National Institute for Health and Care Excellence

Final

Neonatal parenteral nutrition

[C] Energy needs

NICE guideline NG154

Evidence reviews

February 2020

Final

These evidence reviews were developed by the National Guideline Alliance which is part of the Royal College of Obstetricians and Gynaecologists

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ISBN: 978-1-4731-3673-1

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Energy needs of preterm and term babies

Review question

How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Introduction

Providing the optimal level of energy for babies receiving parenteral nutrition (PN) is very important. If nutritional deficits occur during early postnatal life, there is an increased risk of mortality and respiratory conditions, and detrimental effects on growth and neurodevelopment. Conversely, providing energy in excess of needs has been associated with impaired liver function, and increased adiposity. Determining the optimal energy needs of preterm and term babies receiving PN as their main source of nutrition is therefore important for optimal outcomes.

Summary of the protocol

Please see Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Intervention	• Different kcal/kg/day
Comparison	• Each other

Outcomes	**Critical**
	• Body composition (e.g., measured as lean mass, fat-free mass, fat mass, adipose tissue)
	• Nitrogen accretion
	• Growth/anthropometric measures
	  ○ Head circumference
	  ○ Weight gain
	  ○ Height gain
	Important
	• Mortality
	• Adverse effects of PN:
	  ○ PN related liver disease (abnormal liver function, cholestasis, conjugated hyperbilirubinaemia, intrahepatocellular lipid)
	  ○ Hyperglycaemia
	  ○ Hypophosphataemia/hypercalcaemia
	• Energy intake (as the actual amount given)

PN: Parenteral nutrition

For full details see the review protocol in appendix A.

Clinical evidence

Included studies

As limited RCT evidence was available, we also included observational studies. Six studies were identified for inclusion in this review (Duffy 1981, Forsyth 1995, Morgan 2014, Pineault 1988, Tan 2008, Zlotkin 1981).

Two Randomised controlled trials (RCTs) and 1 cross-over RCT compared high versus low energy intake (Forsyth 1995, Morgan 2014, Tan 2008).

Three studies had multiple groups within the high versus low energy comparison. One RCT compared high versus low energy intake for 2 different sources of amino acids (Duffy 1981). One observational study compared high versus low energy intake for 2 different energy sources (low fat and high fat; Pineault 1988). One observational study compared high versus low energy intake at different levels of nitrogen intake (Zlotkin 1981). For these studies, groups within high energy intake and low energy intake were combined for the purpose of analysis.

Although the actual energy intake differed across included studies, all studies were combined into one comparison of high versus low energy intake. This meant that for each individual study, the arm with the higher intake was included in the high energy arm and the arm with the lower intake was included in the low energy arm, even if the low energy arm of some studies was higher than the high energy arm of other studies. However, if there was significant heterogeneity on any outcome, the energy intakes of individual studies were examined to see if this might explain the difference between studies. RCT and observational evidence was analysed separately.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D, and GRADE tables in appendix F.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusions are provided, in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Duffy 1981 RCT Canada	N= 24 Preterm babies with BW <1600g Mean GA 29.6 weeks (SD 1.8)	High energy (n=12) Target total calorie intake of 93 kcal/kg/day Amigen (casein amino acid) or Vamin (crystalline amino acid	Low energy (n=12) Target total calorie intake of 68 kcal/kg/day Amigen (casein amino acid) or Vamin (crystalline amino acid	• Nitrogen balance • Nitrogen retention • Weight gain • Energy intake	Vamin has a higher nitrogen content than Amigen, which affected nitrogen intake. The Vamin and Amigen groups were combined for the purpose of analysis in order to compare high

Study	Population	Intervention	Comparison	Outcomes	Comments
	Mean BW 1261g (SD 198)	mixture patterned on egg albumin)	mixture patterned on egg albumin)		energy and low energy groups.
Forsyth 1995 Cross-over RCT UK	N = 20 Inclusion criteria not reported Mean GA 30.9 weeks (SD 1.8) Mean BW 1314g (SD 291)	High glucose regimen (n=20) 12 g/kg/day (8.3 mg/kg/minute) of glucose	Low glucose regimen (n=20) 8 g/kg/day (5.5 mg/kg/minute) of glucose	• Energy intake	After 24 hours, infants were changed to the alternative regimen which was continued again for 24 hours.
Morgan 2014 RCT UK	N = 135 Babies <29 weeks, weighing <1200g; admitted within 48 hours of birth Mean GA 26.7 weeks (SD 1.4) Mean BW 892g (SD 171)	SCAMP (n=66) Target total calorie intake of 108 kcal/kg/day	Control (n=69) Target total calorie intake of 85 kcal/kg/day	• Head circumference • Weight gain • Mortality • Hyperbilirubinaemia • Energy intake	Study was not powered to assess differences in major complications.
Pineault 1988 Observational study Canada	N = 16 Appropriate-for-gestational-age babies with unchanging clinical conditions Mean GA 35 weeks (SD 2.8) Mean BW	High energy (n=8) Target total calorie intake of 80 kcal/kg^{-1}/d^{-1}	Low energy (n=8) Target total calorie intake of 60 kcal/kg^{-1}/d^{-1}	• Nitrogen balance • Nitrogen retention • Head circumference • Weight gain • Length gain • Energy intake	All babies completed both a low fat (1g/kg^{-1}/d^{-1} lipids) and high fat (3g/kg^{-1}/d^{-1} lipids) nutrition phase. The high fat and low fat groups were combined (where analyses were not reported separately) for the purpose of analysis in order to compare high

Study	Population	Intervention	Comparison	Outcomes	Comments
	2150g (SD 447)				energy and low energy groups.
Tan 2008 RCT UK	N = 114 Babies <29 weeks; admitted within 7 days of birth Mean GA 26.1 weeks (SD 1.5) Mean BW 913g (SD 221)	Hyperalimentation (n=55) Target total calorie intake of 117 kcal/kg/day	Control (n=59) Target total calorie intake of 93 kcal/kg/day	• Head circumference (as measured by occipitofrontal circumference) • Weight gain • Length gain • Lower leg length • Mid-arm circumference • Energy intake	Study was not powered to detect a difference in head circumference
Zlotkin 1981 Observational study Canada	N = 22 Premature babies that were appropriate size for gestational age Mean GA 29.2 weeks (Range 25-33) Mean BW Not reported	High energy (n=18) Target non-protein calorie intake 80 kcal/kg/day Nitrogen intake of 320, 480 or 640mg/kg/day	Low energy (n=12) Target non-protein calorie intake 50 kcal/kg/day Nitrogen intake of 480 or 640 mg/kg/day	• Nitrogen retention • Weight gain • Length gain • Energy intake	Babies with hyperbilirubinaemia were assigned to the low energy group and babies without hyperbilirubinaemia were assigned to the high energy group; 8 babies were included in more than one group. A low energy, low nitrogen group was not included due to risk of very poor nitrogen retention and growth. The low, medium and high nitrogen groups were combined for the purpose of analysis in order to compare high energy and low energy groups.

BW: birthweight; GA: gestational age; RCT: randomised controlled trial; SCAMP: standardised, concentrated with added macronutrients parenteral; SD: standard deviation.

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

GRADE was conducted to assess the quality of outcomes. Evidence was identified for critical and important outcomes. The clinical evidence profiles can be found in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question. A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material D for details.

