	-	The mean length ranged from **38.6 to 48.2** cm	MD **0.62 cm lower** (1.51 lower to 0.27 higher)
Head circumference (cm) at latest follow-up (at discharge or 32 weeks chronological age)											
82 (2 RCTs)	serious[a]	serious[f]	not serious	serious[e]	none	⨁◯◯◯ Very low	36	46	-	The mean head circumference ranged from **28.1 to 35.7** cm	MD **0.56 cm lower** (1.18 lower to 0.06 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Delayed feeding	Early feeding		Risk with delayed feeding	Risk difference with early feeding
Feed intolerance by hospital discharge											
187 (2 RCTs)	serious[a]	not serious	not serious	serious[d]	none	⨁⨁◯◯ Low	26/94 (27.7%)	27/93 (29.0%)	**RR 1.03** (0.66 to 1.60)	277 per 1000	**8 more per 1000** (from 94 fewer to 166 more)
Duration of hospitalization (days to discharge)											
1100 (10 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	533	567	-	The mean duration ranged from **30.1 to 102** days to discharge	MD **3.2 days fewer** (5.74 fewer to 0.66 fewer)

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded one level: serious risk of bias due to the randomization process (allocation concealment, i.e. not blinded), missing outcome data (important levels of loss to follow-up), measurement of the outcome (poor allocation concealment or not blinded to intervention group), selection of the reported result (no protocol)

[b] Downgraded one level: imprecision (wide CI crossing the line of no effect, representing both appreciable benefit and appreciable harm)

[c] Downgraded one level: heterogeneity (only 1 study and could not assess inconsistency)

[d] Downgraded one level: imprecision due to small sample size, i.e. optimal information size not met (i.e. the total number of patients included is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial) for dichotomous outcomes and wide CI crossing the line of no effect representing both appreciable benefit and appreciable harm

[e] Downgraded one level: imprecision due to small sample size, i.e. optimal information size not met (i.e. the total number of patients included is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial) for continuous outcomes and wide CI crossing the line of no effect representing both appreciable benefit and appreciable harm

[f] Downgraded one level: heterogeneity (I^2 = 98%)

A.7. Responsive and scheduled feeding

GRADE Table A.7: Comparison – Responsive feeding versus scheduled feeding

Source: Talej M, Smith ER, Lauria ME, Chitale R, Ferguson K, He S. Responsive feeding for preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092F.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Scheduled feeding	Responsive feeding		Risk with scheduled feeding	Risk difference with responsive feeding
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Morbidity – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Weight (g) by hospital discharge											
183 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	94	89	-	The mean weight ranged from **1840 to 2379** g	MD **22.21 g lower** (130.63 lower to 86.21 higher)
Weight (g/day) by hospital discharge											
213 (2 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	106	107	-	The mean weight ranged from **14.6 to 34.1** g/day	MD **2.8 g/day lower** (3.39 lower to 2.22 lower)
Weight (g/kg per day) by hospital discharge											
372 (5 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	⨁◯◯◯ Very low	188	184	-	The mean weight ranged from **1.25 to 16.8** g/kg per day	MD **0.99 g/kg per day lower** (2.45 lower to 0.46 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Scheduled feeding	Responsive feeding		Risk with scheduled feeding	Risk difference with responsive feeding
Duration of hospitalization (days to discharge)											
342 (5 RCTs)	serious[a]	serious[c]	not serious	serious[b]	none	⨁◯◯◯ Very low	172	170	-	The mean duration of hospitalization ranged from **14.5 to 115.9** days	MD **1.42 days fewer** (5.43 fewer to 2.59 more)
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial

Explanations

[a] Downgraded one level: some concerns of bias due to the randomization process (allocation concealment, i.e. not blinded) and selection of the reported result (no protocol)

[b] Downgraded one level: imprecision due to small sample size, i.e. optimal information size not met (i.e. the total cumulative study population comprises fewer than 400 participants for continuous outcomes) and wide CI crossing the line of no effect representing both appreciable benefit and appreciable harm

[c] Downgraded one level: heterogeneity ($I^2 > 70\%$)

A.8. Fast and slow advancement of feeding

GRADE Table A.8: Comparison – Fast versus slow advancement of enteral feeds

Source: Yang WC, Fogel A, Lauria ME, Ferguson K, Smith ER. Fast feed advancement for preterm and low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092G.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants: Slow enteral feeding advancement	No. of participants: Fast enteral feeding advancement	Relative risk (RR) (95% CI)	Anticipated absolute effects: Risk with slow enteral feeding advancement	Anticipated absolute effects: Risk difference with fast enteral feeding advancement
Mortality by hospital discharge											
4132 (11 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	164/2107 (7.8%)	150/2025 (7.4%)	**RR 0.93** (0.73 to 1.18)	78 per 1000	**5 fewer per 1000** (from 21 fewer to 14 more)
Necrotizing enterocolitis by hospital discharge											
4291 (12 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	120/2192 (5.5%)	106/2099 (5.1%)	**RR 0.89** (0.68 to 1.15)	55 per 1000	**6 fewer per 1000** (from 18 fewer to 8 more)
Sepsis by hospital discharge											
3648 (9 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	513/1863 (27.5%)	464/1785 (26.0%)	**RR 0.92** (0.83 to 1.03)	275 per 1000	**22 fewer per 1000** (from 47 fewer to 8 more)
Apnoea by hospital discharge											
153 (2 RCTs)	serious[b]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	29/76 (38.2%)	21/77 (27.3%)	**RR 0.72** (0.47 to 1.12)	382 per 1000	**107 fewer per 1000** (from 202 fewer to 46 more)
Feed intolerance by hospital discharge											
1114 (8 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	173/566 (30.6%)	156/548 (28.5%)	**RR 0.92** (0.77 to 1.10)	306 per 1000	**24 fewer per 1000** (from 70 fewer to 31 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Slow enteral feeding advancement	Fast enteral feeding advancement		Risk with slow enteral feeding advancement	Risk difference with fast enteral feeding advancement
Time to regain birth weight (days) during admission											
993 (6 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High	510	483	-	The mean time to regain birthweight ranged from **11.88 to 22.7** days	MD **3.69 days fewer** (4.44 fewer to 2.95 fewer)
Weight-for-age z score (WAZ) by hospital discharge											
2793 (1 RCT)	not serious	serious[d]	not serious	serious[a]	none	⨁⨁◯◯ Low	1399	1394	-	The mean WAZ score at discharge was **-1.5**	MD **0 WAZ score** (0.08 lower to 0.08 higher)
Weight (g/kg per day) by hospital discharge											
131 (1 RCT)	not serious	serious[d]	not serious	serious[a]	none	⨁⨁◯◯ Low	65	66	-	The mean weight at discharge was **11.7** g/kg per day	MD **0.5 g/kg per day more** (1.19 fewer to 2.19 more)
Weight (g) by hospital discharge											
100 (1 RCT)	not serious	serious[d]	not serious	serious[a]	none	⨁⨁◯◯ Low	50	50	-	The mean weight at discharge was **1225** g	MD **29.0 g fewer** (74.89 fewer to 16.89 more)
Length – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Head circumference z score (HCZ) by hospital discharge											
2793 (1 RCT)	not serious	serious[d]	not serious	serious[a]	none	⨁⨁◯◯ Low	1399	1394	-	The mean HCZ score was **-0.7**	MD **0.1 HCZ score lower** (0.22 lower to 0.02 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Slow enteral feeding advancement	Fast enteral feeding advancement		Risk with slow enteral feeding advancement	Risk difference with fast enteral feeding advancement
Neurodevelopmental disability at 24 months corrected age											
2325 (1 RCT)	not serious	serious[d]	not serious	serious[a]	none	⨁⨁◯◯ Low	321/1169 (27.5%)	354/1156 (30.6%)	**RR 1.12** (0.98 to 1.27)	275 per 1000	**33 more per 1000** (from 5 fewer to 74 more)
Duration of hospitalization (days to discharge)											
3864 (7 RCTs)	not serious	serious[e]	not serious	not serious	none	⨁⨁⨁◯ Moderate	1948	1916	-	The mean duration ranged from **12.1 to 62.8** days	MD **3.08 days fewer** (4.34 fewer to 1.81 fewer)

CI: confidence interval; HCZ: head circumference z score; MD: mean difference; RCT: randomized controlled trial; RR: relative risk; WAZ: weight-for-age z score

Explanations

[a] Downgraded one level: imprecision due to wide CI crossing the line of no effect representing both appreciable benefit and appreciable harm

[b] Downgraded one level: serious risk of bias due to the randomization process (allocation concealment, i.e. not blinded)

[c] Downgraded one level: imprecision due to small sample size, i.e. optimal information size not met (i.e. total cumulative study population comprises fewer than 300 participants) for dichotomous outcomes and wide CI crossing the line of no effect representing both appreciable benefit and appreciable harm)

[d] Downgraded one level: heterogeneity as only 1 study and could not assess inconsistency

[e] Downgraded one level: serious unexplained heterogeneity (I^2 = 79%)

A.9. Duration of exclusive breastfeeding (EBF)

GRADE Table A.9: Comparison – EBF for less than 6 months versus for six months

Source: Yang WC, Lauria ME, Fogel A, Ferguson K, Smith ER. Duration of exclusive breastfeeding for preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092H.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							EBF for 6 months	EBF for < 6 months		Risk with EBF for 6 months	Risk difference with EBF for < 6 months
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Diarrhoea (% days with diarrhoea) at 26 weeks chronological age											
119 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	59	60	-	The mean days with diarrhoea was **5.4**%	MD **2.6% lower** (5.2 lower to 0)
Fever (% days with fever) at 26 weeks chronological age											
119 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	59	60	-	The mean days with fever was **8.0**%	MD **0.7% lower** (3.4 lower to 2 higher)
Weight-for-age z score (WAZ) at corrected age 12 months											
188 (1 RCT)	not serious	serious[b]	not serious	serious[c]	none	⨁⨁◯◯ Low	93	95	-	The mean WAZ score at corrected age 12 months was **-1.8**	MD **0.1 WAZ score higher** (0.2 lower to 0.4 higher)
Weight gain (g) from 16 to 26 weeks of chronological age											
119 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	59	60	-	The mean weight gain was **1017** g	MD **13 g lower** (143 lower to 117 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							EBF for 6 months	EBF for < 6 months		Risk with EBF for 6 months	Risk difference with EBF for < 6 months
Length gain (cm) from 16 to 26 weeks of age											
119 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	59	60	-	The mean length gain was **4.5** cm	MD **0.2 cm lower** (0.6 lower to 0.2 higher)
Motor development milestone: age in months when reported to be able to raise head											
108 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	56	52	-	The mean age when reported to be able to raise head was **1.0** months	MD **0 months** (0.3 lower to 0.3 higher)
Motor development milestone: age in months when reported to be able to raise head and chest											
108 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	56	52	-	The mean age when reported to be able to raise head and chest was **1.9** months	MD **0.1 months lower** (0.7 lower to 0.5 higher)
Motor development milestone: age in months when reported to be able to roll over											
108 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	56	52	-	The mean age when reported to be able to roll over was **3.8** months	MD **0 months** (0.7 lower to 0.7 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							EBF for 6 months	EBF for < 6 months		Risk with EBF for 6 months	Risk difference with EBF for < 6 months
Motor development milestone: age in months when reported to be able to crawl											
108 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	56	52	-	The mean age when reported to be able to crawl was **6.8** months	MD **0.6 months higher** (0.1 lower to 1.3 higher)
Motor development milestone: age in months when reported to be able to sit from lying position											
108 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	56	52	-	The mean age when reported to be able to sit from lying position was **7.4** months	MD **0.6 months higher** (0 to 1.2 higher)
Motor development milestone: infants who are reported to be able to walk by the age of 12 months											
99 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	9/50 (18.0%)	13/49 (26.5%)	**RR 1.47** (0.69 to 3.13)	180 per 1000	**85 more per 1000** (from 56 fewer to 383 more)

