National Institute for Health and Care Excellence

Draft for consultation

Faltering growth in children: recognition and management

Appendix J

Clinical guideline

GRADE evidence profiles

April 2017

Draft for Consultation

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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1 Weight loss in the first days of life

1.1 In babies under 4 weeks what percentage of weight loss is associated with adverse outcomes?

Table 1: Modified GRADE profile for % birth weight loss thresholds at 2 and 3 days to predict adverse outcomes in exclusively breastfed neonates

No of studies	n	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Weight loss of 8% or more of birth weight on day 2 of life to predict hyperbilirubinemia measured with AAP-2004 criteria										
1	874	serious[1]	no serious inconsistency	serious indirectness[2]	no serious imprecision	0.47 [0.40, 0.53]	0.62 [0.59, 0.66]	1.24 [1.04, 1.47]	0.86 [0.75,0.98]	Low
Weight loss of 11% or more of birth weight on day 3 of life to predict hyperbilirubinemia measured with AAP-2004 criteria										
1	874	serious[1]	no serious inconsistency	serious indirectness[2]	no serious imprecision	0.12 [0.08, 0.17]	0.94 [0.92, 0.95]	1.90 [1.19 to 3.03]	0.94 [0.89, 0.99]	Low
Weight loss of 8% or more of birth weight (median follow up 3 days to predict hypernatraemia measured with sodium concentration level>145 mEq/L										
1	1001	serious[1]	no serious inconsistency	serious indirectness[2]	serious imprecision[3]	1.00 [0.16, 1.00]	0.73 [0.70, 0.76]	3.73 [1.85, 5.20]	Cannot calculate	Very low

a Risk of bias assessed using the CASP checklist for clinical prediction tools
b Inconsistency was assessed visually according to the differences in point estimates of sensitivity as this was considered to be the primary measure of interest and overlap in confidence intervals
c Indirectness was assessed using the CASP checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the result was judged to be very seriously imprecise
1 Downgraded one level for risk of bias – people evaluating outcomes knew the weight loss group
2 Downgraded one level for indirectness - not 10% birth weight loss threshold.
3 Downgraded one level for imprecision - The judgement of precision was based on the confidence interval of sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses both 75% and 90%, the result was judged to be very seriously imprecise

2 Faltering growth after the first days of life

2.1 Thresholds for concern and measurement of weight, height or length

Table 2: Modified GRADE profile of anthropometric criteria to predict serious undernutrition (defined as BMI < 5th centile and conditional weight gain < 5th centile) in infants aged 2 to 6 months

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Gomez criterion										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	0.40 [0.29, 0.52]	0.99 [0.99, 1.00]	60 [37,96]	0.60 [0.50,0.72]	moderate
Waterlow criterion										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	0.29 [0.19, 0.40]	0.99 [0.99, 1.00]	53 [30,93]	0.72 [0.62,0.83]	moderate
BMI < 5th centile										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	1.00 [0.95, 1.00]	0.97 [0.97, 0.98]	35 [28,41]	Cannot calculate	moderate
Weight < 5th centile										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious imprecision[1]	0.68 [0.56, 0.78]	0.98 [0.97, 0.98]	32 [24,41]	0.33 [0.24, 0.46]	low
Length < 5th centile										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	0.17 [0.09, 0.27]	0.97 [0.96, 0.97]	4.90 [2.90,8.27]	0.86 [0.78,0.95]	moderate
Weight downward crossing ≥ 2 major centiles										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious imprecision[1]	0.71 [0.60, 0.81]	0.87 [0.85, 0.88]	5.32 [4.52,6.27]	0.33 [0.23,0.47]	low
Conditional weight gain < 5th centile										

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	1.00 [0.95, 1.00]	0.97 [0.97, 0.98]	37 [30,44]	Cannot calculate	moderate

a Risk of bias assessed using CASP clinical prediction rule checklist
b Inconsistency was assessed visually according to the differences in point estimates of sensitivity as this was considered to be the primary measure of interest and overlap in confidence intervals
c Indirectness was assessed using the CASP clinical prediction rule checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise
1 Downgraded by one level because the confidence interval of sensitivity (the primary measure of interest) crosses the 75% threshold
2 Downgraded by one level because the prediction rule was not validated in a separate population. It was unclear whether the predictor variables and the outcome were evaluated in a blinded fashion, but this is unlikely to have affected the results.