Excluded studies

No studies were identified which were applicable to this review question.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation

Evidence statements

Clinical Evidence statements

Nitrogen accretion

Nitrogen retention (%)

- Low quality evidence from 1 RCT (n=24) showed a clinically important difference in nitrogen retention between babies who received high energy intake compared with low energy intake, with increased nitrogen retention in the group of babies receiving high energy intake. However, there was uncertainty around the effect: Mean difference (MD) 14.00% (95% CI 4.52 to 23.48).
- Very low quality evidence from 2 observational studies (n=66) showed a clinically important difference in nitrogen retention between babies who received high energy intake compared with low energy intake, with increased nitrogen retention in the group of babies receiving high energy intake. However, there was uncertainty around the effect: MD 12.16% (95% CI 1.73 to 22.58).

Nitrogen balance (mg/kg/day)

- Low quality evidence from 1 RCT (n=24) showed a clinically important difference in nitrogen balance between babies who received high energy intake compared with low energy intake, with higher nitrogen balance in the group of babies receiving high energy intake. However, there was uncertainty around the effect: MD 66.00mg/kg/day (95% CI 14.98 to 117.02).
- Very low quality evidence from 2 observational studies (n=62) showed a clinically important difference in nitrogen balance between babies who received high energy intake compared with low energy intake, with higher nitrogen balance in the group of babies

receiving high energy intake. However, there was uncertainty around the effect: MD 33.59mg/kg/day (95% CI 5.65 to 61.52).

Head circumference

Head circumference (mm) at 7, 14, 21 and 28 days and 36 weeks' corrected gestational age (CGA)

- High quality evidence from 1 RCT (n=135) showed no clinically important difference in head circumference at 7 days (MD 1.00mm [95% CI -3.39 to 5.39]) and 14 days (MD 2.00mm [95% CI -2.39 to 6.39]) between babies who received high energy intake compared with low energy intake.
- Moderate quality evidence from the 1 RCT (n=135) showed no clinically important difference between head circumference at 21 days (MD 4.00mm [95% CI -1.07 to 9.07]) and at 28 days (MD 6.00mm [95% CI 0.43 to 11.57]) between babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effects.
- Very low quality evidence from 2 RCTs (n=240) showed no clinically important difference in head circumference at 36 weeks' CGA in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effect: MD 1.04mm (95% CI -6.80 to 8.88).

Head circumference z-score at 36 weeks' CGA

- Low quality evidence from 1 RCT (n=114) showed no clinically important difference in head circumference z-score at 36 weeks' CGA in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effect: MD -0.20 (95% CI -0.62 to 0.22).

Head circumference gain (cm/week)

- Very low quality evidence from 1 observational study (n=15) showed a clinically important difference in head circumference gain between babies who received high energy intake compared with low energy intake, with greater head circumference gain in the group of babies receiving high energy intake. However, there was uncertainty around the effect: MD 0.40mm/week (95% CI 0.02 to 0.78).

Weight gain

Weight (g) at 7, 14, 21 and 28 days and 36 weeks' corrected gestational age (CGA)

- High quality evidence from 1 RCT (n=135) showed no clinically important difference in weight at 7 days in babies who received high energy intake compared with low energy intake: MD 31.00g (95% CI -8.22 to 70.22).
- Moderate quality evidence from 1 RCT (n=135) showed no clinically important difference in weight at 14 days (MD 55.00g [95% CI 9.24 to 100.76]), 21 days (MD 75.00g [95% CI 20.78 to 129.22]) and at 28 days (MD 57.00g [95% CI -8.70 to 122.70]) in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effects. Moderate quality evidence from 2 RCTs (n=238) showed no clinically important difference in weight at 36 weeks' CGA in babies who received high energy intake compared with low energy intake: MD 77.31g (95% CI 8.89 to 145.74).

Weight gain (g/day)

- Very low quality evidence from 1 RCT (n=24) showed no clinically important difference in weight gain in babies who received high energy intake compared with low energy intake. However, there was high uncertainty around the effect: MD 10.00g/day (95% CI -21.7 to 41.7).

Weight gain (g/kg/day)

- Very low quality evidence from 2 observational studies (n=46) showed a clinically important difference in weight gain between babies who received high energy intake compared with low energy intake, with greater weight gain in the group of babies receiving high energy intake. However, there was uncertainty around the effect: MD 7.12g/kg/day (95% CI -0.75 to 14.99).

Weight z-score at 36 weeks' CGA

- Low quality evidence from 1 RCT (n=114) showed no clinically important difference in weight z-score at 36 weeks' CGA in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effect: MD 0.10 (95% CI -0.21 to 0.41).

Mid-arm circumference (cm) at 36 weeks' CGA

- Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in mid-arm circumference at 36 weeks' CGA in babies who received high energy intake compared with low energy intake: MD 0.10cm (95% CI -0.19 to 0.39).

Height gain

Length (cm) at 36 weeks' CGA

- Low quality evidence from 1 RCT (n=114) showed no clinically important difference in length at 36 weeks' CGA in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effect: MD 0.50cm (95% CI -0.31 to 1.31).

Length gain (cm/week)

- Very low quality evidence from 2 observational studies (n=41) showed a clinically important difference in length gain between babies who received high energy intake compared with low energy intake, with greater length gain in the group of babies receiving high energy intake However, there was uncertainty around the effect: MD 0.29cm/week (95% CI 0.12 to 0.46)

Length z-score at 36 weeks' CGA

- Low quality evidence from 1 RCT (n=114) showed no clinically important difference in length z-score at 36 weeks' CGA in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effect: MD 0.30 (95% CI -0.16 to 0.76).

Lower leg length (cm) at 36 weeks' CGA

- Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in lower leg length at 36 weeks' CGA in babies who received high energy intake compared with low energy intake: MD 0.00cm (95% CI -0.26 to 0.26).

Mortality

- Low quality evidence from 1 RCT showed no clinically important difference in rate of mortality at 28 days (Relative risk (RR) 1.17 [95% CI 0.45 to 3.07; n=150]) and at 36 weeks' CGA (RR 0.93 [95% CI 0.44 to 1.95; n=127]) in babies who received high energy intake compared with low energy intake. However, there was high uncertainty around the effects.

Conjugated hyperbilirubinaemia (conjugated bilirubin > 50 mmol/L)

- Low quality evidence from 1 RCT (n=135) showed a clinically important difference in rate of conjugated hyperbilirubinaemia at 28 days between babies who received high energy intake compared with low energy intake, with conjugated hyperbilirubinaemia associated

with receiving high energy intake. However, there was high uncertainty around the effect: RR 0.78 (95% CI 0.29 to 2.14).

- Very low quality evidence from 1 RCT (n=127) showed no clinically important difference in rate of conjugated hyperbilirubinaemia at 36 weeks' CGA in babies who received high energy intake compared with low energy intake. However, there was high uncertainty around the effect: RR 1.10 [95% CI 0.54 to 2.22).

Energy intake

Energy intake (kcal/kg/d) in the first 48 hours of life and at week 1, 2, 3 and 4

- Low quality evidence from 1 RCT (N=20) showed a clinically important difference in energy intake in the first 48 hours of life between babies who received high energy intake compared with low energy intake, with greater energy intake in the group of babies receiving high energy intake. However, there was uncertainty around the effect: MD 15.30kcal/kg/day (95% CI 4.07to 26.53).
- High quality evidence from 1 RCT (n=135) showed a clinically important difference in energy intake at week 1 (MD 7.00kcal/kg/day [95% CI 4.61 to 9.39]) and week 2 (MD 17kcal/kg/day [95% CI 9.87 to 24.13]), with greater energy intake in the group of babies receiving high energy intake.
- Moderate quality evidence from 1 RCT (n=135) showed no clinically important difference in energy intake at week 3 (MD 9.00kcal/kg/day [95% CI -2.35 to 20.35]) and week 4 (MD 5.00kcal/kg/day (95% CI -5.24 to 15.24]). However, there was uncertainty around the effects.