CI: confidence interval; EBF: early breastfeeding; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded one level: serious risk of bias (lack of allocation concealment as randomization was performed by week of birth in the Dewey 1999 study)

[b] Downgraded one level: serious inconsistency (only 1 study is available, so it could not be evaluated)

[c] Downgraded one level: serious imprecision (wide CIs crossing line of no effect)

A.10. Micronutrient supplementation

GRADE Table A.10a: Comparison – Iron supplementation versus no iron supplementation

Source: Manapurath RM, Gadapani Pathak B, Sinha B, Upadhyay RP, Choudhary TS, Chandola TR, et al. Enteral iron supplementation in preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092I.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No supplementation	Iron supplementation		Risk with no supplementation	Risk difference with iron supplementation
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Sepsis by latest follow-up (median 8 [IQR 8 to 9] weeks)											
270 (4 RCTs)	serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	15/133 (11.3%)	16/137 (11.7%)	**RR 1.08** (0.56 to 2.07)	113 per 1000	**9 more per 1000** (from 50 fewer to 121 more)
Necrotizing enterocolitis by latest follow-up (median 9 [IQR 8.5 to 9.5] weeks)											
194 (2 RCTs)	serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	8/97 (8.2%)	13/97 (13.4%)	**RR 1.54** (0.69 to 3.46)	82 per 1000	**45 more per 1000** (from 26 fewer to 203 more)
Feed intolerance by latest follow-up (mean 8 weeks)											
238 (2 RCTs)	very serious[b]	not serious	not serious	very serious[b]	none	⨁◯◯◯ Very low	21/133 (15.8%)	11/105 (10.5%)	**RR 1.05** (0.49 to 2.27)	158 per 1000	**8 more per 1000** (from 81 fewer to 201 more)
Anaemia prevalence by latest follow-up (26 weeks)											
381 (2 RCTs)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ Moderate	13/129 (10.1%)	6/252 (2.4%)	**RR 0.25** (0.10 to 0.62)	101 per 1000	**76 fewer per 1000** (from 91 fewer to 38 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No supplementation	Iron supplementation		Risk with no supplementation	Risk difference with iron supplementation
Haemoglobin (g/l) by latest follow-up (median 20 [IQR 8 to 26] weeks)											
506 (5 RCTs)	serious[d]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	184	322	-	The mean haemoglobin ranged from **102 to 117.5** g/l	MD **4.79 g/l higher** (2.9 higher to 6.69 higher)
Ferritin (µg/ml) by latest follow-up (median14 [IQR 8 to 26] weeks)											
607 (6 RCTs)	very serious[e]	serious[e]	not serious	serious[e]	none	⨁◯◯◯ Very low	237	370	-	The mean ferritin ranged from **15 to 88.4** µg/ml	MD **8.76 µg/ml higher** (0.85 lower to 18.37 higher)
Weight (g) by latest follow-up (median 26 [IQR 8 to 36] weeks)											
574 (5 RCTs)	serious[f]	not serious	not serious	serious[f]	none	⨁⨁◯◯ Low	230	344	-	The mean weight ranged from **2154 to 14 600** g	MD **35.31 g higher** (64.53 lower to 135.15 higher)
Length (cm) by latest follow-up (median 26 [IQR 8 to 183] weeks)											
384 (3 RCTs)	serious[d]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	136	248	-	The mean length ranged from **57.3 to 97.4** cm	MD **0.69 cm higher** (0.01 higher to 1.37 higher)
Head circumference (cm) by latest follow-up (median 26 [IQR 8 to 183] weeks)											
385 (3 RCTs)	serious[f]	not serious	not serious	serious[f]	none	⨁⨁◯◯ Low	136	249	-	The mean head circumference ranged from **40.9 to 49.9** cm	MD **0.09 cm fewer** (0.4 fewer to 0.21 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No supplementation	Iron supplementation		Risk with no supplementation	Risk difference with iron supplementation
Cognitive development by latest follow-up (365 weeks)											
199 (1 RCT)	serious[g]	serious[g]	not serious	very serious[g]	none	⨁◯◯◯ Very low	7/70 (10.0%)	4/129 (3.1%)	**RR 0.31** (0.09 to 1.02)	100 per 1000	**69 fewer per 1000** (from 91 fewer to 2 more)
Behaviour by latest follow-up (365 weeks)											
185 (1 RCT)	serious[g]	serious[g]	not serious	very serious[g]	none	⨁◯◯◯ Very low	4/72 (5.6%)	5/113 (4.4%)	**RR 0.80** (0.22 to 2.87)	56 per 1000	**11 fewer per 1000** (from 43 fewer to 104 more)

CI: confidence interval; IQR: interquartile range; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by three levels: very serious risk of bias; very serious imprecision (suboptimal sample size, wide CI); very serious inconsistency (substantial variation of point estimates across studies, high heterogeneity)

[b] Downgraded by three levels: very serious risk of bias; very serious imprecision (wide CI, suboptimal sample size)

[c] Downgraded by one level: serious imprecision, the number of events was small (only 2 studies in which the intervention groups had been combined)

[d] Downgraded by one level: serious risk of bias

[e] Downgraded by three levels: very serious risk of bias; serious imprecision (wide CI); serious inconsistency (high heterogeneity)

[f] Downgraded by two levels: serious risk of bias; serious imprecision (wide CI)

[g] Downgraded by three levels: serious risk of bias; very serious imprecision (suboptimal sample size, wide CI); serious inconsistency (small number of studies)

GRADE Table A.10b: Comparison – Zinc supplementation versus no zinc supplementation

Source: Sinha B, Dudeja N, Chowdhury R, Choudhary TS, Upadhyay RP, Rongsen-Chandola T, et al. Enteral zinc supplementation in preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092J.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No zinc supplementation	Enteral zinc supplementation		Risk with no zinc supplementation	Risk difference with enteral zinc supplementation
Mortality by latest follow-up (median 26 [IQR 14 to 152.1] weeks)											
8801 (6 RCTs)	not serious	serious[a]	not serious	serious[a]	none	⨁⨁◯◯ Low	4285	4516	**RR 0.73** (0.46 to 1.16)	0 per 1000	**1 fewer per 1000** (from 1 fewer to 0 fewer)
Hospitalization by latest follow-up (median 26 [IQR 20 to 26] weeks)											
277 (2 RCTs)	serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	101	176	**RR 0.70** (0.24 to 2.00)	0 per 1000	**1 fewer per 1000** (from 2 fewer to 0 fewer)
Weight (g) at latest follow-up (median 22 [IQR 13.5 to 39] weeks)											
798 (8 RCTs)	serious[c]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	382	416	-	The mean weight ranged from **1889 to 8134.8** g	MD **378.57 g more** (275.26 more to 481.88 more)
Length (cm) at latest follow-up (median 36.1 [IQR 20 to 52.1] weeks)											
529 (6 RCTs)	serious[d]	serious[d]	not serious	not serious	none	⨁⨁◯◯ Low	250	279	-	The mean length ranged from **44.1 to 72.9** cm	MD **2.92 cm more** (1.53 more to 4.31 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No zinc supplementation	Enteral zinc supplementation		Risk with no zinc supplementation	Risk difference with enteral zinc supplementation
Head growth (cm) at latest follow-up (median 20 [IQR 13 to 24] weeks)											
466 (5 RCTs)	very serious[e]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	218	248	-	The mean head growth ranged from **32.2 to 44.6** cm	MD **0.56 cm more** (0.23 more to 0.9 more)
Diarrhoea at latest follow-up (median 26 [IQR 20.1 to 52.1] weeks)											
1947 (6 RCTs)	serious[f]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	953	994	**RR 0.81** (0.68 to 0.97)	0 per 1000	**1 fewer per 1000** (from 1 fewer to 1 fewer)
Acute respiratory infection at latest follow-up (median 13 [IQR 6 to 20] weeks)											
172 (2 RCTs)	very serious[g]	not serious	serious[g]	serious[g]	none	⨁◯◯◯ Very low	85	87	**RR 0.32** (0.09 to 1.17)	0 per 1000	**0 fewer per 1000** (from 1 fewer to 0 fewer)
Sepsis at latest follow-up (median 17 [IQR 14 to 20] weeks)											
265 (2 RCTs)	not serious	not serious	serious[h]	serious[h]	none	⨁⨁◯◯ Low	131	134	**RR 1.12** (0.62 to 2.02)	0 per 1000	**1 fewer per 1000** (from 2 fewer to 1 fewer)
Mental development scores at latest follow-up (median 52 weeks)											
301 (2 RCTs)	very serious[i]	serious[i]	not serious	not serious	none	⨁◯◯◯ Very low	120	181	-	The mean mental development scores ranged from **109.1 to 113** points	MD **4.18 points lower** (6.51 lower to 1.85 lower)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No zinc supplementation	Enteral zinc supplementation		Risk with no zinc supplementation	Risk difference with enteral zinc supplementation
Psychomotor development scores at latest follow-up (median 52 weeks)											
301 (2 RCTs)	very serious[j]	serious[j]	not serious	serious[j]	none	⨁◯◯◯ Very low	120	181	-	The mean psychomotor development scores ranged from **94 to 100.4** points	MD **5.75 points higher** (4.83 lower to 16.33 higher)

CI: confidence interval; IQR: interquartile range; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by two levels: serious inconsistency (I^2 = 58.9%, *P* = 0.18, non-overlapping of CIs on visual inspection of the forest plot), serious imprecision (wide CI)

[b] Downgraded by three levels: very serious risk of bias (all included studies have high risk of bias); serious inconsistency (I^2 = 82.3%, *P* = 0.50, inconsistency suspected on visual inspection of the forest plot); serious imprecision (wide CI)

[c] Downgraded by one level: serious risk of bias (the high-quality studies contributed to 43% of the weightage in the meta-analyses)

[d] Downgraded by two levels: serious risk of bias (the high-quality studies contributed to 32.9% of the weightage in the meta-analyses); serious inconsistency (I^2 = 77.2%, *P* = 0.00, inconsistency suspected on visual inspection of the forest plot). Publication bias was suspected only for the outcome of length; however, we have not downgraded for this given that there were fewer than 10 studies included in the analysis.