Table 3: Modified GRADE profile of anthropometric criteria to predict serious undernutrition (defined as BMI < 5th centile and conditional weight gain < 5th centile) in infants aged 6 to 11 months

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Gomez criterion										
1	3692	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	0.17 [0.09, 0.28]	1.00 [0.99, 1.00]	50 [23,110]	0.84 [0.75,0.93]	moderate
Waterlow criterion										
1	3692	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	0.17 [0.09, 0.28]	1.00 [1.00, 1.00]	76 [31,182]	0.84 [0.75,0.93]	moderate
BMI < 5th centile										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	1.00 [0.95, 1.00]	0.97 [0.97, 0.98]	38 [31,45]	Cannot calculate	moderate
Weight < 5th centile										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious imprecision[1]	0.76 [0.64, 0.85]	0.96 [0.96, 0.97]	21 [17,26]	0.25 [0.16,0.39]	low
Length < 5th centile										

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	0.02 [0.00, 0.08]	0.97 [0.96, 0.97]	0.44 [0.06,3.12]	1.02 [0.99,1.05]	moderate
Weight downward crossing ≥ 2 major centiles										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	serious imprecision[1]	0.85 [0.74, 0.92]	0.80 [0.79, 0.82]	4.29 [3.80,4.84]	0.19 [0.11,0.33]	low
Conditional weight gain < 5th centile										
1	3789	serious risk of bias[2]	no serious inconsistency	no serious indirectness	no serious imprecision	1.00 [0.95, 1.00]	0.97 [0.96, 0.97]	31 [35,36]	Cannot calculate	moderate

a Risk of bias assessed using CASP clinical prediction rule checklist
b Inconsistency was assessed visually according to the differences in point estimates of sensitivity as this was considered to be the primary measure of interest and overlap in confidence intervals
c Indirectness was assessed using the CASP clinical prediction rule checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise
1 Downgraded by one level because the confidence interval of sensitivity (the primary measure of interest) crosses the 75% threshold
2 Downgraded by one level because the prediction rule was not validated in a separate population. It was unclear whether the predictor variables and the outcome were evaluated in a blinded fashion, but this is unlikely to have affected the results

Table 4: Modified GRADE profile of negative change in weight for age during 4 to 6 months of age (defined as weight-for-age z score change of ≥ -0.85) to predict underweight during the first 2 years of life (defined as weight-for-length ratio z score ≤-1.67)

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Negative change in weight-for-age z score										
1	458	Serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.06 [0.04,0.09]	0.97 [0.96,–0.98]	2.00 [2.31, 124]	0.97 (0.07	Moderate
Negative change in weight-for-age z score, in those with birth weight < 3.0 kilograms										
1	131	Serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.02 [0.0,0.07]	0.98 [0.96,1.00]	1.00 [3.28, 182]	1.00 [0.07, 3.62]	Moderate

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Negative change in weight-for-age z score in those with birth weight ≥ 3.0 kilograms										
1	327	Serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.07 [0.05,0.10]	0.97 [0.96,0.98]	2.33 [2.24, 120]	0.96 [0.07, 3.66]	Moderate

CI confidence interval, LR likelihood ratio
a Risk of bias assessed using CASP clinical prediction rule checklist
b Inconsistency was assessed visually according to the differences in point estimates of sensitivity as this was considered to be the primary measure of interest and overlap in confidence intervals
c Indirectness was assessed using the CASP clinical prediction rule checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise
1 Downgraded by one level because the prediction rule was not validated in a separate population. It was unclear whether the predictor variables and the outcome were evaluated in a blinded fashion, but this is unlikely to have affected the results.