Cumulative energy intake (kcal/kg) in the first 28 days of life

- Low quality evidence from 2 RCTs (n=249) showed no clinically important difference in cumulative energy intake in the first 28 days of life in babies who received high energy intake compared with low energy intake. However, there was uncertainty around the effect: MD 165.26 (95% CI 93.78 to 236.73).

Energy intake (kcal/kg/day) – timeframe unclear

- Moderate quality evidence from 1 RCT (n=24) showed a clinically important difference in energy intake between babies receiving high energy intake compared with low energy intake, with greater energy intake in the group of babies receiving high energy intake: MD 25.00kcal/kg/day (95% CI 18.58 to 31.42).
- Very low quality evidence from 1 observational study (n=16) showed a clinically important difference in energy intake between babies receiving high energy intake compared with low energy intake, with greater energy intake in the group of babies receiving high energy intake: MD 18.20kcal/kg/day (95% CI 15.65 to 20.75).

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that body composition, nitrogen accretion and anthropometric measures should be included as critical outcomes as these are most directly influenced by overall energy intake. Mortality rates, PN associated liver disease, hyperglycaemia, hypophosphataemia, and hypercalcaemia were considered important outcomes, as these will be influenced by energy intake and other factors. The actual energy intake received by the

baby was also selected as an important outcome because the actual intake could differ from the provided energy.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE methodology. The observational evidence was very low quality due to risk of bias in the included studies and uncertainty around the effects. The RCT evidence ranged from very low to high quality and was mainly downgraded due to uncertainty around the effects. There was also some heterogeneity across studies, selection bias, attrition bias and selective reporting bias. Blinding of pharmacists and personnel involved in administering PN was not possible in the RCTs due to safety reasons, however it was reported that this is unlikely to have affected clinical care so evidence was not downgraded for this reason. One of the included studies had a cross over design that only covered the first 48 hours after birth (Forsyth 1995), two studies included enteral feeding as well as parenteral feeding (Morgan 2014; Tan 2008), and one study assigned babies with hyperbilirubinaemia to the low energy arm (Zlotkin 1981).

The committee noted that the included studies differed according to the amount of macronutrients and energy intake, thus were not entirely comparable, and that the protocols in older studies did not reflect current practice.

Benefits and harms

There was evidence from RCT and observational studies that nitrogen retention and balance were higher in babies who received high energy intake compared with low energy intake; however, there was uncertainty around the effects.

The RCT evidence showed no clinically important differences in head circumference measured during the first 4 weeks of life and at 36 weeks' controlled for gestational age. However, there was uncertainty around these effects and there was some observational evidence of greater gains in head circumference with high energy intake compared with low energy intake.

RCT evidence showed no clinically important differences between groups for any weight or height outcomes; however, there was uncertainty around the effects. There was greater weight and height gain shown in two observational studies but evidence was very low quality and one study, which showed the greatest difference between groups, assigned babies with hyperbilirubinaemia to low energy intake; therefore, it is unclear whether differences in growth outcomes are due to energy intake or hyperbilirubinaemia.

There were no clinically important differences in mortality based on energy intake, although there was high uncertainty around the effects. There was some evidence of reduced hyperbilirubinaemia at 28 days in babies who received high energy intake compared with low energy intake; however, there was uncertainty around the effect and this difference was not observed at 36 weeks' CGA.

There was inconsistent evidence regarding whether babies who were prescribed high energy intake actually received higher energy intake than those prescribed low energy intake. Clinically important differences were observed in the first two weeks of life, but these differences were not observed in the third and fourth week of life, or for cumulative energy intake over the first 4 weeks of life. However, PN was decreased during the transition to enteral feeding, and was discontinued when 50 to 75% of nutrition was received from enteral feeds; therefore, differences may have been harder to detect during periods with lower PN. Further evidence from 1 RCT and 1 observational study where the timeframe for nutritional intake was unclear also showed higher energy intake in babies who were prescribed high energy. Therefore, the committee agreed that the evidence showed it was feasible to provide higher energy intakes.

The committee decided that they could not make recommendations on a specific ideal energy intake for all babies based on the limited evidence available. The committee also noted that the composition of macronutrient intake differed between trial groups, which makes it difficult to conclude if differences are based on energy intake or intake of other macronutrients such as protein. The recommendations were therefore based on informal consensus of the committee. They used their experience and expertise to conduct a theoretical exercise, taking into account knowledge regarding physiological and metabolic requirements of babies. In this exercise the committee worked backwards from the individual nutrients (for which there was evidence for the ranges advised and in which they had greater confidence – see section 1.5 of the guideline) and converted their respective dosages into calories.

The committee discussed the number of days over which energy intake should increase to reach the intended maintenance level, and agreed to align this with the recommendations on lipid, carbohydrates and amino acid increases (see section 1.5 of the guideline). The committee agreed that babies who start PN in the first 4 days after birth should have a starting range and increase up to a maintenance range over approximately 4 days. This timeframe was primarily selected because neonatal metabolic adaptation occurs in the early days of life, enabling the baby to metabolise the nutrients delivered. In addition, fluid volume allowances are commonly increased over the first few days of life and this means that increasing amounts of nutrition can be given parenterally. For babies starting PN after the first 4 days of life early metabolic adaptation is likely to have taken place and their fluid volume allowances would have already increased so this allows parenteral nutrition to be started using maintenance ranges.

Based on committee knowledge that PN-related complications would be higher in term babies that are critically ill or have just had surgery, they decided that giving energy intake in the lower range would be more appropriate for these groups because term babies' energy stores tend to be more replete. However, they only made this recommendation for term babies who are critically because in critically ill preterm babies, who have limited nutritional stores, prioritising nutritional intake may be more important.

Cost effectiveness and resource use

No economic studies were identified which were applicable to this review question.

The committee explained that recommendations pertaining to an optimal nutritional intake in preterm and term babies who are receiving PN would not incur extra resource implications to the health care system.

The committee noted that getting the right nutritional intake may result in avoiding additional costs associated with nutritional deficit or providing energy in excess. For example, nutritional deficits which may occur during PN are known to be negatively associated with mortality, respiratory, growth and neurodevelopmental outcomes and may require expensive NHS care. Similarly, providing energy in excess of needs is associated with impaired liver function, and increased adiposity which also require expensive care.

The committee explained that recommendations in this area reflect practice across many units and as such cost savings to the NHS, if any, are likely to be negligible.

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Appendices

Appendix A – Review protocols

Review protocol for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Field (based on PRISMA-P)	Content
Review question	How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?
Type of review question	Intervention
Objective of the review	What are the energy needs of preterm and term babies receiving parenteral nutrition?
Eligibility criteria – population/disease/condition/issue/domain	• Babies born preterm, up to 28 days after their due birth date (preterm babies) • Babies born at term, up to 28 days after their birth (term babies)
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Different kcal/kg/day
Eligibility criteria – comparator(s)/control or reference (gold) standard	• Each other

Outcomes and prioritisation	**Critical outcomes**:
	• Body composition (measured as lean mass, fat-free mass, fat mass, adipose tissue)
	• Nitrogen accretion
	• Growth/anthropometric measures
	  ○ Head circumference
	  ○ Weight gain
	  ○ Height gain
	
	Important Outcomes:
	• Mortality
	• Adverse effects of PN:
	  ○ PN related liver disease (abnormal liver function, cholestasis, conjugated hyperbilirubinaemia, intrahepatocellular lipid)
	  ○ Hyperglycaemia
	  ○ Hypophosphataemia/hypercalcaemia
	• Energy intake (as the actual amount given)

Field (based on PRISMA-P)	Content
Eligibility criteria – study design	Systematic reviews of RCTs RCTs Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs (if no evidence from RCTs or comparative cohort studies available and are recent i.e., in the last 2 years-authors will be contacted for further information).
Other inclusion exclusion criteria	No sample size restriction No date restriction Clinical settings that provide neonatal care or specialist paediatric care. UK and non-UK studies (non-UK studies from middle and high income countries according to WHO/World Bank criteria).
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analysis: Babies born preterm, up to 28 days after their due birth date (preterm babies) Babies born at term, up to 28 days after their birth (term babies) Subgroup analysis: The following groups will be considered for subgroup analysis: Age of baby (first 2 weeks versus later) Preterm (extremely preterm <28 weeks GA; very preterm: 28-31 weeks GA; moderately preterm: 32-36 weeks GA) Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g) Critically ill babies IUGR Specialist versus standard neonatal care Important confounders (when comparative observational studies are included for interventional reviews) Age of baby (first 2 weeks versus later) Birthweight: low birthweight (<2500g); very low birthweight (<1500g) and extremely low birthweight (<1000g) Actual dose received Other underlying conditions (e.g., chronic lung disease) Sex of baby Gestation (preterm vs. term)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer.