[e] Downgraded by two levels: very serious risk of bias (all the included studies are of low quality)

[f] Downgraded by one level: serious risk of bias (the high-quality studies contributed to 43.0% of the weightage in the meta-analyses)

[g] Downgraded by three levels: very serious risk of bias (both the included studies are of low quality); serious indirectness (only two studies with small sample size reported this outcome); serious imprecision (wide CI)

[h] Downgraded by two levels: serious indirectness (only two studies with small sample size reported this outcome); serious imprecision (wide CI)

[i] Downgraded by two levels: very serious risk of bias (all the included studies are of low quality); serious inconsistency (I^2 = 57.7%, *P* = 0.03 inconsistency suspected on visual inspection of the forest plot)

[j] Downgraded by three levels: very serious risk of bias (all the included studies are of low quality); serious inconsistency (I^2= 97.7%, *P* = 0.30, inconsistency suspected on visual inspection of the forest plot); serious imprecision (wide CIs)

GRADE Table A.10c: Comparison – Vitamin D supplementation versus no vitamin D supplementation

Source: Kumar M, Shaikh S, Sinha B, Upadhyay RP, Choudhary TS, Chandola TR, et al. Enteral vitamin D supplementation in preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092K.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Placebo	Vitamin D		Risk with placebo	Risk difference with vitamin D
Mortality by latest follow-up (6 months of age)											
2179 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	24/1076 (2.2%)	35/1103 (3.2%)	**RR 1.81** (0.92 to 3.56)	22 per 1000	**18 more per 1000** (from 2 fewer to 57 more)
Severe morbidity* at latest follow-up (median 17 [IQR 8 to 26] weeks)											
2179 (2 RCTs)	serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	208/1076 (19.3%)	206/1103 (18.7%)	**RR 0.94** (0.72 to 1.24)	193 per 1000	**12 fewer per 1000** (from 54 fewer to 46 more)
Bronchopulmonary dysplasia at latest follow-up (8 weeks)											
100 (1 RCT)	serious[c]	serious[c]	not serious	serious[c]	none	⨁◯◯◯ Very low	16/36 (44.4%)	22/64 (34.4%)	**RR 0.77** (0.47 to 1.27)	444 per 1000	**102 fewer per 1000** (from 236 fewer to 120 more)
Weight-for-age z scores (WAZ) at 6 months of age											
1273 (1 RCT)	not serious	serious[d]	not serious	not serious	none	⨁⨁⨁◯ Moderate	646	627	-	The mean WAZ score was **-1.60**	MD **0.12 WAZ score higher** (0.01 higher to 0.23 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Placebo	Vitamin D		Risk with placebo	Risk difference with vitamin D
WAZ scores at 3 to 6 years of age											
912 (1 RCT)	not serious	serious[e]	not serious	serious[e]	none	⨁⨁◯◯ Low	466	446	-	The mean WAZ score was **-1.90**	MD **0.07 WAZ score lower** (0.18 lower to 0.04 higher)
Length/height-for-age z scores (LAZ/HAZ) at 6 months of age											
1258 (1 RCT)	not serious	serious[d]	not serious	not serious	none	⨁⨁⨁◯ Moderate	638	620	-	The mean LAZ/HAZ score was **-1.95**	MD **0.12 LAZ/HAZ score higher** (0.03 higher to 0.21 higher)
LAZ/HAZ scores at 3 to 6 years of age											
912 (1 RCT)	not serious	serious[e]	not serious	serious[e]	none	⨁⨁◯◯ Low	466	446	-	The mean LAZ/HAZ score was **-1.85**	MD **0.07 LAZ/HAZ score higher** (0.05 lower to 0.19 higher)
Head circumference-for-age z scores (HCAZ) at 6 months of age											
1259 (1 RCT)	not serious	serious[c]	not serious	serious[c]	none	⨁⨁◯◯ Low	642	617	-	The mean HCAZ score was **-0.77**	MD **0.08 HCAZ score lower** (0.17 lower to 0.01 higher)
Cognitive impairment[#] at 104 weeks; assessed with BSID III											
70 (1 RCT)	very serious[f]	serious[f]	not serious	serious[f]	none	⨁◯◯◯ Very low	11/28 (39.3%)	14/42 (33.3%)	**RR 0.85** (0.45 to 1.59)	393 per 1000	**59 fewer per 1000** (from 216 fewer to 232 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Placebo	Vitamin D		Risk with placebo	Risk difference with vitamin D
Neurodevelopmental impairment^ at 104 weeks; assessed with BSID III and Gross Motor Function Classification System (GMFCS)											
71 (1 RCT)	very serious[f]	serious[f]	not serious	serious[f]	none	⨁◯◯◯ Very low	15/28 (53.6%)	16/43 (37.2%)	**RR 0.69** (0.41 to 1.17)	536 per 1000	**166 fewer per 1000** (from 316 fewer to 91 more)
Serum alkaline phosphatase§ (IU/l) at 6 months											
265 (1 RCT)	serious[c]	serious[c]	not serious	serious[c]	none	⨁◯◯◯ Very low	8/131 (6.1%)	3/134 (2.2%)	**RR 0.37** (0.10 to 1.36)	61 per 1000	**38 fewer per 1000** (from 55 fewer to 22 more)
Vitamin D deficiency* at latest follow-up (6 months)											
504 (2 RCTs)	serious[g]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	183/258 (70.9%)	97/246 (39.4%)	**RR 0.58** (0.49 to 0.68)	709 per 1000	**298 fewer per 1000** (from 362 fewer to 227 fewer)
Hospitalization by latest follow-up (6 months)											
1468 (2 RCTs)	serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	109/740 (14.7%)	105/728 (14.4%)	**RR 0.84** (0.42 to 1.66)	147 per 1000	**24 fewer per 1000** (from 85 fewer to 97 more)

BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CI: confidence interval; GMFCS: Gross Motor Function Classification System; HCAZ: head circumference-for-age z scores; IQR: interquartile range; IU: international unit; LAZ/HAZ: length/height-for-age z scores; MD: mean difference; RCT: randomized controlled trial; RDS: respiratory distress syndrome; RR: relative risk; WAZ: weight-for-age z score

* Any (at least one) serious morbidity assessed with: any severe morbidity (hospital admission or outpatient visits with diagnoses selected based on clinical judgment that represented severe illness: pneumonia, persistent diarrhoea, dysentery, severe fever, severe protein energy malnutrition, ear infections, meningitis and septicaemia), RDS, early-onset sepsis (≤ 72 hours), late-onset sepsis (> 72 hours) and culture-positive meningitis

Cognitive impairment was defined as a cognitive composite score on the BSID-III of < 85

^ Neurodevelopmental impairment assessed as any of the following: a cognitive composite score on the BSID-III of < 85, moderate or severe cerebral palsy with a GMFCS score of 2 or higher, hearing impairment, bilateral visual impairment
§ Serum alkaline phosphatase (ALP) assessed by level > 500 U/L
ᵗ Vitamin D deficiency assessed by level < 20 µg/ml

Explanations
[a] Downgraded by two levels: serious risk of bias; serious imprecision (wide CI)
[b] Downgraded by three levels: serious risk of bias; serious inconsistency (high heterogeneity); serious imprecision (wide CI)
[c] Downgraded by three levels: serious risk of bias; serious inconsistency (small number of studies); serious imprecision (wide CI)
[d] Downgraded by one level: serious inconsistency (small number of studies)
[e] Downgraded by two levels: serious inconsistency (small number of studies); serious imprecision (wide CI)
[f] Downgraded by three levels: very serious risk of bias; serious inconsistency (small number of studies); serious imprecision (wide CI)
[g] Downgraded by one level: serious risk of bias

GRADE Table A10d: Comparison – Vitamin A supplementation versus no vitamin A supplementation

Source: Manapurath RM, Kumar M, Pathak BG, Chowdhury R, Sinha B, Choudhary T, et al. Enteral low-dose vitamin A supplementation in preterm or low birth weight infants to prevent morbidity and mortality: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092L.

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With low dose vitamin A supplementation	Relative risk (RR) (95% CI)	Risk with placebo	Risk difference with low dose vitamin A supplementation
Mortality by latest follow-up (mean: 10.3 weeks)											
800 (4 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	61/399 (15.3%)	45/401 (11.2%)	**RR 0.74** (0.53 to 1.02)	153 per 1000	**40 fewer per 1000** (from 72 fewer to 3 more)
Sepsis by latest follow-up (mean: 12.3 weeks)											
646 (3 RCTs)	serious[b]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	63/322 (19.6%)	54/324 (16.7%)	**RR 0.87** (0.64 to 1.19)	196 per 1000	**25 fewer per 1000** (from 70 fewer to 37 more)
Bronchopulmonary dysplasia at latest follow-up (mean: 11.75 weeks)											
746 (4 RCTs)	not serious	serious[c]	not serious	serious[c]	none	⨁⨁◯◯ Low	125/370 (33.8%)	103/376 (27.4%)	**RR 0.77** (0.50 to 1.16)	338 per 1000	**78 fewer per 1000** (from 169 fewer to 54 more)
Retinopathy of prematurity at latest follow-up (mean: 11.75 weeks)											
742 (4 RCTs)	not serious	serious[c]	not serious	serious[c]	none	⨁⨁◯◯ Low	64/368 (17.4%)	50/374 (13.4%)	**RR 0.69** (0.37 to 1.30)	174 per 1000	**54 fewer per 1000** (from 110 fewer to 52 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							With placebo	With low dose vitamin A supplementation		Risk with placebo	Risk difference with low dose vitamin A supplementation
Patent ductus arteriosus at latest follow-up (mean: 7 weeks)											
350 (2 RCTs)	not serious	serious[c]	not serious	serious[c]	none	⨁⨁◯◯ Low	36/175 (20.6%)	24/175 (13.7%)	**RR 0.66** (0.21 to 2.06)	206 per 1000	**70 fewer per 1000** (from 163 fewer to 218 more)
Seizures at latest follow-up (10 weeks)											
154 (1 RCT)	not serious	serious[d]	not serious	serious[d]	none	⨁⨁◯◯ Low	20/77 (26.0%)	15/77 (19.5%)	**RR 0.82** (0.54 to 1.25)	260 per 1000	**47 fewer per 1000** (from 119 fewer to 65 more)
Pulmonary haemorrhage at latest follow-up (10 weeks)											
154 (1 RCT)	not serious	serious[d]	not serious	serious[d]	none	⨁⨁◯◯ Low	11/77 (14.3%)	5/77 (6.5%)	**RR 0.60** (0.30 to 1.21)	143 per 1000	**57 fewer per 1000** (from 100 fewer to 30 more)
Pneumothorax at latest follow-up (10 weeks)											
154 (1 RCT)	not serious	serious[d]	not serious	serious[d]	none	⨁⨁◯◯ Low	17/77 (22.1%)	11/77 (14.3%)	**RR 0.75** (0.46 to 1.21)	221 per 1000	**55 fewer per 1000** (from 119 fewer to 46 more)
Necrotizing enterocolitis at latest follow-up (mean: 12.33 weeks)											
604 (3 RCTs)	serious[e]	serious[e]	not serious	serious[e]	none	⨁◯◯◯ Very low	20/301 (6.6%)	20/303 (6.6%)	**RR 1.05** (0.71 to 1.57)	66 per 1000	**3 more per 1000** (from 19 fewer to 38 more)