2.2 Assessment of child and maternal feeding behaviour

Table 5: Modified GRADE profile of child and maternal feeding behaviour for the prediction of sustained weight faltering in the first year

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Poor appetite (low appetite at 6 weeks or 12 months, or borderline appetite at both); assessed by questionnaire										
1	501	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.56 [0.35, 0.76]	0.71 [0.67, 0.75]	1.93 [1.33,2.81]	0.62 [0.40,0.97]	very low
Low appetite at 6 weeks (versus borderline or normal appetite); assessed by questionnaire										
1	749	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.18 [0.07, 0.35]	0.98 [0.97, 0.99]	10.00 [4.06,24.65]	0.83 [0.71,0.98]	low
Borderline or low appetite at 6 weeks (versus normal appetite); assessed by questionnaire										
1	749	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.55 [0.36, 0.72]	0.73 [0.69, 0.76]	2.00 [1.43,2.80]	0.62 [0.43,0.91]	low

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
Low appetite at 12 months (versus borderline or normal appetite); assessed by questionnaire										
1	573	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.35 [0.17, 0.56]	0.88 [0.86, 0.91]	3.01 [1.69,5.35]	0.74 [0.56,0.98]	low
Borderline or low appetite at 12 months (versus normal appetite); assessed by questionnaire										
1	573	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.69 [0.48, 0.86]	0.49 [0.45, 0.53]	1.36 [1.04,1.78]	0.63 [0.35,1.12]	very low
Highly avoidant eating behaviour at 12 months (versus medium or low); assessed by questionnaire										
1	574	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.23 [0.09, 0.44]	0.91 [0.89, 0.93]	2.63 [1.24,5.59]	0.84 [0.68,1.04]	low
Medium or highly avoidant eating behaviour at 12 months (versus low); assessed by questionnaire										
1	574	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.58 [0.37, 0.77]	0.70 [0.66, 0.74]	1.90 [1.34,2.71]	0.61 [0.39,0.95]	very low
High maternal feeding anxiety at 12 months (versus borderline or normal); assessed by questionnaire										
1	574	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.54 [0.33, 0.74]	0.71 [0.67, 0.75]	1.86 [1.26,2.75]	0.65 [0.42,1.00]	low
Borderline or high maternal feeding anxiety at 12 months (versus normal); assessed by questionnaire										
1	574	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.88 [0.68, 0.97]	0.25 [0.22, 0.29]	1.17 [1.00,1.38]	0.49 [0.17,1.43]	very low
High response to food refusal at 8 months (versus medium or low); assessed by questionnaire										
1	598	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	0.35 [0.17, 0.56]	0.81 [0.78, 0.85]	1.83 [1.05,3.18]	0.81 [0.61,1.07]	low
Medium or high response to food refusal at 8 months (versus low); assessed by questionnaire										
1	598	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.81 [0.61, 0.93]	0.39 [0.35, 0.43]	1.32 [1.08,1.61]	0.50 [0.22,1.10]	very low

No of studies	N	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Sens [95% CI]	Spec [95% CI]	LR+ [95% CI]	LR- [95% CI]	Quality
High response to food refusal at 12 months (versus medium or low); assessed by questionnaire										
1	477	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.61 [0.39, 0.80]	0.58 [0.54, 0.63]	1.46 [1.04,2.07]	0.67 [0.40,1.12]	very low
Medium or high response to food refusal at 12 months (versus low)); assessed by questionnaire										
1	477	Very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	0.83 [0.61, 0.95]	0.17 [0.14, 0.21]	1.00 [0.82,1.21]	1.01 [0.41,2.52]	very low

CI confidence interval, LR likelihood ratio
a Risk of bias assessed using CASP checklist
b Inconsistency was assessed visually according to the differences in point estimates of sensitivity as this was considered to be the primary measure of interest and overlap in confidence intervals
c Indirectness was assessed using the CASP checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise
1 Downgraded by two levels due to risk of bias: it was unclear whether outcome assessors or participants were blinded to the study outcome and the feeding behaviour parameters assessed in the study were not clearly defined
2 Downgraded by one level because the confidence interval of sensitivity (the primary measure of interest) crosses the 75% threshold