Field (based on PRISMA-P)	Content
	A random sample of the references identified in the search will be sifted by a second reviewer. This sample size will be 10% of the total, or 100 studies if the search identifies fewer than 1000 studies. All disagreements in study inclusion will be discussed and resolved between the two reviewers. The senior systematic reviewer or guideline lead will be involved if discrepancies cannot be resolved between the two reviewers.
Data management (software)	Data Analysis Where data is available, pair-wise meta-analysis using a fixed effects model, will be used to combine results from similar studies, this will be performed using Cochrane Review Manager (RevMan5). Heterogeneity will be considered, and if a random-effects model is considered more appropriate, it will be conducted. Quality Assessment Appraisal of methodological quality will be conducted using the appropriate tool: ROBIS (systematic reviews and meta-analyses), Cochrane risk of bias tool for RCT (RCT or comparative cohort studies). Cochrane risk of bias tool, ROBINS-I (Non-randomised studies) The quality of evidence for each outcome will be assessed using GRADEpro: Outcomes will be downgraded if the randomisation and/or concealment methods are unclear or inadequate. Outcomes will also be downgraded if there is considerable missing data (if there is a dropout of more than 20%, or if there is a difference of >20% between groups. Heterogeneity will be assessed using the I2, outcomes will be downgraded once if I2 >50%, twice if I2 >80%. Imprecision: Outcomes will be downgraded if the 95% CI is imprecise (i.e. crosses 0.8 or 1.25, (dichotomous) or -0.5 or 0.5 (continuous)). Outcomes will be downgraded two levels depending on how many lines of imprecision are crossed. If the clinical decision threshold is NOT crossed, we will consider whether the criterion for Optimal Information Size is met, if not we will downgrade one level for dichotomous outcomes with less than 300 events, and downgrade one level for continuous outcomes when less than 400 participants are included. Clinical effectiveness For dichotomous outcomes, minimal important differences will be considered using thresholds of RR >0.80 and <1.25. For continuous outcomes, minimal important differences will be considered 0.5 times the SD of the control group
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.
Identify if an update	This is not an update.
Author contacts	Developer: The National Guideline Alliance

Field (based on PRISMA-P)	Content
	https://www.nice.org.uk/guidance/indevelopment/gid-ng10037
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014.
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see appendix B.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual 2014. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual 2014.
Methods for analysis – combining studies and exploring (in)consistency	For details of the methods please see supplementary material C.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots. Trial registries will be examined to identify missing evidence: Clinical trials.gov, NIHR Clinical Trials Gateway.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Joe Fawke (Consultant Neonatologist and Honorary Senior Lecturer, University Hospitals Leicester NHS Trust) in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details of the methods please see supplementary material C.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.

Field (based on PRISMA-P)	Content
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
PROSPERO registration number	Not registered with PROSPERO.

CDSR: Cochrane Database of Systematic Reviews; DARE: Database of Abstracts of Reviews of Effects; GA: gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IUGR: intrauterine growth restriction; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PN: parenteral nutrition; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies of interventions; ROBIS; risk of bias in systematic reviews; SD: standard deviation; UK: United Kingdom; WHO: World Health Organisation.

Appendix B – Literature search strategies

Literature search strategies for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	INFANT, NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURE BIRTH/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	exp INFANT, PREMATURE/
6	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
7	(pre#mie? or premie or premies).ti,ab.
8	exp INFANT, LOW BIRTH WEIGHT/
9	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
10	((LBW or VLBW) adj5 infan$).ti,ab.
11	INTENSIVE CARE, NEONATAL/
12	INTENSIVE CARE UNITS, NEONATAL/
13	NICU?.ti,ab.
14	or/1-13
15	PARENTERAL NUTRITION/
16	PARENTERAL NUTRITION, TOTAL/
17	PARENTERAL NUTRITION SOLUTIONS/
18	ADMINISTRATION, INTRAVENOUS/
19	INFUSIONS, INTRAVENOUS/
20	CATHETERIZATION, CENTRAL VENOUS/
21	exp CATHETERIZATION, PERIPHERAL/
22	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
23	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
24	drip?.ti,ab.
25	or/15-24
26	ENERGY INTAKE/
27	(energy adj5 (need$ or requir$ or receiv$ or intake? or amount? or optimal$ or optimis$ or target? or goal? or suffic$)).ti,ab.
28	((kcal? or kilocalorie? or calori$) adj5 (need$ or requir$ or receiv$ or intake? or amount? or optimal$ or optimis$ or target? or goal? or suffic$)).ti,ab.
29	((kcal? or kilocalorie?) adj3 (kg? or kilogram?) adj3 (d or day)).ti,ab.
30	or/26-29
31	ENERGY METABOLISM/
32	(energy adj3 (metabolism or expend$)).ti,ab.
33	or/31-32
34	14 and 25 and 30
35	14 and 25 and 33
36	or/34-35
37	limit 36 to english language
38	LETTER/
39	EDITORIAL/
40	NEWS/
41	exp HISTORICAL ARTICLE/
42	ANECDOTES AS TOPIC/
43	COMMENT/
44	CASE REPORT/
45	(letter or comment*).ti.
46	or/38-45
47	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
48	46 not 47
49	ANIMALS/ not HUMANS/
50	exp ANIMALS, LABORATORY/
51	exp ANIMAL EXPERIMENTATION/
52	exp MODELS, ANIMAL/
53	exp RODENTIA/
54	(rat or rats or mouse or mice).ti.
55	or/48-54
56	37 not 55