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With low dose vitamin A supplementation	Relative risk (RR) (95% CI)	Risk with placebo	Risk difference with low dose vitamin A supplementation
Periventricular leukomalacia at latest follow-up (17 weeks)											
262 (1 RCT)	not serious	serious[d]	not serious	serious[d]	none	⨁⨁◯◯ Low	27/130 (20.8%)	18/132 (13.6%)	**RR 0.66** (0.38 to 1.14)	208 per 1000	**71 fewer per 1000** (from 129 fewer to 29 more)
Intraventricular haemorrhage at latest follow-up latest (mean: 13.5 weeks)											
450 (2 RCTs)	serious[e]	serious[e]	not serious	serious[e]	none	⨁◯◯◯ Very low	12/224 (5.4%)	12/226 (5.3%)	**RR 1.00** (0.46 to 2.17)	54 per 1000	**0 fewer per 1000** (from 29 fewer to 63 more)
Weight (kg) at latest follow-up (discharge or 16 weeks)											
188 (1 RCT)	not serious	serious[d]	not serious	serious[d]	none	⨁⨁◯◯ Low	94	94	-	The mean weight was **3.08** kg	MD **0.02 kg more** (0.2 fewer to 0.24 more)
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Length of hospital stay											
450 (2 RCTs)	not serious	serious[f]	not serious	very serious[f]	none	⨁◯◯◯ Very low	224	226	-	The mean length of stay ranged from **43.40 to 105.17** days	MD **8.76 days fewer** (32.1 fewer to 14.58 more)

Certainty assessment							Summary of findings				
							No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With low dose vitamin A supplementation		Risk with placebo	Risk difference with low dose vitamin A supplementation
Serum retinol concentration (ug/ml) at latest follow-up (8 weeks)											
36 (1 RCT)	not serious	serious[g]	not serious	serious[g]	none	⨁⨁◯◯ Low	18	18	-	The mean concentration was **16.4** µg/ml	MD **4.7 µg/ml higher** (1.2 higher to 8.2 higher)

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious imprecision (wide CI)

[b] Downgraded by two levels: serious risk of bias; serious imprecision (wide CI)

[c] Downgraded by two levels: serious inconsistency (high heterogeneity); serious imprecision (wide CI)

[d] Downgraded by two levels: serious inconsistency (small number of studies); serious imprecision (wide CI)

[e] Downgraded by three levels: serious risk of bias; serious inconsistency (high heterogeneity); serious imprecision (wide CI)

[f] Downgraded by three levels: serious inconsistency (high heterogeneity); very serious imprecision (suboptimal sample size, wide CI)

[g] Downgraded by two levels: serious inconsistency (small number of studies); serious imprecision (suboptimal sample size)

GRADE Table A.10e: Comparison – Calcium and phosphorous supplementation versus no calcium or phosphorous supplementation

Source: Kumar M, Chowdhury R, Sinha B, Upadhyay RP, Chandola TR, Mazumder S, et al. Enteral calcium or phosphorus supplementation in preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092M.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No supplementation	$CaPO_4$ supplementation		Risk with no supplementation	Risk difference with $CaPO_4$ supplementation
Weight (g) at latest follow-up (6 weeks)											
40 (1 RCT)	very serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	20	20	-	The mean weight was **2483.00** g	MD **138.50 g more** (82.16 fewer to 359.16 more)
Length (cm) at latest follow-up (6 weeks)											
40 (1 RCT)	very serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	20	20	-	The mean length was **47.04** cm	MD **0.77 cm more** (0.92 fewer to 2.46 more)
Head circumference (cm) at latest follow-up (6 weeks)											
40 (1 RCT)	very serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	20	20	-	The mean head circumference was **34.31** cm	MD **0.33 cm more** (0.3 fewer to 0.96 more)
Serum alkaline phosphatase (IU/L) at latest follow-up (median 55 [IQR 6 to 104] weeks)											
122 (2 RCTs)	very serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	71	51	-	The mean serum alkaline phosphatase ranged from **539.85 to 772.4** IU/L	MD **126.11 IU/L lower** (298.5 lower to 46.27 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No supplementation	$CaPO_4$ supplementation		Risk with no supplementation	Risk difference with $CaPO_4$ supplementation
Serum calcium (mg/dl) at latest follow-up (6 weeks)											
40 (1 RCT)	very serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	20	20	-	The mean serum calcium was **8.39** mg/dl	MD **0.54 mg/dl higher** (0.19 lower to 1.27 higher)
Serum phosphorus (IU) at latest follow-up (6 weeks)											
40 (1 RCT)	very serious[a]	serious[a]	not serious	serious[a]	none	⨁◯◯◯ Very low	20	20	-	The mean serum phosphorus was **4.36** IU	MD **0.07 IU higher** (0.22 lower to 0.36 higher)
Osteopenia/rickets at latest follow-up (median 6 [IQR 5 to 104] weeks)											
159 (3 RCTs)	serious[c]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	47/87 (54.0%)	21/72 (29.2%)	**RR 0.68** (0.46 to 0.99)	540 per 1000	**173 fewer per 1000** (from 292 fewer to 5 fewer)

CI: confidence interval; IQR: interquartile range; IU: international units; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by three levels: very serious risk of bias; serious inconsistency (small number of studies); serious imprecision (wide CI)

[b] Downgraded by three levels: very serious risk of bias; serious inconsistency (high heterogeneity [I^2 = 73.42%]); serious imprecision (wide CI)

[c] Downgraded by two levels: serious risk of bias; serious imprecision (suboptimal sample size)

GRADE Table A.10f: Comparison – Multiple micronutrient (MMN) supplementation versus no MMN supplementation

Source: Kumar M, Chowdhury R, Sinha B, Upadhyay RP, Chandola TR, Mazumder S, et al. Enteral multiple micronutrient supplementation in preterm and low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092N.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No MMN supplementation	MMN supplementation		Risk with no MMN supplementation	Risk difference with MMN supplementation
Wasting at latest follow-up (median 91 [IQR 78 to 104] weeks)											
398 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	26/202 (12.9%)	22/196 (11.2%)	**RR 0.86** (0.50 to 1.48)	129 per 1000	**18 fewer per 1000** (from 64 fewer to 62 more)
Stunting at latest follow-up (median 91 [IQR 78 to 104] weeks)											
399 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	46/203 (22.7%)	54/196 (27.6%)	**RR 1.17** (0.83 to 1.66)	227 per 1000	**39 more per 1000** (from 39 fewer to 150 more)
Underweight at latest follow-up (median 91 [IQR 78 to 104] weeks)											
396 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	36/201 (17.9%)	48/195 (24.6%)	**RR 1.22** (0.85 to 1.76)	179 per 1000	**39 more per 1000** (from 27 fewer to 136 more)
Change in weight-for-height z scores (WHZ) between baseline (median 7 [IQR 6 to 8] weeks) and endline (median 91 [IQR 78 to 104] weeks)											
358 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	188	170	-	The mean change in WHZ score ranged from **-0.76 to -0.55** points	MD **0.01 WHZ points lower** (0.31 lower to 0.29 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No MMN supplementation	MMN supplementation		Risk with no MMN supplementation	Risk difference with MMN supplementation
Change in height-for-age z scores (HAZ) between baseline (median 7 [IQR 6 to 8] weeks) and endline (median 91 [IQR 78 to 104] weeks)											
372 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	193	179	-	The mean change in HAZ score ranged from **-0.35 to -0.26** points	MD **0.07 HAZ points higher** (0.19 lower to 0.33 higher)
Change in weight-for-age z scores (WAZ) between baseline (median 7 [IQR 6 to 8] weeks) and endline (median 91 [IQR 78 to 104] weeks)											
383 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	198	185	-	The mean change in WAZ score ranged from **-0.38 to -0.21** points	MD **0.05 WAZ points higher** (0.2 lower to 0.3 higher)
WHZ scores at latest follow-up (median [IQR]: 91 [78 to 104] weeks)											
385 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	199	186	-	The mean WHZ score ranged from **-0.96 to -0.41** points	MD **0.04 WHZ points lower** (0.3 lower to 0.22 higher)
HAZ scores at latest follow-up (median [IQR]: 91 [78 to 104] weeks)											
392 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	201	191	-	The mean HAZ score ranged from **-1.40 to -1.19** points	MD **0.06 HAZ points lower** (0.28 lower to 0.17 higher)
WAZ scores at latest follow-up (median [IQR]: 91 [78 to 104] weeks)											
392 (2 RCTs)	serious[a]	not serious	not serious	serious[a]	none	⨁⨁◯◯ Low	201	191	-	The mean WAZ score ranged from **-1.98 to -0.91** points	MD **0.01 WAZ points lower** (0.27 lower to 0.25 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No MMN supplementation	MMN supplementation		Risk with no MMN supplementation	Risk difference with MMN supplementation
Cognition at latest follow-up (78 weeks); assessed with BSID-III											
27 (1 RCT)	very serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	17	10	-	The mean BSID-III score was **47.76** points	MD **2.64 points higher** (0.48 lower to 5.76 higher)
Receptive language at latest follow-up (78 weeks); assessed with BSID-III											
27 (1 RCT)	very serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	17	10	-	The mean BSID-III score was **17.71** points	MD **1.19 points higher** (0.33 lower to 2.71 higher)
Expressive language at latest follow-up (78 weeks); assessed with BSID-III											
27 (1 RCT)	very serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	17	10	-	The mean BSID-III score was **18.76** points	MD **0.94 points higher** (1.13 lower to 3.01 higher)
Fine motor at latest follow-up (78 weeks); assessed with BSID-III											
27 (1 RCT)	very serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	17	10	-	The mean BSID-III score was **33.47** points	MD **1.03 points higher** (1.13 lower to 3.19 higher)
Gross motor at latest follow-up (78 weeks); assessed with BSID-III											
27 (1 RCT)	very serious[b]	serious[b]	not serious	serious[b]	none	⨁◯◯◯ Very low	17	10	-	The mean BSID-III score was **46.76** points	MD **1.14 points higher** (0.56 lower to 2.84 higher)

BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CI: confidence interval; HAZ: height-for-age z score; IQR: interquartile range; MD: mean difference; RCT: randomized controlled trial; RR: relative risk; WAZ: weight-for-age z score; WHZ: weight-for-height z score

Explanations

[a] Downgraded by two levels: serious risk of bias; serious imprecision (wide CI)

[b] Downgraded by three levels: very serious risk of bias; serious inconsistency (only 1 study so inconsistency could not be assessed); very serious imprecision (wide CI, suboptimal sample size)

A.11. Probiotics

GRADE Table A.11: Comparison – Any probiotics versus no probiotics

Source: Sharif S, Meader N, Oddie SJ, Rojas-Reyes MX, McGuire W. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2020;(10):CD005496. doi:10.1002/14651858.CD005496.pub5.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No probiotics	Probiotics		Risk with no probiotics	Risk difference with probiotics
Mortality at hospital discharge											
10 170 (51 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	322/4990 (6.5%)	250/5180 (4.8%)	**RR 0.76** (0.65 to 0.89)	65 per 1000	**15 fewer per 1000** (from 23 fewer to 7 fewer)
Necrotizing enterocolitis at hospital discharge											
10 604 (54 RCTs)	serious[a]	not serious	not serious	not serious	publication bias strongly suspected[b]	⨁⨁◯◯ Low	319/5192 (6.1%)	180/5412 (3.3%)	**RR 0.54** (0.45 to 0.65)	61 per 1000	**28 fewer per 1000** (from 34 fewer to 22 fewer)
Invasive infection at hospital discharge											
9762 (47 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	829/4779 (17.3%)	764/4983 (15.3%)	**RR 0.89** (0.82 to 0.97)	173 per 1000	**19 fewer per 1000** (from 31 fewer to 5 fewer)
Severe neurodevelopmental impairment at 18 months to 3 years of age											
1518 (5 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	145/746 (19.4%)	155/772 (20.1%)	**RR 1.03** (0.84 to 1.26)	194 per 1000	**6 more per 1000** (from 31 fewer to 51 more)