2.3 What interventions related to dietary advice or supplementation are effective in the management of faltering growth?

Table 6: Summary clinical evidence profile Comparison 1: counselling + nutritional supplement versus counselling alone for faltering growth

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Counselling + nutritional supplement	Counselling alone	Relative (95% CI)	Absolute	Quality	Importance
weight for age (follow-up 30 days; measured with: percentile change from baseline; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Counselling + nutritional supplement**	**Counselling alone**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	53	51	-	MD 2.48 higher (0.53 to 4.43 higher)	VERY LOW	CRITICAL
weight for age (follow-up 60 days; measured with: percentile change from baseline; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	51	-	MD 5.93 higher (3.12 to 8.74 higher)	LOW	CRITICAL
weight for age (follow-up 90 days; measured with: percentile change from baseline; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	51	-	MD 8.03 higher (4.86 to 11.2 higher)	LOW	CRITICAL
height for age (follow-up 30 days; measured with: percentile change from baseline; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	53	51	-	MD 1.85 higher (0.31 lower to 4.01 higher)	VERY LOW	CRITICAL
height for age (follow-up 60 days; measured with: percentile change from baseline; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Counselling + nutritional supplement**	**Counselling alone**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	none	53	51	-	MD 3.17 higher (1.09 to 5.25 higher)	VERY LOW	CRITICAL
height for age (follow-up 90 days; measured with: percentile change from baseline; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53	51	-	MD 5.24 higher (2.82 to 7.66 higher)	LOW	CRITICAL

1 Evidence was downgraded by 2 due to unclear allocation sequence generation, unclear allocation concealment, significant difference in baseline characteristics, incomplete outcome data were not clearly addressed, and knowledge of the allocated interventions was not adequately prevented during the study.
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (± 0.5 x 4.04 = ±2.02)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (± 0.5 x 3.36 = ±1.68)
4 Evidence was downgrade by 1 due to serious imprecision as 95% CI crossed one default MID (± 0.5 x 4.24 = ±2.12)

Table 7: Summary clinical evidence profile Comparison 2: routine treatments + bovine colostrum versus routine treatments alone for faltering growth

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine treatments + bovine colostrum	Routine treatments alone	Relative (95% CI)	Absolute		
weight for age (follow-up 1 months; measured with: Gomez index; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	60	-	MD 0.71 higher (1.68 lower to 3.1 higher)	MODERATE	CRITICAL
weight for age (follow-up 2 months; measured with: Gomez Index; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	60	60	-	MD 2.73 higher (0.21 to 5.25 higher)	LOW	CRITICAL
weight for age (follow-up 3 months; measured with: Gomez Index; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	60	60	-	MD 4.6 higher (1.63 to 7.57 higher)	LOW	CRITICAL
height for age (follow-up 1 months; measured with: Waterlow index; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	60	-	MD 0.08 higher (1.22 lower to 1.38 higher)	MODERATE	CRITICAL
height for age (follow-up 2 months; measured with: Waterlow index; Better indicated by higher values)												
1	randomis	seriou	no serious	no serious	no serious	none	60	60	-	MD	MODERA	CRITICA

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Routine treatments + bovine colostrum	Routine treatments alone	Relative (95% CI)	Absolute		
	ed trials	s[1]	inconsistency	indirectness	imprecision					0.55 higher (0.83 lower to 1.93 higher)	TE	L
height for age (follow-up 3 months; measured with: Waterlow index; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	60	60	-	MD 1.2 higher (0.19 lower to 2.59 higher)	LOW	CRITICAL

1 Evidence was downgraded by 1 due to unclear allocation concealment and knowledge of the allocated interventions was not adequately prevented during the study.
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (± 0.5 x 4.05 = ±3.52)
3 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (± 0.5 x 8.31 = ±4.15)
4 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (± 0.5 x 3.89 = ±1.94