Databases: Embase; and Embase Classic

#	Searches
1	NEWBORN/
2	(neonat$ or newborn$ or new-born$ or baby or babies).ti,ab.
3	PREMATURITY/
4	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 (birth? or born)).ab,ti.
5	((preterm$ or pre-term$ or prematur$ or pre-matur$) adj5 infan$).ti,ab.
6	(pre#mie? or premie or premies).ti,ab.
7	exp LOW BIRTH WEIGHT/
8	(low adj3 birth adj3 weigh$ adj5 infan$).ti,ab.
9	((LBW or VLBW) adj5 infan$).ti,ab.
10	NEWBORN INTENSIVE CARE/
11	NEONATAL INTENSIVE CARE UNIT/
12	NICU?.ti,ab.
13	or/1-12
14	PARENTERAL NUTRITION/
15	TOTAL PARENTERAL NUTRITION/
16	PERIPHERAL PARENTERAL NUTRITION/
17	PARENTERAL SOLUTIONS/
18	INTRAVENOUS FEEDING/
19	INTRAVENOUS DRUG ADMINISTRATION/
20	exp INTRAVENOUS CATHETER/
21	(parenteral$ or intravenous$ or intra-venous$ or IV or venous$ or infusion?).ti,ab.
22	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
23	drip?.ti,ab.
24	or/14-23
25	CALORIC INTAKE/
26	(energy adj5 (need$ or requir$ or receiv$ or intake? or amount? or optimal$ or optimis$ or target? or goal? or suffic$)).ti,ab.
27	((kcal? or kilocalorie? or calori$) adj5 (need$ or requir$ or receiv$ or intake? or amount? or optimal$ or optimis$ or target? or goal? or suffic$)).ti,ab.
28	((kcal? or kilocalorie?) adj3 (kg? or kilogram?) adj3 (d or day)).ti,ab.
29	or/25-28
30	ENERGY METABOLISM/
31	(energy adj3 (metabolism or expend$)).ti,ab.
32	or/30-31
33	13 and 24 and 29
34	13 and 24 and 32
35	or/33-34
36	limit 35 to english language
37	letter.pt. or LETTER/
38	note.pt.
39	editorial.pt.
40	CASE REPORT/ or CASE STUDY/
41	(letter or comment*).ti.
42	or/37-41
43	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
44	42 not 43
45	ANIMAL/ not HUMAN/
46	NONHUMAN/
47	exp ANIMAL EXPERIMENT/
48	exp EXPERIMENTAL ANIMAL/
49	ANIMAL MODEL/
50	exp RODENT/
51	(rat or rats or mouse or mice).ti.
52	or/44-51
53	36 not 52

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

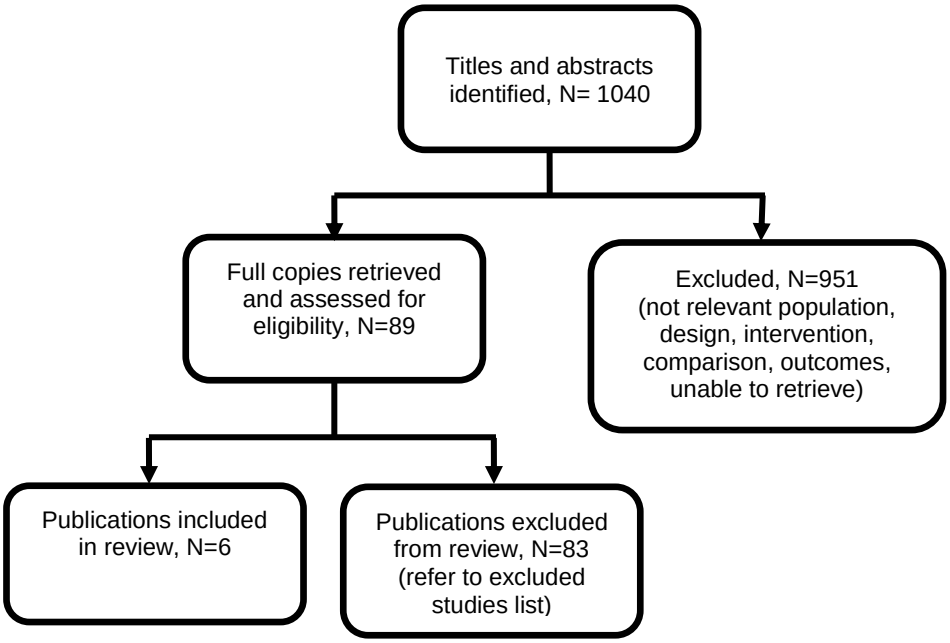
#	Searches
1	MeSH descriptor: [INFANT, NEWBORN] this term only
2	(neonat* or newborn* or new-born* or baby or babies):ti,ab
3	MeSH descriptor: [PREMATURE BIRTH] this term only
4	((preterm* or pre-term* or prematur* or pre-matur*) near/5 (birth? or born)).ab,ti.
5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*):ti,ab

#	Searches
7	(pre#mie? or premie or premies):ti,ab
8	MeSH descriptor: [INFANT, LOW BIRTH WEIGHT] explode all trees
9	(low near/3 birth near/3 weigh* near/5 infan*):ti,ab
10	((LBW or VLBW) near/5 infan*):ti,ab
11	MeSH descriptor: [INTENSIVE CARE, NEONATAL] this term only
12	MeSH descriptor: [INTENSIVE CARE UNITS, NEONATAL] this term only
13	NICU?:ti,ab
14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	MeSH descriptor: [PARENTERAL NUTRITION] this term only
16	MeSH descriptor: [PARENTERAL NUTRITION, TOTAL] this term only
17	MeSH descriptor: [PARENTERAL NUTRITION SOLUTIONS] this term only
18	MeSH descriptor: [ADMINISTRATION, INTRAVENOUS] this term only
19	MeSH descriptor: [INFUSIONS, INTRAVENOUS] this term only
20	MeSH descriptor: [CATHETERIZATION, CENTRAL VENOUS] this term only
21	MeSH descriptor: [CATHETERIZATION, PERIPHERAL] explode all trees
22	(parenteral* or intravenous* or intra-venous* or IV or venous* or infusion?):ti,ab
23	((peripheral* or central*) near/3 (line? or catheter*)):ti,ab
24	drip?:ti,ab
25	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	MeSH descriptor: [ENERGY INTAKE] this term only
27	(energy near/5 (need* or requir* or receiv* or intake? or amount? or optimal* or optimis* or target? or goal? or suffic*)):ti,ab
28	((kcal? or kilocalorie? or calori*) near/5 (need* or requir* or receiv* or intake? or amount? or optimal* or optimis* or target? or goal? or suffic*)):ti,ab
29	((kcal? or kilocalorie?) and (kg? or kilogram?) and (d or day)):ti,ab
30	#26 or #27 or 28 or #29
31	MeSH descriptor: [ENERGY METABOLISM] this term only
32	(energy near/3 (metabolism or expend*)):ti,ab
33	#31 or #32
34	#14 and #25 and #30
35	#14 and #25 and #33
36	#34 or #35

Appendix C – Clinical evidence study selection

Clinical study selection for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Figure 1: PRISMA Flow chart of clinical article selection for review question on energy needs of preterm and term babies.



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Table 3: Clinical evidence table for included studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Duffy, B., Gunn, T., Collinge, J., Pencharz, P., The effect of varying protein quality and energy intake on the nitrogen metabolism of parenterally fed very low birthweight (<1600 g) infants, Pediatric Research, 15, 1040-1044, 1981 Ref Id 688873 Country/ies where the study was carried out Canada Study type RCT Aim of the study	Sample size n = 24 Amigen high energy: n = 6 Amigen low energy: n = 6 Vamin high energy: n = 6 Vamin low energy: n = 6 Characteristics Birth weight (g) - mean (SE) Amigen high energy: 1197 (80) Amigen low energy: 1165 (79) Vamin High energy: 1394 (84) Vamin low energy: 1289 (80) Gestational age (week) - mean (SE) Amigen High energy: 29.7 (0.4) Amigen low energy: 28.8 (0.8)	Interventions All infants received approximately 2.67 (±0.3) g/kg/day amino acid. infants were randomised to: Amigen high energy: 93kcal/kg/day casein amino acid Amigen low energy: 68kcal/kg/day casein amino acid Vamin high energy: 93kcal/kg/day crystalline amino acid mixture based on egg albumin Vamin low energy: 68kcal/kg/day crystalline amino acid mixture based on egg albumin	Details The amino acid solutions contained dextrose, mineral and vitamins and were either infused alone (in the low energy groups) or in combination with 10% Intralipid (in the high energy groups). Daily fluid, amino acid, and mineral intakes per kg were similar for all groups. PN was started within the first 24 hours of life and infusion rates were increased as tolerated. Most infants required continuous airway-distending pressure and many required respirator assistance during the first week of life.	Results Nitrogen balance (mg/kg/day) - mean (SE) Amigen high energy: 187 (20) Amigen low energy: 125 (20) Vamin high energy: 284 (7) Vamin low energy: 214 (20) Nitrogen retention (%) - mean (SE) Amigen high energy: 56 (4) Amigen low energy: 39 (6) Vamin high energy: 72 (2) Vamin low energy: 61 (4) Weight gain (g/day) - mean (SE)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk. Infants were randomly allocated within the first 24 hours of life, however no details provided on randomisation. Allocation concealment: Unclear risk. Infants were randomly allocated within 24 hours of life, however no details provided on the allocation concealment. Performance bias Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment and it would be likely those responsible for nursing and clinical procedures would not be blinded for safety reasons. Detection bias Blinding of outcome assessment: Unclear risk. It was unclear whether outcome assessors