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious risk of bias (serious study limitations due to uncertainty about methods used to generate random sequence, conceal allocation and mask outcome assessment in 12 trials)

[b] Downgraded by one level: serious publication bias (funnel plot asymmetry and statistical evidence consistent with trial size; trials favouring controls missing)

[c] Downgraded by one level: serious imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit)

A.12. Emollients

GRADE Table A.12a: Comparison 1 – Topical oil versus no topical oil

Source: Cleminson J, McGuire W. Topical emollient for preventing infection in preterm infants. Cochrane Database Syst Rev. 2021;(5):CD001150. doi:10.1002/14651858.CD001150.pub4.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No topical oil	Topical oil		Risk with no topical oil	Risk difference with topical oil
Mortality by hospital discharge or latest follow-up											
1119 (11 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	148/583 (25.4%)	123/536 (22.9%)	**RR 0.94** (0.82 to 1.08)	254 per 1000	**15 fewer per 1000** (from 46 fewer to 20 more)
Invasive infection by hospital discharge											
3256 (9 RCTs)	serious[a]	serious[c]	not serious	not serious	none	⨁⨁◯◯ Low	91/1653 (5.5%)	59/1603 (3.7%)	**RR 0.71** (0.52 to 0.96)	55 per 1000	**16 fewer per 1000** (from 26 fewer to 2 fewer)
Necrotizing enterocolitis by hospital discharge											
72 (1 RCT)	serious[d]	serious[h]	not serious	serious[g]	none	⨁◯◯◯ Very low	2/36 (5.6%)	0/36 (0.0%)	**RR 0.20** (0.01 to 4.03)	56 per 1000	**44 fewer per 1000** (from 55 fewer to 168 more)
Bronchopulmonary dysplasia by hospital discharge											
72 (1 RCT)	serious[d]	serious[h]	not serious	serious[g]	none	⨁◯◯◯ Very low	15/36 (41.7%)	14/36 (38.9%)	**RR 0.93** (0.53 to 1.64)	417 per 1000	**29 fewer per 1000** (from 196 fewer to 267 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No topical oil	Topical oil		Risk with no topical oil	Risk difference with topical oil
Retinopathy of prematurity by hospital discharge											
72 (1 RCT)	serious[d]	serious[h]	not serious	serious [g]	none	⨁◯◯◯ Very low	4/36 (11.1%)	4/36 (11.1%)	**RR 1.00** (0.27 to 3.69)	111 per 1000	**0 fewer per 1000** (from 81 fewer to 299 more)
Rate of weight gain (g/kg per day) by hospital discharge											
433 (7 RCTs)	serious[d]	serious[e]	not serious	not serious	none	⨁⨁◯◯ Low	227	206	-	The mean rate of weight gain ranged from **6.6 to 14.9** g/kg per day	MD **2.93 g/kg per day more** (2.11 more to 3.76 more)
Change in crown–heel length (mm/week) by hospital discharge											
358 (6 RCTs)	serious[d]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	191	167	-	The mean change in crown-heel length ranged from **5.6 to 7.7** mm/week	MD **1.34 mm/week more** (0.2 more to 2.47 more)
Change in head circumference (mm/week) by hospital discharge											
358 (6 RCTs)	serious[d]	not serious	not serious	serious[f]	none	⨁⨁◯◯ Low	191	167	-	The mean change in head circumference ranged from **4 to 7.2** mm/week	MD **0.66 mm/week higher** (0.54 lower to 1.85 higher)
Moderate to severe cognitive developmental delay at 24 months of age											
51 (1 RCT)	serious[d]	serious[h]	not serious	serious [g]	none	⨁◯◯◯ Very low	7/24 (29.2%)	2/27 (7.4%)	**RR 0.25** (0.06 to 1.11)	292 per 1000	**219 fewer per 1000** (from 274 fewer to 32 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No topical oil	Topical oil		Risk with no topical oil	Risk difference with topical oil
Moderate to severe language developmental delay at 24 months of age											
51 (1 RCT)	serious[d]	serious[h]	not serious	serious [g]	none	⨁◯◯◯ Very low	11/24 (45.8%)	6/27 (22.2%)	**RR 0.48** (0.21 to 1.11)	458 per 1000	**238 fewer per 1000** (from 362 fewer to 50 more)
Moderate to severe motor developmental delay at 24 months of age											
51 (1 RCT)	serious[d]	serious[h]	not serious	serious [g]	none	⨁◯◯◯ Very low	7/24 (29.2%)	2/27 (7.4%)	**RR 0.25** (0.06 to 1.11)	292 per 1000	**219 fewer per 1000** (from 274 fewer to 32 more)
Moderate to severe socio-emotional developmental delay at 24 months of age											
51 (1 RCT)	serious[d]	serious[h]	not serious	serious [g]	none	⨁◯◯◯ Very low	6/24 (25.0%)	2/27 (7.4%)	**RR 0.30** (0.07 to 1.33)	250 per 1000	**175 fewer per 1000** (from 232 fewer to 83 more)

BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious risk of bias (unclear random sequence generation or allocation concealment; caregivers and investigators not masked in any trials)

[b] Downgraded by one level: inconsistency (there was evidence of unexplained moderate heterogeneity in this meta-analysis, $I^2 = 52\%$)

[c] Downgraded by one level: imprecision (95% CI 0.82 to 1.08, consistent with potentially important benefit or harm)

[d] Downgraded by one level: serious risk of bias (caregivers and investigators not masked in any trials)

[e] Downgraded by one level: inconsistency (there was evidence of unexplained moderate heterogeneity in this meta-analysis, $I^2 = 62\%$)

[f] Downgraded by one level: imprecision (95% CI -0.54 to 1.85, consistent with potentially important benefit or harm)

[g] Downgraded by one level: imprecision (very small sample size)

[h] Downgraded by one level: inconsistency cannot be assessed (single study)

GRADE Table A.12b: Comparison 2 – Topical ointment or cream versus no topical ointment or cream

Source: Cleminson J, McGuire W. Topical emollient for preventing infection in preterm infants. Cochrane Database Syst Rev. 2021;(5):CD001150. doi:10.1002/14651858.CD001150.pub4.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants (%)		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No topical ointment or cream	Topical ointment or cream		Risk with no topical ointment or cream	Risk difference with topical ointment or cream
Mortality by hospital discharge											
2067 (7 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	205/1011 (20.3%)	167/1056 (15.8%)	**RR 0.87** (0.75 to 1.03)	203 per 1000	**26 fewer per 1000** (from 51 fewer to 6 more)
Invasive infection by hospital discharge											
2086 (8 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	232/1019 (22.8%)	263/1067 (24.6%)	**RR 1.13** (0.97 to 1.31)	228 per 1000	**30 more per 1000** (from 7 fewer to 71 more)
Necrotizing enterocolitis by hospital discharge											
1472 (4 RCTs)	serious[d]	not serious	not serious	serious[e]	none	⨁⨁◯◯ Low	53/731 (7.3%)	67/741 (9.0%)	**RR 1.25** (0.89 to 1.76)	73 per 1000	**18 more per 1000** (from 8 fewer to 55 more)
Bronchopulmonary dysplasia by hospital discharge											
1009 (2 RCTs)	serious[d]	not serious	not serious	serious[f]	none	⨁⨁◯◯ Low	244/508 (48.0%)	241/501 (48.1%)	**RR 1.00** (0.88 to 1.14)	480 per 1000	**0 fewer per 1000** (from 58 fewer to 67 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants (%)		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							No topical ointment or cream	Topical ointment or cream		Risk with no topical ointment or cream	Risk difference with topical ointment or cream
Retinopathy of prematurity by hospital discharge											
952 (1 RCT)	serious[d]	serious[g]	not serious	serious[h]	none	⨁◯◯◯ Very low	96/477 (20.1%)	95/475 (20.0%)	**RR 0.99** (0.77 to 1.28)	201 per 1000	**2 fewer per 1000** (from 46 fewer to 56 more)
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious risk of bias (unclear random sequence generation in many trials; caregivers and investigators not masked in any trials). In one trial (Darmstadt, 2005), there was a disruption in the method of the randomization process, which may have contributed to an unequal distribution of infants between groups.

[b] Downgraded by one level: imprecision (95% CI 0.75 to 1.03, consistent with no effect or substantial benefit)

[c] Downgraded by one level: imprecision (95% CI 0.97 to 1.31, consistent with no effect or substantial harm)

[d] Downgraded by one level: serious risk of bias (caregivers and investigators not masked in any trials)

[e] Downgraded by one level: imprecision (95% CI 0.89 to 1.76, consistent with no effect or substantial harm)

[f] Downgraded by one level: imprecision (95% CI 0.88 to 1.14, consistent with no effect or substantial harm)

[g] Downgraded by one level: inconsistency (cannot be assessed – single study)

[h] Downgraded by one level: imprecision (95% CI 0.77 to 1.28, consistent with no effect or substantial harm)

B. Care for complications

B.1. Continuous positive airway pressure (CPAP) for respiratory distress syndrome

GRADE Table B.1a: Comparison 1 – Any CPAP for versus supplemental oxygen

Source: Ho JJ, Subramaniam P, Davis PG. Continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev. 2020;(10):CD002271. doi:10.1002/14651858.CD002271.pub3.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Supplemental oxygen	Any CPAP		Risk with supplemental oxygen	Risk difference with CPAP
Mortality by hospital discharge											
322 (5 RCTs)	serious[a,b]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	38/162 (23.5%)	20/160 (12.5%)	**RR 0.53** (0.34 to 0.83)	235 per 1000	**110 fewer per 1000** (from 155 fewer to 40 fewer)
Use of mechanical ventilation by hospital discharge											
233 (3 RCTs)	serious[c]	serious[d]	serious[e]	serious[f]	none	⊕◯◯◯ Very low	59/120 (49.2%)	38/113 (33.6%)	**RR 0.72** (0.54 to 0.96)	492 per 1000	**138 fewer per 1000** (from 226 fewer to 20 fewer)
Treatment failure (death or use of additional ventilatory support) by hospital discharge											
322 (5 RCTs)	serious[c]	serious[d]	serious[a]	serious[b]	none	⊕◯◯◯ Very low	84/162 (51.9%)	51/160 (31.9%)	**RR 0.64** (0.50 to 0.82)	519 per 1000	**187 fewer per 1000** (from 259 fewer to 93 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Supplemental oxygen	Any CPAP		Risk with supplemental oxygen	Risk difference with CPAP
Pneumothorax by hospital discharge											
270 (4 RCTs)	not serious	not serious	serious[a]	serious[b]	none	⨁⨁◯◯ Low	8/139 (5.8%)	18/131 (13.7%)	**RR 2.48** (1.16 to 5.30)	58 per 1000	**85 more per 1000** (from 9 more to 247 more)
Bronchopulmonary dysplasia (oxygen dependency at 28 days)											
209 (2 RCTs)	not serious	not serious	serious[a]	very serious[g]	none	⨁◯◯◯ Very low	6/108 (5.6%)	5/101 (5.0%)	**RR 1.04** (0.35 to 3.13)	56 per 1000	**2 more per 1000** (from 36 fewer to 118 more)
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; CPAP: continuous positive airway pressure; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: three of four studies performed in the pre-surfactant era

[b] Downgraded by one level: serious imprecision (data derived from four small studies)

[c] Downgraded by one level: serious risk of bias (lack of blinding of the intervention for a subjective outcome)