Table 8: Summary clinical evidence profile Comparison 3: nutrient-dense formula versus energy-supplemented formula for faltering growth

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrient-dense formula versus	Energy-supplemented formula	Relative (95% CI)	Absolute		
median weight gain (follow-up 6 weeks; measured with: g /kg/ day; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	N = 26 Median = 7.2 g/kg per day	N = 23 Median = 7.6 g/kg per day	-	ns	MODERATE	CRITICAL
median change (follow-up 6 weeks; measured with: weight z-score; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	N = 26 Median (range) = 0.29 (-0.6 to 1.5)	N = 23 Median (range) = 0.49 (-0.9 to 2.3)	-	ns	MODERATE	CRITICAL
median linear growth (follow-up 6 weeks; measured with: cm per week; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	N = 26 Median = 0.67 cm per week	N = 23 Median = 0.60 cm per week	-	ns	MODERATE	CRITICAL
median change in length (follow-up 6 weeks; measured with: z-score; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	N = 26 Median (range) = -0.18 (-1.7 to 1.2)	N = 23 Median (range) = -0.28 (-1.3 to 2.1)	-	ns	MODERATE	CRITICAL
median MUAC (measured with: cm per week; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Not calculable	none	-	-	-	ns	MODERATE	CRITICAL

1 Evidence was downgraded by 1 due to unclear concealment of allocation and knowledge of the allocated interventions not clearly adequately prevented during the study.

Table 9: Summary clinical evidence profile Comparison 4: nutrient-enriched formula versus standard term formula for faltering growth

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nutrient-enriched formula**	**Standard term formula**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
weight (change from baseline) (follow-up 9 months; measured with: kg; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	121	126	-	MD 0.21 higher (0.02 lower to 0.44 higher)	HIGH	CRITICAL
weight (change from baseline) (follow-up 18 months; measured with: g; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	118	122	-	MD 0.25 higher (0.03 lower to 0.53 higher)	MODERATE	CRITICAL
weight (follow-up 9-18 months; measured with: g ; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	122	-	MD 0.1 lower (0.26 lower to 0.06 higher)	HIGH	CRITICAL
length (change from baseline) (follow-up 9 months; measured with: cm; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nutrient-enriched formula**	**Standard term formula**	**Relative (95% CI)**	**Absolute**		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[2]	none	121	126	-	MD 1.1 higher (0.4 to 1.8 higher)	MODERATE	CRITICAL
length (change from baseline) (follow-up 18 months; measured with: cm; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[3]	none	118	122	-	MD 1 higher (0.23 to 1.77 higher)	MODERATE	CRITICAL
length (follow-up 9-18 months; measured with: cm; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	122	-	MD 0.33 lower (0.87 lower to 0.21 higher)	HIGH	CRITICAL
OFC (change from baseline) (follow-up 9 months; measured with: cm; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[4]	none	121	126	-	MD 0.5 higher (0.1 to 0.9 higher)	MODERATE	CRITICAL
OFC (change from baseline) (follow-up 18 months; measured with: cm; Better indicated by higher values)												
1	randomised trials	no seriou	no serious inconsistenc	no serious indirectnes	Serious[5]	none	118	122	-	MD 0.6 higher	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nutrient-enriched formula	Standard term formula	Relative (95% CI)	Absolute	Quality	Importance
		s risk of bias	y	s						(0.18 to 1.02 higher)		
OFC (follow-up 9-18 months; measured with: cm; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	118	122	-	MD 0.01 lower (0.2 lower to 0.18 higher)	HIGH	CRITICAL

1 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (± 0.5 x 1.13 = ±0.13)
2 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (± 0.5 x 3 = ±1.5)
3 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default (± 0.5 x 3.2 = ±0.64)
4 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default (± 0.5 x 1.8 = ±0.9)
5 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default (± 0.5 x 1.8 = ±0.9

2.4 What is the effectiveness of non-nutritional interventions in the management of faltering growth?

Table 10: Summary clinical evidence profile for BPT compared to SDE for persistent feeding difficulties