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the effect of varying protein quality and energy intake on the nitrogen metabolism of small parenterally fed premature infants during the first week of life. Study dates Not stated. Source of funding Not stated.	Vamin high energy: 30.0 (1.0) Vamin low energy: 29.8 (0.8) Inclusion criteria Preterm infants with birth weights <1600 g and informed written consent from the parents. Exclusion criteria Not stated.		Phototherapy was started as soon as an increase in serum bilirubin occurred. Statistical analyses: Statistical analyses were performed using a two-way analysis of variance (amino acid source and energy).	Amigen high energy: 9 (3) Amigen low energy: 16 (10) Vamin high energy: 62 (23) Vamin low energy: 35 (14) <u>Energy intake (kcal/kg/day) - mean (SE)</u> Amigen high energy: 90 (4) Amigen low energy: 66 (3) Vamin high energy: 96 (4) Vamin low energy: 70 (1)	were blind to treatment allocation, however, outcomes are objective. <u>Attrition bias</u> Incomplete outcome data: Low risk. No dropouts. <u>Reporting bias</u> Selective reporting: Low risk. All outcomes reported. <u>Other bias</u> Other sources of bias: Low risk. No other sources of bias detected. Other information Vamin has a higher nitrogen content per gram of amino acid than Amigen, which affected nitrogen intake. The Vamin and Amigen groups were combined for the purpose of analysis in order to compare high energy and low energy groups.
Full citation Forsyth, J. S., Murdock, N., Crighton, A., Low birthweight infants and total parenteral nutrition immediately after birth. III. Randomised study of energy substrate utilisation, nitrogen balance, and carbon	Sample size n = 20 randomised Characteristics Mean (SE) birthweight 1314 (65)g; mean (SE) gestation 30.9 (0.4) weeks. Inclusion criteria None stated. Exclusion criteria None stated.	Interventions Infants were randomly allocated immediately after birth to either a low or high carbohydrate (glucose) intake; after 24 hours they were changed to the alternative regimen which was continued for 24 hours.	Details PN was infused using neonatal infusion pumps and fat and protein intakes were kept constant throughout the study (for both glucose regimens). Indirect calorimetry was conducted for at least 2 hours for each regimen and urine was	Results <u>Outcome: Actual energy intake (kcal/kg/day</u> High glucose regimen (n = 20), mean (SE): 73.3 (4.1) Low glucose regimen (n = 20), mean (SE): 58.0 (4.0)	Limitations Cochrane risk of bias tool <u>Selection bias</u> Random sequence generation: Unclear risk. Infants were randomly allocated immediately after birth, however no details provided on the randomisation. Allocation concealment: Unclear risk. Infants were randomly allocated immediately after birth, however no details provided on the randomisation.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dioxide production, Archives of Disease in Childhood, Fetal and neonatal edition. 73, F13-6, 1995 Ref Id 439240 Country/ies where the study was carried out United Kingdom (Scotland) Study type Cross-over RCT Aim of the study To investigate energy substrate utilisation and nitrogen balance in low birthweight infants receiving total parental nutrition and compare two different glucose intakes on carbon dioxide production during the first days of life. Study dates Not stated. Source of funding Chest, Heart and Stroke Association (Scotland); Scottish		High glucose regimen: 12g/kg/day (8.3mg/kg/minute) Low glucose regimen: 8g/kg/day (5.5mg/kg/minute)	collected to measure nitrogen. Power analysis: Not stated Statistical analyses: Outcomes were compared using ANOVA and paired t tests.		<u>Performance bias</u> Blinding of participants and personnel: Unclear risk. Infants would be unaware of their assignment and it would be likely those responsible for nursing and clinical procedures would not be blinded for safety reasons, however this would unlikely effect clinical care. <u>Detection bias</u> Blinding of outcome assessment: Low risk. Outcomes are objective. <u>Attrition bias</u> Incomplete outcome data: Low risk for energy intake (no missing data). High risk for protein retention as no information provided on dropouts (n=8). <u>Reporting bias</u> Selective reporting: Low risk. All outcomes reported (Nitrogen balance reported as protein retention). <u>Other bias</u> Other sources of bias: High risk. A Latin square cross-over experimental design was used where each infant serves as his or her own control. Regimens were alternated each 24 hour period following allocation immediately after birth. Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Home and Health Department; Cow & Gate Nutricia.					Authors recommend a parenteral regimen consisting of glucose 10-12 g/kg/day, amino acids 1.5-2.0 g/kg/day, and lipid 1.8-2.0 g/kg/day to meet energy and protein requirements for the maintenance and continued growth of infants considered to be sufficiently unwell
Full citation Morgan, C, McGowan, P, Herwitker, S, Hart, Ae, Turner, Ma, Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study, Pediatrics, 133, e120-8, 2014 Ref Id 701507 Country/ies where the study was carried out United Kingdom (England) Study type RCT Aim of the study	Sample size n = 227 met birth weight/gestation criteria n = 196 eligible to take part (n=10 early deaths, n=8 unexpected to survive, n=3 congenital anomaly, n=10 early cranial ultrasound scan anomaly) n = 150 randomised (SCAMP n = 74; Control n = 76; n=40 refused consent, n=6 unavailable for consent) n = 135 available for analysis (SCAMP n = 66 [n = 8 deaths before 28 days]; Control n = 69 [n= 7 deaths before 28 days]) Characteristics <u>Birthweight (g) - mean (SD)</u> SCAMP: 900 (158)	Interventions All infants received the control PN as soon as possible after birth. Infants were randomised to SCAMP or control, where feasible before 72 hours of age or at least within 120 hours of age. Once randomised, infants maintained their assigned regimen throughout, with the study intervention continuing for 28 completed days of life. SCAMP: Standardised, concentrated neonatal parenteral nutrition formulation used in clinical practice with additional macronutrients (Total calorie intake, kcal/kg per day = 108; maximum protein g/kg per day =	Details Details of PN/enteral nutrition, fluid, and drug infusion were recorded using routine nursing charts. PN was discontinued if enteral feed exceeded 75% total. Amino acid, glucose, lipid and energy intake were calculated from published PN composition data. Electronic patient records were used to collect patient demographic, mortality, and morbidity data (obtained for 36 weeks correct gestational age (CGA) survivors with additional 28-day survivor outcomes for	Results <u>Outcome: Head circumference (mm) - mean (SD)</u> Measurement at Day 7 SCAMP (n = 66): 244 (12) Control (n = 69): 243 (14) Measurement at Day 14 SCAMP (n = 66): 252 (12) Control (n = 69): 250 (14) Measurement at Day 21 SCAMP (n = 66): 261 (14) Control (n = 69): 257 (16) Measurement at Day 28 SCAMP (n = 66): 271 (16)	Limitations Cochrane risk of bias tool <u>Selection bias</u> Random sequence generation: Low risk. Block randomisation codes generated in Stata 10. Allocation concealment: Low risk. Codes were sealed in opaque serially numbered envelopes and given to the pharmacy. Once parental consent was confirmed, the pharmacy opened envelopes sequentially and provided the allocation. <u>Performance bias</u> Blinding of participants and personnel: Unclear risk. Caregivers and parents were blinded but pharmacists were not blinded due to safety reasons. Authors report this is unlikely to have affected clinical care. <u>Detection bias</u> Blinding of outcome assessment: Low risk. Outcomes were objective.