[d] Downgraded by one level: moderate heterogeneity

[e] Downgraded by one level: serious indirectness (two of three studies performed in pre-surfactant era)

[f] Downgraded by one level: serious imprecision (evidence derived from three small studies)

[g] Downgraded by two levels: very serious imprecision

GRADE Table B.1b: Comparison 2 – Early versus delayed CPAP

Source: Ho JJ, Subramaniam P, Sivakaanthan A, Davis PG. Early versus delayed continuous positive airway pressure (CPAP) for respiratory distress in preterm infants. Cochrane Database Syst Rev. 2020;(10):CD002975. doi:10.1002/14651858.CD002975.pub2.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Delayed CPAP	Early CPAP		Risk with delayed CPAP	Risk difference with early CPAP
Mortality by hospital discharge											
119 (4 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	11/67 (16.4%)	9/52 (17.3%)	**RR 0.93** (0.43 to 2.03)	164 per 1000	**11 fewer per 1000** (from 94 fewer to 169 more)
Use of mechanical ventilation by hospital discharge											
119 (4 RCTs)	very serious[c]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	20/67 (29.9%)	13/52 (25.0%)	**RR 0.77** (0.43 to 1.38)	299 per 1000	**69 fewer per 1000** (from 170 fewer to 113 more)
Treatment failure (death or use of additional ventilatory support) – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Pneumothorax by hospital discharge											
98 (2 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	7/56 (12.5%)	6/42 (14.3%)	**RR 1.09** (0.39 to 3.04)	125 per 1000	**11 more per 1000** (from 76 fewer to 255 more)
Bronchopulmonary dysplasia at 36 weeks postmenstrual age											
29 (1 RCT)	not serious	not serious	not serious	extremely serious[b,d]	none	⨁◯◯◯ Very low	1/17 (5.9%)	1/12 (8.3%)	**RR 1.42** (0.10 to 20.49)	59 per 1000	**25 more per 1000** (from 53 fewer to 1000 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Delayed CPAP	Early CPAP		Risk with delayed CPAP	Risk difference with early CPAP
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; CPAP: continuous positive airway pressure; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious risk of bias (concerns about selection bias)

[b] Downgraded by one level: imprecision; concerns about indirectness also taken into account

[c] Downgraded by two levels: risk of bias (selection bias and performance bias)

[d] Downgraded by two levels: very serious imprecision (very wide CIs in the effect estimate: the true effect is likely to be substantially different from the estimate of effect)

B.2. Continuous positive airway pressure (CPAP) immediately after birth

GRADE Table B.2a: Comparison 1 – Immediate CPAP versus supplemental oxygen

Source: Subramaniam P, Ho JJ, Davis PG. Prophylactic or very early initiation of continuous positive airway pressure (CPAP) for preterm infants. Cochrane Database Syst Rev. 2021;(10):CD001243. doi:10.1002/14651858.CD001243.pub4.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Supplemental oxygen	Immediate CPAP		Risk with supplemental oxygen	Risk difference with immediate CPAP
Mortality by hospital discharge											
765 (4 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	19/378 (5.0%)	22/387 (5.7%)	**RR 1.09** (0.60 to 1.96)	50 per 1000	**5 more per 1000** (from 20 fewer to 48 more)
Death or bronchopulmonary dysplasia by hospital discharge											
256 (1 RCT)	not serious	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low	24/125 (19.2%)	18/131 (13.7%)	**RR 0.69** (0.40 to 1.19)	192 per 1000	**60 fewer per 1000** (from 115 fewer to 36 more)
Treatment failure by hospital discharge											
765 (4 RCTs)	serious[c]	serious[d]	not serious	serious[a]	none	⨁◯◯◯ Very low	148/378 (39.2%)	93/387 (24.0%)	**RR 0.60** (0.49 to 0.74)	392 per 1000	**157 fewer per 1000** (from 200 fewer to 102 fewer)
Bronchopulmonary dysplasia at 36 weeks postmenstrual age											
683 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	42/339 (12.4%)	34/344 (9.9%)	**RR 0.76** (0.51 to 1.14)	124 per 1000	**30 fewer per 1000** (from 61 fewer to 17 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Supplemental oxygen	Immediate CPAP		Risk with supplemental oxygen	Risk difference with immediate CPAP
Pneumothorax by hospital discharge											
568 (3 RCTs)	not serious	not serious	not serious	very serious[e]	none	⨁⨁◯◯ Low	14/279 (5.0%)	11/289 (3.8%)	**RR 0.75** (0.35 to 1.61)	50 per 1000	**13 fewer per 1000** (from 33 fewer to 31 more)
Intraventricular haemorrhage grades 3 or 4 by hospital discharge											
486 (2 RCTs)	not serious	not serious	not serious	very serious[e]	none	⨁⨁◯◯ Low	9/240 (3.8%)	9/246 (3.7%)	**RR 0.96** (0.39 to 2.37)	38 per 1000	**2 fewer per 1000** (from 23 fewer to 51 more)

Note: Treatment failure = recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation
CI: confidence interval; CPAP: continuous positive airway pressure; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious imprecision (95% CI includes both potential benefit and potential harm)

[b] Downgraded by two levels: very serious imprecision (wide 95% CI including both potential benefit and potential harm, as well as failure to meet the optimal information size [1 study had < 400 participants])

[c] Downgraded by one level: serious risk of bias (no blinding of intervention or outcome assessment)

[d] Downgraded by one level: serious inconsistency (considerable unexplained heterogeneity across included studies, $I^2 = 70\%$)

[e] Downgraded by two levels: very serious imprecision (extremely wide 95% CI including both potential benefit and potential harm)

GRADE Table B.2b: Comparison 2 – Immediate CPAP versus mechanical ventilation

Source: Subramaniam P, Ho JJ, Davis PG. Prophylactic or very early initiation of continuous positive airway pressure (CPAP) for preterm infants. Cochrane Database Syst Rev. 2021;(10):CD001243. doi:10.1002/14651858.CD001243.pub4.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants: Mechanical ventilation	No. of participants: Immediate CPAP	Relative risk (RR) (95% CI)	Anticipated absolute effects: Risk with mechanical ventilation	Anticipated absolute effects: Risk difference with immediate CPAP
Mortality by hospital discharge											
2358 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	147/1165 (12.6%)	123/1193 (10.3%)	**RR 0.82** (0.66 to 1.03)	126 per 1000	**23 fewer per 1000** (from 43 fewer to 4 more)
Death or bronchopulmonary dysplasia by hospital discharge											
2358 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	547/1165 (47.0%)	495/1193 (41.5%)	**RR 0.89** (0.81 to 0.97)	470 per 1000	**52 fewer per 1000** (from 89 fewer to 14 fewer)
Treatment failure by hospital discharge											
1042 (2 RCTs)	serious[b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	503/512 (98.2%)	257/530 (48.5%)	**RR 0.49** (0.45 to 0.54)	982 per 1000	**501 fewer per 1000** (from 540 fewer to 452 fewer)
Bronchopulmonary dysplasia at 36 weeks postmenstrual age											
2150 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	400/1051 (38.1%)	372/1099 (33.8%)	**RR 0.89** (0.80 to 0.99)	381 per 1000	**42 fewer per 1000** (from 76 fewer to 4 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Mechanical ventilation	Immediate CPAP		Risk with mechanical ventilation	Risk difference with immediate CPAP
Pneumothorax by hospital discharge											
2357 (3 RCTs)	not serious	serious[c]	not serious	serious[a]	none	⨁⨁◯◯ Low	67/1165 (5.8%)	85/1192 (7.1%)	**RR 1.24** (0.91 to 1.69)	58 per 1000	**14 more per 1000** (from 5 fewer to 40 more)
Intraventricular haemorrhage grades 3 or 4 by hospital discharge											
2301 (3 RCTs)	not serious	not serious	not serious	serious[d]	none	⨁⨁⨁◯ Moderate	112/1134 (9.9%)	125/1167 (10.7%)	**RR 1.09** (0.86 to 1.39)	99 per 1000	**9 more per 1000** (from 14 fewer to 39 more)
Neurodevelopmental impairment at 18 to 22 months corrected age											
976 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	53/504 (10.5%)	45/472 (9.5%)	**RR 0.91** (0.62 to 1.32)	105 per 1000	**9 fewer per 1000** (from 40 fewer to 34 more)

Note: Treatment failure = recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation
CI: confidence interval; CPAP: continuous positive airway pressure; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious imprecision (95% CI includes both potential benefit and potential harm)
[b] Downgraded by one level: serious risk of bias (serious study limitations due to lack of blinding of intervention or outcome assessors)
[c] Downgraded by one level: serious heterogeneity
[d] Downgraded by one level: serious imprecision (95% CI includes both potential benefit and potential harm)

B.3. Continuous positive airway pressure (CPAP) pressure source

GRADE Table B.3: Comparison – Bubble CPAP versus other pressure sources

Source: Prakash R, De Paoli AG, Davis PG, Oddie SJ, McGuire W. Bubble devices versus other pressure sources for nasal continuous positive airway pressure in preterm infants. Cochrane Database Syst Rev. 2022 (in press).

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Other CPAP pressure sources	Bubble CPAP		Risk with other CPAP pressure sources	Risk difference with bubble CPAP
Mortality by hospital discharge											
1189 (10 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	46/592 (7.8%)	45/597 (7.5%)	**RR 0.93** (0.64 to 1.36)	78 per 1000	**5 fewer per 1000** (from 28 fewer to 28 more)
Treatment failure by hospital discharge											
1230 (13 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	132/614 (21.5%)	101/616 (16.4%)	**RR 0.76** (0.60 to 0.95)	215 per 1000	**52 fewer per 1000** (from 86 fewer to 11 fewer)
Pneumothorax by hospital discharge											
1340 (14 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	21/667 (3.1%)	15/673 (2.2%)	**RR 0.73** (0.40 to 1.34)	31 per 1000	**9 fewer per 1000** (from 19 fewer to 11 more)
Nasal injury by hospital discharge											
753 (8 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	18/377 (4.8%)	45/376 (12.0%)	**RR 2.29** (1.37 to 3.82)	48 per 1000	**62 more per 1000** (from 18 more to 135 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Other CPAP pressure sources	Bubble CPAP		Risk with other CPAP pressure sources	Risk difference with bubble CPAP
Bronchopulmonary dysplasia (oxygen dependency at 28 days)											
603 (7 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	49/293 (16.7%)	39/310 (12.6%)	**RR 0.76** (0.53 to 1.10)	167 per 1000	**40 fewer per 1000** (from 79 fewer to 17 more)
Neurodevelopmental impairment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; CPAP: continuous positive airway pressure; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: serious risk of bias (serious study design limitations; high risk of bias due to lack of blinding of clinicians and outcome assessment in all trials)

[b] Downgraded by one level: serious imprecision (95% CI around estimate consistent with substantial harm or benefit)

B.4. Methylxanthines for treatment of apnoea

GRADE Table B.4: Comparison – Methylxanthines versus placebo or no methylxanthine treatment

Source: Marques K, Roehr CC, Bruschettini M, Davis PG, Soll R. Methylxanthine for the prevention and treatment of apnea in preterm infants. Cochrane Database Syst Rev. 2022 (in press).