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPT	SDE	Relative (95% CI)	Absolute	Quality	Importance

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**BPT**	**SDE**	**Relative (95% CI)**	**Absolute**		
Energy intake (% RDI) (measured with: Mealtime Record Form; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	12	8	-	mean 1.60 lower (16.64 lower to 13.44 higher)	VERY LOW	IMPORTANT
Protein intake (% RDI) (measured with: Mealtime Record Form; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	Serious[4]	none	12	8	-	mean 25 lower (54.85 lower to 4.85 higher)	VERY LOW	IMPORTANT

1 Generation of a randomised sequence, method used to conceal the allocation and blinding of outcome assessors has not been reported.
2 Included participants presented with severe feeding difficulties and not with faltering growth
3 Evidence was downgraded by 2 due to very serious imprecision as 95% CI crossed 2 default MIDs (23.2 x ±0.5 = ± 11.6)
4 Evidence was downgrade by 1 due to serious imprecision as 95% CI crossed 1 default MID (34.9 x ± 0.5 = ±17.1)

3 Organisation of care

3.1 In the management of infants and preschool children what is the most effective service delivery with regard to the configuration and working arrangements of multidisciplinary teams?

Table 11: GRADE profile for structured health visitor management compared to routine weighing only for faltering growth

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured health visitor management	Routine weighing only	Relative (95% CI)	Absolute	Quality	Importance
anthropometric meas at home visit - Weight (follow-up 3 years; measured with: SD score; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	68	65	-	MD 0.33 higher (0.01 to 0.65 higher)	LOW	CRITICAL
anthropometric meas at home visit - Weight deficit (follow-up 3 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[3]	none	68	65	-	MD 0.36 higher (0.07 to 0.65 higher)	LOW	CRITICAL
anthropometric meas at home visit - Height (follow-up 3 years; measured with: SD score; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[4]	none	68	65	-	MD 0.34 higher (0.03 to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured health visitor management	Routine weighing only	Relative (95% CI)	Absolute		
										0.65 higher)		
anthropometric meas at home visit - Height deficit (follow-up 3 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[5]	none	68	65	-	MD 0.3 higher (0.01 lower to 0.61 higher)	LOW	CRITICAL
weight (SD score) at last follow up (follow-up 3 years; measured with: SD score; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[6]	none	120	109	-	MD 0.33 higher (0.06 to 0.6 higher)	LOW	CRITICAL
weight deficit at last follow up (follow-up 3 years; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[7]	none	120	109	-	MD 0.35 higher (0.11 to 0.59 higher)	LOW	CRITICAL
parent or carer satisfaction - service received from the health visitor (follow-up 3 years; measured with: structured interviews; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[8]	none	68	66	-	MD 0.3 higher (0.05 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured health visitor management	Routine weighing only	Relative (95% CI)	Absolute	Quality	Importance
										0.65 higher)		
Parent or carer satisfaction - how often saw the heath visitor (follow-up 3 years; measured with: structured interviews ; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[9]	none	68	66	-	MD 0.2 higher (0.13 lower to 0.53 higher)	LOW	CRITICAL
Parent or carer satisfaction - how did you feel about getting your child weighted? (follow-up 3 years; measured with: structured interviews ; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[10]	none	68	66	-	MD 0.2 lower (0.68 lower to 0.28 higher)	LOW	CRITICAL
Parent or carer satisfaction - how would you describe your child's appetite - at 1 year? (follow-up 1 year; measured with: structured interviews ; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious[11]	none	68	66	-	MD 0.4 lower (1.01 lower to 0.21 higher)	LOW	CRITICAL
parent or carer satisfaction - how would you describe your child's appetite - at time of interview? (follow-up 3 years; measured with: structured interviews ; Better indicated by higher values)												
1	randomis	seriou	no serious	no serious	Serious[12]	none	68	66	-	MD 0.5	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Structured health visitor management	Routine weighing only	Relative (95% CI)	Absolute	Quality	Importance
	ed trials	s[1]	inconsistency	indirectness						higher (0.11 lower to 1.11 higher)		