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To investigate the effect of a Standardised, Concentrated With Added Macronutrients Parenteral (SCAMP) nutrition regimen on head circumference (HC) and falling SD scores in very preterm babies. Study dates October 2009 to July 2012 Source of funding Bliss via the Innovation in Care Programme; Newborn appeal; National Institute for Health Research (through the Cheshire, Merseyside and North Wales Medicines for Children Research Network).	Control: 884 (183) Gestational age (weeks) - mean (SD) SCAMP: 26.8 (1.3) Control: 26.6 (1.4) Age (hours) PN started - median (IQR) SCAMP: 3 (2 to 6) Control: 3 (2 to 8) Age (hours) study PN started - median (IQR) SCAMP: 70 (46 to 94) Control: 67 (47 to 93) Inclusion criteria Infants were eligible to take part if they were born <29 weeks' gestation, weighed <1200g, were admitted within 48 hours of birth to the neonatal intensive care unit (NICU) at Liverpool Women's Hospital (LWH), and parental consent was given. Exclusion criteria Infants were excluded if they were thought unlikely to survive, had major congenital or chromosomal abnormalities, or known to have a parenchymal brain lesion on cranial	3.8; maximum lipid, g/kg per day = 3.8, maximum glucose g/kg per day = 15.6). Control: Standardised, concentrated neonatal parenteral nutrition formulation used in clinical practice without any additional macronutrients (Total calorie intake, kcal/kg per day = 85; maximum protein g/kg per day = 2.8; maximum lipid, g/kg per day = 2.8, maximum glucose g/kg per day = 13.5).	morbidities related to PN complications). Statistical analysis: Analysis was conducted using Stata 11, SPSS 20 and R 2.15.1. Primary outcome was analysed using a general linear model, controlling for stratum based on gestational age, and checked with sensitivity analyses. Longitudinal joint modelling of head circumference and survival was conducted. Between group t tests, chi squared tests and linear models were generated as appropriate.	Control (n = 69): 265 (17) Measurement at 36 weeks' corrected gestational age SCAMP (n = 63): 316 (13) Control (n = 63): 311 (15) Outcome: Weight (g) - mean (SD) Measurement at Day 7 SCAMP (n = 66): 934 (123) Control (n = 69): 903 (153) Measurement at Day 14 SCAMP (n = 66): 1044 (152) Control (n = 69): 989 (171) Measurement at Day 21 SCAMP (n = 66): 1147 (173) Control (n = 69): 1072 (209) Measurement at Day 28 SCAMP (n = 66): 1269 (222) Control (n = 69): 1212 (242)	Complete blinding to intervention at cot side. Attrition bias Incomplete outcome data: Low risk. There were no study withdrawals (apart from deaths). Reporting bias Selective reporting: Low risk. All outcomes reported. Other bias Other sources of bias: Low risk. None. Other information Study was not powered to assess differences in major complications.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ultrasound scan before 48 hours of age.			Measurement at 36 weeks' corrected gestational age: SCAMP (n = 62): 2082 (293) Control (n = 62): 1976 (346) Outcome: Mortality - number (%) Measurement at Day 28 SCAMP (n = 66): 8 (11) Control (n = 69): 7 (9) 36 weeks' corrected gestational age: SCAMP (n = 63): 11 (15) Control (n = 64): 12 (16) Outcome: Conjugated hyperbilirubinaemia (conjugated bilirubin > 50 mmol/L) - number (%) Measurement at Day 28 SCAMP (n = 66): 6 (9) Control (n = 69): 8 (12) 36 weeks' corrected gestational age: SCAMP (n = 63): 13 (21) Control (n = 64): 12 (19)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Outcome: Calorie intake (kcal/kg /per day) - mean (SD) Total (Week 1) SCAMP (n = 66): 74 (7) Control (n = 69): 68 (6) Parenteral (Week 1) SCAMP (n = 66): 70 (8) Control (n = 69): 63 (6) Total (Week 2) SCAMP (n = 66): 109 (10) Control (n = 69): 95 (9) Parenteral (Week 2) SCAMP (n = 66): 82 (23) Control (n = 69): 65 (19) Total (Week 3) SCAMP (n = 66): 110 (15) Control (n = 69): 105 (9) Parenteral (Week 3) SCAMP (n = 66): 40 (36) Control (n = 69): 31 (31) Total (Week 4) SCAMP (n = 66): 115 (17) Control (n = 69): 113 (23) Parenteral (Week 4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				SCAMP (n = 66): 23 (34) Control (n = 69): 18 (26) <u>Outcome: Calorie intake (kcal/kg/per 28d) - mean (SD)</u> Cumulative total (day 1 - 28) SCAMP (n = 66): 2851 (251) Control (n = 69): 2664 (307) Cumulative parenteral (day 1 - 28) SCAMP (n = 66): 1500 (555) Control (n = 69): 1237 (461)	
Full citation Pineault, M., Chessex, P., Bisaillon, S., Brisson, G., Total parenteral nutrition in the newborn: impact of the quality of infused energy on nitrogen metabolism, American Journal of Clinical Nutrition, 47, 298-304, 1988 Ref Id	Sample size N=16 (all babies were included in both the low fat and high fat groups) 60 kcal/kg^{-1}/d^{-1}; low fat: n=8 60 kcal/kg^{-1}/d$^{-1;}$ high fat: n=8 80 kcal/kg^{-1}/d^{-1}; low fat: n=8 80 kcal/kg^{-1}/d^{-1}; high fat: n=8 Characteristics	Interventions Babies were divided into two groups based on calorie intake needed to either maintain energy requirements (60 kcal/kg^{-1}/d^{-1}) or achieve normal growth (80 kcal/kg^{-1}/d^{-1}). Each baby completed two nutrition phases where they received either low fat (1g/kg^{-1}/d^{-1} lipids) or high fat (3g/kg^{-1}/d^{-1} lipids). Parental nutrition for the four groups comprised of:	Details Each infant received two 6-day periods of isocaloric and isonitrogenous (450 mg/kg^{-1}/day^{-1}) infusions, provided through a peripheral line. The only difference between the two periods was the source of calories (quantities of glucose and lipids). The caloric value of amino acids and glucose were	Results <u>Nitrogen balance (mg/kg^{-1}/day^{-1}) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1}; low fat (n=8) 216 (27.0) 60 kcal/kg^{-1}/d$^{-1;}$ high fat (n=8): 224 (18.0) 80 kcal/kg^{-1}/d^{-1}; low fat (n=8): 250 (8.0) 80 kcal/kg^{-1}/d^{-1}; high fat (n=8): 245 (10.0) <u>Nitrogen retention (%) - mean (SE)</u>	Limitations Quality of study assessed using ROBINS-I Confounding bias: Low risk. Selection of participants' bias: Low risk. Classification of interventions bias: Low risk. Intervention groups clearly defined. Deviations from intended interventions bias: Unclear risk. Protocol violations, if any occurred, are not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