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Placebo or no methylxanthine treatment	Any methylxanthine	Relative risk (RR) (95% CI)	Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Mortality at hospital discharge											
154 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	6/73 (8.2%)	3/81 (3.7%)	**RR 0.49** (0.14 to 1.78)	82 per 1000	**42 fewer per 1000** (from 71 fewer to 64 more)
Apnoeic episodes by hospital discharge											
43 (1 RCT)	serious[a]	not serious	not serious	very serious[b,c]	none	⨁◯◯◯ Very low	9/22 (40.9%)	6/21 (28.6%)	**RR 0.70** (0.30 to 1.62)	409 per 1000	**123 fewer per 1000** (from 286 fewer to 254 more)
Positive-pressure ventilation after institution of treatment by hospital discharge											
192 (5 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	11/92 (12.0%)	3/100 (3.0%)	**RR 0.34** (0.12 to 0.97)	120 per 1000	**79 fewer per 1000** (from 105 fewer to 4 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Placebo or no methylxanthine treatment	Any methylxanthine		Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Supplemental oxygen at 36 weeks postmenstrual age											
805 (1 RCT)	not serious	not serious	not serious	serious[d]	none	⨁⨁⨁◯ Moderate	141/392 (36.0%)	107/413 (25.9%)	**RR 0.72** (0.58 to 0.89)	360 per 1000	**101 fewer per 1000** (from 151 fewer to 40 fewer)
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Death or major neurodevelopmental disability at latest follow up (5 years)											
767 (1 RCT)	not serious	not serious	not serious	serious[d]	none	⨁⨁⨁◯ Moderate	153/367 (41.7%)	141/400 (35.3%)	**RR 0.85** (0.71 to 1.01)	417 per 1000	**63 fewer per 1000** (from 121 fewer to 4 more)

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: risk of bias (lack of blinding)

[b] Downgraded by one level: imprecision (small overall sample size)

[c] Downgraded by one level: imprecision (CI consistent with meaningful harms or benefit)

[d] Downgraded by one level: imprecision (only 1 trial reported, although with adequate sample size)

B.5. Methylxanthines for extubation

GRADE Table B.5: Comparison – Methylxanthines versus placebo or no methylxanthine treatment

Source: Marques K, Roehr CC, Bruschettini M, Davis PG, Soll R. Methylxanthine for the prevention and treatment of apnea in preterm infants. Cochrane Database Syst Rev. 2022 (in press).

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Placebo or no methylxanthine treatment	Any methylxanthine	Relative risk (RR) (95% CI)	Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Death or major neurodevelopmental disability at 5 years											
676 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	189/360 (52.5%)	141/316 (44.6%)	**RR 0.85** (0.73 to 0.99)	525 per 1000	**79 fewer per 1000** (from 142 fewer to 5 fewer)
Failed extubation by hospital discharge											
197 (6 RCTs)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate	45/89 (50.6%)	27/108 (25.0%)	**RR 0.48** (0.32 to 0.71)	506 per 1000	**263 fewer per 1000** (from 344 fewer to 147 fewer)
Supplemental oxygen at 36 weeks postmenstrual age											
704 (2 RCTs)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate	224/368 (60.9%)	165/336 (49.1%)	**RR 0.81** (0.70 to 0.92)	609 per 1000	**116 fewer per 1000** (from 183 fewer to 49 fewer)
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: imprecision (only 1 trial reporting, though with adequate sample size)

[b] Downgraded by one level: imprecision (small overall sample size)

B.6. Methylxanthines for prevention of apnoea

GRADE Table B.6: Comparison – Methylxanthines versus placebo or no methylxanthine treatment

Source: Marques K, Roehr CC, Bruschettini M, Davis PG, Soll R. Methylxanthine for the prevention and treatment of apnea in preterm infants. Cochrane Database Syst Rev. 2022 (in press).

Certainty assessment							Summary of findings				
							No. of participants			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Placebo or no methylxanthine treatment	Any methylxanthine	Relative risk (RR) (95% CI)	Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Mortality by hospital discharge											
129 (3 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	4/63 (6.3%)	11/66 (16.7%)	**RR 2.19** (0.85 to 5.68)	63 per 1000	**76 more per 1000** (from 10 fewer to 297 more)
Apnoeic episodes by hospital discharge											
104 (2 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	32/52 (61.5%)	6/52 (11.5%)	**RR 0.19** (0.09 to 0.41)	615 per 1000	**498 fewer per 1000** (from 560 fewer to 363 fewer)
Positive-pressure ventilation by hospital discharge											
208 (4 RCTs)	not serious	not serious	not serious	very serious[b,c]	none	⨁⨁◯◯ Low	5/104 (4.8%)	7/104 (6.7%)	**RR 1.33** (0.48 to 3.72)	48 per 1000	**16 more per 1000** (from 25 fewer to 131 more)
Supplemental oxygen at 36 weeks postmenstrual age											
541 (3 RCTs)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate	106/263 (40.3%)	88/278 (31.7%)	**RR 0.78** (0.63 to 0.97)	403 per 1000	**89 fewer per 1000** (from 149 fewer to 12 fewer)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Placebo or no methylxanthine treatment	Any methylxanthine		Risk with placebo or no methylxanthine treatment	Risk difference with any methylxanthine
Death or major neurodevelopmental disability at 5 years											
423 (1 RCT)	not serious	not serious	not serious	serious[d]	none	⨁⨁⨁◯ Moderate	88/204 (43.1%)	94/219 (42.9%)	**RR 1.00** (0.80 to 1.24)	431 per 1000	**0 fewer per 1000** (from 86 fewer to 104 more)

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: risk of bias (lack of blinding)

[b] Downgraded by one level: imprecision (small overall sample size)

[c] Downgraded by one level: imprecision (CI consistent with meaningful harms or benefit)

[d] Downgraded by one level: imprecision (only 1 trial reporting, though with adequate sample size)

C. Family involvement and support

C.1. Family involvement in routine care

GRADE Table C.1: Comparison – Family involvement in routine care versus usual hospital care

Source: North K, Whelan R, Folger LV, Lawford H, Olson I, Driker S, et al. Family involvement in the routine care of hospitalized preterm or low birth weight infants: a systematic review and meta-analysis. Pediatrics. 2022;150(Suppl 1). doi:10.1542/peds.2022-057092O.

Certainty assessment							Summary of findings				
							No. of participants		Relative effect (odds ratio [OR]) (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Standard hospital care	Family involvement strategies		Risk with standard hospital care	Risk difference with family involvement strategies
Mortality by hospital discharge											
2378 (4 RCTs)	serious[a]	not serious	not serious	very serious[b]	none	⨁◯◯◯ Very low	18/1184 (1.5%)	22/1194 (1.8%)	**OR 1.05** (0.53 to 2.09)	15 per 1000	**1 fewer per 1000** (from 7 fewer to 16 more)
Infection by hospital discharge											
2843 (6 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	115/1391 (8.3%)	118/1452 (8.1%)	**OR 0.79** (0.53 to 1.16)	83 per 1000	**16 fewer per 1000** (from 37 fewer to 12 more)
Necrotizing enterocolitis by hospital discharge											
2809 (6 RCTs)	not serious	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low	51/1404 (3.6%)	45/1405 (3.2%)	**OR 0.81** (0.46 to 1.44)	30 per 1000	**7 fewer per 1000** (from 19 fewer to 15 more)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative effect (odds ratio [OR]) (95% CI)	Anticipated absolute effects	
							Standard hospital care	Family involvement strategies		Risk with standard hospital care	Risk difference with family involvement strategies
Bronchopulmonary dysplasia by hospital discharge											
3085 (7 RCTs)	not serious	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low	331/1517 (21.8%)	339/1568 (21.6%)	**OR 0.74** (0.53 to 1.03)	218 per 1000	**47 fewer per 1000** (from 89 fewer to 5 more)
Retinopathy of prematurity by hospital discharge											
2552 (8 RCTs)	not serious	serious[d]	not serious	not serious	none	⨁⨁⨁◯ Moderate	147/1208 (12.2%)	105/1343 (7.8%)	**OR 0.52** (0.34 to 0.80)	122 per 1000	**54 fewer per 1000** (from 77 fewer to 22 fewer)
Intraventricular haemorrhage by hospital discharge											
2555 (5 RCTs)	not serious	serious[d]	not serious	very serious[b]	none	⨁◯◯◯ Very low	111/1273 (8.7%)	151/1282 (11.8%)	**OR 0.74** (0.36 to 1.54)	87 per 1000	**21 fewer per 1000** (from 54 fewer to 41 more)
Growth velocity (g/day) by hospital discharge											
2215 (3 RCTs)	serious[a]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	1078	1137	-	The mean growth velocity (g/day) ranged from 23.7 to 36.7 g/day.	MD **2.09 g/day higher** (1.27 higher to 2.91 higher)
Length of hospital stay											
4452 (11 RCTs)	serious[a]	serious[d]	not serious	not serious	none	⨁⨁◯◯ Low	2237	2215	-	The mean length of hospital stay ranged from 13.0 to 62.1 days	MD **2.91 days lower** (5.15 lower to 0.68 lower)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative effect (odds ratio [OR]) (95% CI)	Anticipated absolute effects	
							Standard hospital care	Family involvement strategies		Risk with standard hospital care	Risk difference with family involvement strategies
Any breastfeeding by hospital discharge											
2546 (5 RCTs)	serious[a]	very serious[e]	not serious	not serious	none	⨁◯◯◯ Very low	1072/1370 (78.2%)	951/1176 (80.9%)	**OR 2.60** (0.77 to 8.79)	782 per 1000	**121 more per 1000** (from 48 fewer to 187 more)
Predominant or exclusive breastfeeding by hospital discharge											
1759 (3 RCTs)	very serious[f]	not serious	not serious	not serious	none	⨁⨁◯◯ Low	607/960 (63.2%)	544/799 (68.1%)	**OR 1.34** (1.10 to 1.65)	632 per 1000	**65 more per 1000** (from 22 more to 107 more)
Neurodevelopment at hospital discharge or term corrected age (i.e. 37 weeks postmenstrual age)											
422 (2 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	182	240	-	The mean neurodevelopment was 67.9 to 70.2 points	MD **1.11 points higher** (0.21 higher to 2.01 higher)

CI: confidence interval; OR: odds ratio; RCT: randomized controlled trial

Explanations

[a] Downgraded by one level: serious risk of bias (uncertainty about methods used to generate random sequence, conceal allocation and blind assessments)

[b] Downgraded by two levels: very serious imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit, small sample size, optimal information size not met)

[c] Downgraded by one level: serious imprecision of effect estimate (95% CI around estimate consistent with substantial harm or benefit)

[d] Downgraded by one level: serious inconsistency in effect estimates (moderate heterogeneity; I^2 30–50%)

[e] Downgraded by two levels: very serious inconsistency in effect estimates (high heterogeneity; $I^2 > 50\%$)

[f] Downgraded by two levels: very serious risk of bias (uncertainty about methods used to generate random sequence, conceal allocation, and blind assessments; serious study limitations in most trials)

C.2. Family support

GRADE Table C.2a: Comparison 1 – Education and counselling versus usual care

Source: Bedwell C, Lavender T, Tate N, Danna VA. Interventions to support parents, families and carers in caring for premature or low birth weight (LBW) infants in the home: a systematic review and meta-analysis. medRxiv. 2022:2022.10.25.22281452v1. doi:10.1101/2022.10.25.22281452.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Education and counselling		Risk with usual care	Risk difference with education and counselling
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Morbidity – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Infant weight (g) at 60 days follow-up											
184 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	92	92	-	The mean infant weight was **3315** g	MD **305 g higher** (228 higher to 382 higher)
Infant weight (g) at 120 days follow-up											
57 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	29	28	-	The mean infant weight was **5240** g	MD **410 g higher** (406.03 higher to 414.97 higher)
Infant length (cm) at 60 days follow-up											