1 Evidence was downgraded by 1 due to unclear/unreported allocation concealment, unclear/unreported blinding, and unclear/unreported incomplete outcome data.
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 0.94 = ±0.47)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 0.85 = ±0.42)
4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 0.92 = ±0.46)
5 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 0.92 = ±0.46)
6 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 1.06= ±0.53)
7 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 0.93 = ±0.46)
8 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 1.1 = ±0.55)
9 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 0.98 = ± 0.49)
10 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 1.12 = ± 0.6)
11 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 1.9 = ±0.95)
12 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.50 x 2 = ±1)

Table 12: GRADE profile for specialised home visit + outpatient clinic compared to clinic only for faltering growth

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Specialised home visit + outpatient clinic	clinic only	Relative (95% CI)	Absolute	Quality	Importance
weight (follow-up 1 year; measured with: SD score; Better indicated by higher values)												
1	randomised trials	no serious risk	no serious inconsistency	no serious indirectness	serious[1]	none	42	41	-	MD 0.17 higher	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Specialised home visit + outpatient clinic	clinic only	Relative (95% CI)	Absolute	Quality	Importance
		of bias								(0.1 lower to 0.44 higher)		
height (follow-up 1 year; measured with: (SD score); Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[2]	none	42	41	-	MD 0.13 higher (0.2 lower to 0.46 higher)	MODERATE	CRITICAL
mental developmental index (follow-up 1 year; measured with: Bayley Scales of Infant Development; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[3]	none	38	27	-	MD 1.6 lower (7.16 lower to 3.96 higher)	MODERATE	IMPORTANT
psychomotor developmental index (follow-up 1 year; measured with: Bayley Scales of Infant Development; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[4]	none	38	27	-	MD 2.6 higher (4.6 lower to 9.8 higher)	MODERATE	IMPORTANT
referrals to a community dietitian (follow-up 1 year)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Specialised home visit + outpatient clinic**	**clinic only**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/42 (0%)	12/41 (29.3%)	RR 0.04 (0 to 0.58)	281 fewer per 1000 (from 123 fewer to 293 fewer)	HIGH	IMPORTANT
admissions to hospital (follow-up 1 year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[5]	none	6/37 (16.2%)	14/37 (37.8%)	RR 0.43 (0.17 to 0.97)	216 fewer per 1000 (from 11 fewer to 314 fewer)	MODERATE	IMPORTANT
adherence (follow-up 1 year; assessed with: missed more than 3 outpatient appointment)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[6]	none	5/37 (13.5%)	14/37 (37.8%)	RR 0.36 (0.12 to 0.87)	242 fewer per 1000 (from 49 fewer to 333 fewer)	MODERATE	IMPORTANT

1 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.5 x 0.63 = ±0.315)
2 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.5 x 0.85 = ±0.425)
3 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.5 x 11.8 = ±5.94)
4 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (±0.5 x 13.39 = ±6.69)
5 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (0.8)
6 Evidence was downgraded by 1 due to serious imprecision as 95%CI crossed one default MID (0.8)

Table 13: GRADE profile for lay home visit + growth and nutrition clinic compared to clinic only for faltering growth

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lay home visit + growth and nutrition clinic**	**clinic only**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
weight for age - younger (< 12 mo at recruitment) (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	serious[2]	none	28	26	-	MD 0.2 lower (0.76 lower to 0.36 higher)	LOW	CRITICAL
weight for age - older (> 12 mo at recruitment) (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[5]	none	28	34	-	MD 0.1 lower (0.42 lower to 0.22 higher)	MODERATE	CRITICAL
weight for height (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	Serious[6]	none	55	56	-	MD 0.2 lower (0.51	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lay home visit + growth and nutrition clinic	clinic only	Relative (95% CI)	Absolute	Quality	Importance
		bias								lower to 0.11 higher)		
weight for height - younger (< 12 mo at recruitment) (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[7]	none	28	26	-	MD 0.2 lower (0.87 lower to 0.47 higher)	MODERATE	CRITICAL
weight for height - older (> 12 mo at recruitment) (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[8]	none	28	34	-	MD 0.2 lower (0.47 lower to 0.07 higher)	MODERATE	CRITICAL
weight for height (follow-up 4 years; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[9]	none	36	38	-	MD 0.2 lower (0.52 lower to 0.12 higher)	MODERATE	CRITICAL
weight for height (follow-up 8 years; measured with: BMI; Better indicated by higher values)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectnes	Serious[10]	none	47	49	-	MD 1.28 higher	MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lay home visit + growth and nutrition clinic	clinic only	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias		s						(0.12 lower to 2.68 higher)		
height for age (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[11]	none	55	56	-	MD 0.4 higher (0.01 lower to 0.81 higher)	MODERATE	CRITICAL
height for age - younger (< 12 mo at recruitment) (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[12]	none	28	26	-	MD 0.2 higher (0.36 lower to 0.76 higher)	MODERATE	CRITICAL
height for age - older (> 12 mo at recruitment) (follow-up 1 year; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[13]	none	28	34	-	MD 0.2 higher (0.33 lower to 0.73 higher)	MODERATE	CRITICAL
height for age (follow-up 4 years[3]; Better indicated by higher values)												
1	randomise	no	no serious	no serious	Serious[14]	none	36	38	-	MD 0.2	MODERAT	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lay home visit + growth and nutrition clinic	clinic only	Relative (95% CI)	Absolute	Quality	Importance
	d trials	serious risk of bias	inconsistency	indirectness						higher (0.28 lower to 0.68 higher)	E	
height for age (follow-up 8 years[4]; measured with: (z score); Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[15]	none	47	49	-	MD 0.4 higher (0 to 0.8 higher)	MODERATE	CRITICAL
cognitive development (follow-up 1 year; measured with: Bailey Scales of Infant Development; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[16]	none	55	56	-	MD 2.93 higher (3.12 lower to 8.98 higher)	MODERATE	IMPORTANT
cognitive development - younger (< 12 mo at recruitment) (follow-up 1 year; measured with: Bailey Scales of Infant Development; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[17]	none	28	26	-	MD 3.2 higher (6.45 lower to 12.85 higher)	MODERATE	IMPORTANT
cognitive development - older (> 12 mo at recruitment) (follow-up 1 year; measured with: Bailey Scales of Infant Development; Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lay home visit + growth and nutrition clinic	clinic only	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[18]	none	28	34	-	MD 1.1 higher (5.79 lower to 7.99 higher)	MODERATE	IMPORTANT
cognitive development (follow-up 4 years[3]; measured with: Bailey Scales of Infant Development; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[19]	none	55	56	-	MD 6.39 higher (0.69 to 12.09 higher)	MODERATE	IMPORTANT
cognitive development (follow-up 8 years[4]; measured with: IQ; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	Serious[20]	none	47	49	-	MD 2.35 lower (7.75 lower to 3.05 higher)	MODERATE	IMPORTANT

1 evidence was downgraded by 1 due to unclear incomplete outcome data.
2 evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID
3 at child's age 4
4 at child's age 8
5 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 0.7 =± 0.35)
6 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 1 =± 0.5)
7 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 1.1 =± 0.55)
8 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 0.6 =± 0.3)
9 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 0.8 =± 0.4)
10 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 2.28 =± 1.14)

11 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 1.1 =± 0.55)
12 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 1 =± 0.5)
13 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 1 =± 0.5)
14 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 1.1 =± 0.55)
15 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 0.93 =± 0.465)
16 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 16.22 =± 8.11)
17 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 18.7 =±9.35)
18 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 15.2 =± 7.6)
19 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 14.9 =± 7.45)
20 Evidence was downgraded by 1 due to serious imprecision as 95% CI crossed one default MID (±0.5 x 14.8 =± 7.4)