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Education and counselling		Risk with usual care	Risk difference with education and counselling
184 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	92	92	-	The mean infant length was **48.7** cm	MD **1.5 cm higher** (1.08 higher to 1.92 higher)
Infant length (cm) at 120 days follow-up											
57 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	29	28	-	The mean infant length was **58.6** cm	MD **1.2 cm higher** (0.2 higher to 2.6 higher)
Motor development at 6 months of age; assessed using BSID-III											
7 (1 RCT)	serious[d]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	4	3	-	-	SMD **0.38 SD higher** (1.15 lower to 1.19 higher)
Cognitive development at 4–6 months of age; assessed with BSID-III											
64 (3 RCTs)	serious[a]	not serious	not serious	serious[c]	none	⨁⨁◯◯ Low	33	31	-	-	SMD **0.67 SD higher** (0.16 higher to 1.17 higher)
Infant temperament at 6 months of age; assessed with Short Temperament Scale											
155 (2 RCTs)	very serious[a,e]	not serious	not serious	serious[c]	none	⨁◯◯◯ Very low	76	79	-	-	SMD **0.26 SD higher** (0.29 lower to 0.81 higher)
Mother–infant interaction at 6 weeks of age; assessed with (Nursing Child Assessment Satellite Training) NCAST– Feeding Scale											

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Education and counselling		Risk with usual care	Risk difference with education and counselling
142 (1 RCT)	serious[f]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	76	66	-	The mean mother-infant interaction score was **62.5** points	MD **1.8 points higher** (0.21 higher to 3.81 higher)
Mother–infant interaction at 3 months of age; assessed with Nursing Child Assessment Teaching Scale (NCATS)											
196 (1 RCT)	serious[d]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	102	94	-	The mean mother-infant interaction score was **37.4** points	MD **0.8 points higher** (0.6 higher to 2.2 higher)
Mother–infant interaction at 6 months of age; assessed with Synchrony Scale											
63 (1 RCT)	serious[d]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	31	32	-	The mean mother-infant interaction score was **0.24** points	MD **21 points higher** (0.11 higher to 0.67 higher)
Mother–infant interaction at 12 months of age; assessed with free-play procedure – high-quality maternal behaviour											
93 (1 RCT)	not serious	serious[b]	not serious	not serious	none	⨁⨁⨁◯ Moderate	46	47	-	The mean mother-infant interaction score was **0.41** points	MD **0.1 points higher** (0.01 lower to 0.21 higher)
Duration of exclusive breastfeeding (weeks)											

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Education and counselling		Risk with usual care	Risk difference with education and counselling
128 (1 RCT)	serious[f]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	64	64	-	The mean duration was **24.2** weeks	MD **2 weeks higher** (5.48 lower to 9.48 higher)
Exclusive breastfeeding at 2–3 months of age											
244 (2 RCTs)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	38/122 (31.1%)	67/122 (54.9%)	**RR 1.71** (1.26 to 2.31)	311 per 1000	**221 more per 1000** (from 81 more to 408 more)

BSID: Bayley Scales of Infant and Toddler Development, third edition; CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SMD: standardized mean difference

Explanations

[a] Downgraded by one level: risk of bias (randomization and allocation concealment not described; blinding of assessors not clear)

[b] Downgraded by one level: heterogeneity (only 1 study so heterogeneity cannot be assessed)

[c] Downgraded by one level: imprecision (due to small sample size, i.e. optimal information size not met [i.e. the total number of patients included is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial])

[d] Downgraded by one level: risk of bias (randomization and allocation concealment not explained; high attrition > 10%)

[e] Downgraded by one level: risk of bias (high attrition > 10%)

[f] Downgraded by one level: risk of bias (unclear if outcome assessors blinded)

GRADE Table C.2b: Comparison 2 – Peer support versus usual care

Source: Bedwell C, Lavender T, Tate N, Danna VA. Interventions to support parents, families and carers in caring for premature or low birth weight (LBW) infants in the home: a systematic review and meta-analysis. medRxiv. 2022:2022.10.25.22281452v1. doi:10.1101/2022.10.25.22281452.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Peer support interventions		Risk with usual care	Risk difference with peer support interventions
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Morbidity – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

GRADE Table C.2c: Comparison 3 – Discharge preparation versus usual care

Source: Bedwell C, Lavender T, Tate N, Danna VA. Interventions to support parents, families and carers in caring for premature or low birth weight (LBW) infants in the home: a systematic review and meta-analysis. medRxiv. 2022:2022.10.25.22281452v1. doi:10.1101/2022.10.25.22281452.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Digital communication		Risk with usual care	Risk difference with digital communication
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Emergency hospital visits by 2 months post-discharge											
173 (1 observational study)	serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	31/85 (36.5%)	20/88 (22.7%)	**RR 0.62** (0.39 to 1.00)	365 per 1000	**139 fewer per 1000** (from 222 fewer to 0 fewer)
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Maternal–infant interaction at 1 month follow-up; assessed with the Mother and Baby Interaction Scale (MABISC)											
129 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	70	59	-	The mean maternal–infant interaction score was **10.5** points	MD **0.8 points lower** (1.84 lower to 0.24 higher)
Maternal–infant interaction at 4-month follow-up; assessed with the Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS)											
85 (1 RCT)	very serious[a,d]	not serious	not serious	serious[c]	none	⨁◯◯◯ Very low	43	42	-	The median maternal–infant interaction score was **9.0** points	MD **0.9 points lower** (2.09 lower to 0.29 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Digital communication		Risk with usual care	Risk difference with digital communication
Exclusive breastfeeding at 1–2 months											
688 (2 RCTs)	serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	207/361 (57.3%)	185/327 (56.6%)	**RR 1.02** (0.89 to 1.16)	573 per 1000	**11 more per 1000** (from 63 fewer to 92 more)

CI: confidence interval; RCT: randomized controlled trial; RR: relative risk

Explanations

[a] Downgraded by one level: risk of bias (unclear if outcome assessors or participants blinded)

[b] Downgraded by one level: heterogeneity (only 1 study so heterogeneity cannot be assessed)

[c] Downgraded by one level: imprecision (small sample size, i.e. optimal information size not met [i.e. the total number of patients included is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial])

[d] Downgraded by one level: risk of bias (lack of adjustment for confounding)

GRADE Table C.2d: Comparison 4 – Digital information systems versus usual care

Source: Bedwell C, Lavender T, Tate N, Danna VA. Interventions to support parents, families and carers in caring for premature or low birth weight (LBW) infants in the home: a systematic review and meta-analysis. medRxiv. 2022:2022.10.25.22281452v1. doi:10.1101/2022.10.25.22281452.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Digital information		Risk with usual care	Risk difference with digital information
Mortality – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Emergency hospital visits up to 2 months post-discharge											
89 (1 RCT)	serious[a]	serious[b]	not serious	serious[c]	none	⊕◯◯◯ Very low	Usual care: median 1 (range 0–6) Digital communication intervention: median 1 (range 0–7)				
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Neurodevelopment – not measured											
-	-	-	-	-	-	-	-	-	-	-	-

CI: confidence interval; RCT: randomized controlled trial

Explanations

[a] Downgraded one level: risk of bias (unclear if outcome assessors or participants blinded)

[b] Downgraded one level: heterogeneity (only 1 study so heterogeneity cannot be assessed)

[c] Downgraded one level: imprecision due to small sample size, i.e. optimal information size not met [i.e. the total number of patients included is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial])

C.3. Home visits

GRADE Table C.3: Comparison – Home visits to support families to provide care versus usual care

Source: Bedwell C, Lavender T, Tate N, Danna VA. Interventions to support parents, families and carers in caring for premature or low birth weight (LBW) infants in the home: a systematic review and meta-analysis. medRxiv. 2022:2022.10.25.22281452v1. doi:10.1101/2022.10.25.22281452.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Home visits		Risk with usual care	Risk difference with home visits
Mortality by 6 months of age											
6984 (1 RCT)	not serious	serious[a]	not serious	not serious	none	⨁⨁⨁◯ Moderate	166/3331 (5.0%)	138/3653 (3.8%)	**RR 0.71** (0.57 to 0.89)	50 per 1000	**14 fewer per 1000** (from 21 fewer to 5 fewer)
Mortality by 12 months of age											
970 (1 study)	serious[d]	serious[a]	not serious	not serious	none	⨁⨁◯◯ Low	14/485 (2.9%)	1/485 (0.2%)	**RR 0.14** (0.02 to 1.16)	29 per 1000	**25 fewer per 1000** (from 28 fewer to 5 more)
Hospitalization by 12 months of age											
970 (1 study)	serious[d]	serious[a]	not serious	not serious	none	⨁⨁◯◯ Low	485	485	-	The mean hospitalization was **0.25 months**	MD **0.34 higher** (0.16 higher to 0.52 higher)
Growth – not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Cognitive development at 10–12 months of age; assessed with BSID-III											
652 (2 RCTs)	serious[b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	329	323	-	-	SMD **0.03 SD higher** (0.12 lower to 0.19 higher)

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	No. of participants		Relative risk (RR) (95% CI)	Anticipated absolute effects	
							Usual care	Home visits		Risk with usual care	Risk difference with home visits
Motor development at 10 months of age; assessed with BSID-III											
136 (1 RCT)	not serious	serious[a]	not serious	serious[c]	none	⨁⨁◯◯ Low	67	69	-	-	SMD **0.02 SD lower** (0.35 lower to 0.32 higher)
Infant temperament at 6 months of age; assessed with Infant Behavioural Assessment (IBA)											
161 (1 RCT)	not serious	serious[a]	not serious	serious[c]	none	⨁⨁◯◯ Low	78	83	-	The mean infant temperament was **0** points	MD **0.7 points higher** (0.6 lower to 1.46 higher)
Mother–infant attachment at 6 months of age											
136 (1 RCT)	not serious	serious[a]	not serious	serious[c]	none	⨁⨁◯◯ Low	67	69	-	The mean attachment at 6 months was **101.3** points	MD **1.2 points lower** (2.79 lower to 0.39 higher)
Exclusive breastfeeding at 6 months of age											
7183 (3 RCTs)	serious[b]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	19/3428 (0.6%)	161/3755 (4.3%)	**RR 4.48** (0.28 to 72.63)	6 per 1000	**19 more per 1000** (from 4 fewer to 397 more)
Immunization visits in the first year of life											
136 (1 RCT)	serious[b]	serious[a]	not serious	not serious	none	⨁⨁◯◯ Low	67	69	-	The mean visits were **2.53** visits per year	MD **1.21 visits higher** (0.93 higher to 1.94 higher)

BSID-III: Bayley Scales of Infant and Toddler Development, third edition; CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation; SMD: standardized mean difference

Explanations

[a] Downgraded by one level: heterogeneity (only 1 study so heterogeneity cannot be assessed)

[b] Downgraded by one level: risk of bias (randomization, allocation concealment not clear, blinding of assessors not clear)
[c] Downgraded by one level: imprecision (small sample size, i.e. optimal information size not met [i.e. the total number of patients included is less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial])
[d] Downgraded by one level: risk of bias (lack of adjustment for confounding)

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