394278 Country/ies where the study was carried out Canada Study type Observational study (with cross-over component (component of interest for this review question is based on two separate cohorts)) Aim of the study To determine the influences of the quality (level and source) of infused energy on nitrogen metabolism. Study dates Not stated. Source of funding Medical Research Council of Canada.	<u>Gestational age (weeks) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1}: 36 (1) 80 kcal/kg^{-1}/d^{-1}: 34 (1) <u>Age at study (days) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1}: 9 (1) 80 kcal/kg^{-1}/d^{-1}: 11 (2) <u>Birthweight (g) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1}: 2293 (147) 80 kcal/kg^{-1}/d^{-1}: 2006 (169) <u>Weight at study (g) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1}: 2102 (153) 80 kcal/kg^{-1}/d^{-1}: 1850 (174) <u>Duodenal atresia - number (%)</u> 60 kcal/kg^{-1}/d^{-1}: 2 (25) 80 kcal/kg^{-1}/d^{-1}: 0 (0) <u>Gastroschisis - number (%)</u> 60 kcal/kg^{-1}/d^{-1}: 2 (25) 80 kcal/kg^{-1}/d^{-1}: 2 (25) <u>Necrotising enterocolitis - number (%)</u> 60 kcal/kg^{-1}/d^{-1}: 3 (37.5)	60 kcal/kg^{-1}/d^{-1}; low fat: 11 g/kg/$^{-1}$/day^{-1} glucose; 1g/kg^{-1}/d^{-1} lipids. 60 kcal/kg^{-1}/d$^{-1;}$ high fat: 5 g/kg/$^{-1}$/day^{-1} glucose; 3g/kg^{-1}/d^{-1} lipids. 80 kcal/kg^{-1}/d^{-1}; low fat: 17g/kg^{-1}/day^{-1} glucose; 1g/kg^{-1}/day^{-1} lipids 80 kcal/kg^{-1}/d^{-1}; high fat: 11g/kg^{-1}/day^{-1} glucose; 3g/kg^{-1}/day^{-1} lipids	5.2kcal/g and 3.4kcal/g, respectively. All infusions provided 150 mL/kg/day of total fluids, 3mmol/kg/day sodium, 2mmol/kg/day potassium, 2mmol/kg/day chloride, 1mmol/kg/day calcium, 0.125mmol/kg/day magnesium, 0.8mmol/kg/day phosphorus, 300µg/kg/day zinc, 40µg/kg/day copper and 2.5ml/day multivitamins. Assisted ventilation and supplementary oxygen were not required. Statistical analyses: ANOVA was used to compare results of nutrient and calorie intakes, nitrogen retention, 3-methylhistidine, glycaemia, and blood urea nitrogen. In the case of missing data from one of the	60 kcal/kg^{-1}/d^{-1}; low fat (n=8): 49.7 (5.8) 60 kcal/kg^{-1}/d$^{-1;}$ high fat (n=8): 52.0 (4.2) 80 kcal/kg^{-1}/d^{-1}; low fat (n=8): 57.1 (1.9) 80 kcal/kg^{-1}/d^{-1}; high fat (n=8): 55.9 (2.2) <u>Head circumference increment (cm/week) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1} (n=8): 0.50 (0.12) 80 kcal/kg^{-1}/d^{-1} (n=7): 0.90 (0.15) <u>Weight gain (g/kg^{-1}/d^{-1}) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1} (n=8): 11.5 (2.3) 80 kcal/kg^{-1}/d^{-1} (n=8): 14.6 (2.0) <u>Length gain (cm/week) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1} (n=8): 0.67 (0.17) 80 kcal/kg^{-1}/d^{-1} (n=8): 0.92 (0.22) <u>Energy intake (kcal/kg^{-1}/d^{-1}) - mean (SE)</u> 60 kcal/kg^{-1}/d^{-1} (n=8): 61.9 (0.7) 80 kcal/kg^{-1}/d^{-1} (n=8): 80.1 (1.1)	Missing data bias: Low risk. Data for head circumference was missing for one baby in the 80 kcal/kg^{-1}/d^{-1} group; no other missing data. Measurement of outcomes bias: Low risk. Unlikely that outcome assessors were blind to intervention for safety reasons but all outcomes are objective. Selection of the reported results bias: Moderate risk. Is it unclear why results are reported separately for low fat and high fat groups for nitrogen balance outcomes, but these groups are combined for growth outcomes. Other information Unclear wash-out period between interventions, suggesting potential for carry-over effect from one intervention to the other. However, as the comparison of interest for this review question is energy intake, not source of energy intake, any carry-over effect will not affect the results. The high fat and low fat groups were combined (where analyses were not reported separately) for the purpose of analysis in order to compare high energy and low energy groups.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	80 kcal/kg^{-1}/d^{-1}: 4 (50) Oesophageal atresia - number (%) 60 kcal/kg^{-1}/d^{-1}: 1 (12.5) 80 kcal/kg^{-1}/d^{-1}: 1 (12.5) Feeding intolerance - number (%) 60 kcal/kg^{-1}/d^{-1}: 0 (0) 80 kcal/kg^{-1}/d^{-1}: 1 (12.5) Inclusion criteria Appropriate-for-gestational-age newborn infants demonstrating unchanging clinical conditions. Exclusion criteria Not stated.		periods, Student's *t*-test was used.		
Full citation Tan, M. J., Cooke, R. W., Improving head growth in very preterm infants - A randomised controlled trial I: Neonatal outcomes, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, f337-f341, 2008 Ref Id	Sample size n = 176 eligible to take part n = 142 randomised (Hyperalimentation = 68; Control n = 74; n=26 refused consent, n=8 missed) n = 114 included in the analysis (Hyperalimentation n = 55 [n=13 died]; Control n =59 [n=15 died]) Characteristics	Interventions Hyperalimentation: PN contained 117 kcal/kg/day energy with 16.3g/kg/day dextrose, 4g/kg/day protein, and 4g/kg/day fat. PN was increased stepwise from 1g/kg/day protein and lipid to 4g/kg/day protein and lipid over 7 days. Control: PN contained 93kcal/kg/day energy with 13.5g/kg/day	Details PN began within the first 24 hours after birth when possible. Carbohydrate intake was dependent upon the total fluid allowance of each infant, increased from 60 and 90ml/kg/day to 150 and 165ml/kg/day in the first 5 days. Infants started milk within 48 hours or when clinically stable,	Results Outcome: Occipitofrontal circumference (OFC) at 36 weeks' PMA (Postmenstrual age) (cm) - mean (SD) Hyperalimentation: 31.1 (1.5) Control 31.4 (1.3) Outcome: OFC SDS (standard deviation scores) at 36 weeks' PMA - mean (SD)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk. Variable-length block randomisation was used. Allocation concealment: Low risk. Randomisation codes were kept in sequentially numbered, opaque and sealed envelopes. Performance bias Blinding of participants and personnel: Unclear risk. Participants would be unaware of their assignment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
689997 Country/ies where the study was carried out United Kingdom (England) Study type RCT Aim of the study To investigate the feasibility and effect of hyperalimentation (providing macronutrients above recommended levels) on nutrition and head growth of preterm babies. Study dates January 2004 to January 2007 Source of funding None disclosed.	Birthweight (g) - mean (SD) Hyperalimentation: 911 (224) Control: 914 (219) Gestational age (weeks) - mean (SD) Hyperalimentation: 26 (1.5) Control: 26.2 (1.5) Occipitofrontal circumference (cm) - mean (SD) Hyperalimentation: 24.5 (1.9) Control: 24.3 (1.9) Inclusion criteria Infants born before 29 weeks' gestation, admitted within 7 days of age with written informed parental consent were included. Exclusion criteria Triplets and infants of higher multiplicity, infants admitted after 7 days of age, and infants with major congenital abnormalities were excluded.	dextrose, 3g/kg/day protein, and 3g/kg/day fat. PN was increased stepwise from 1g/kg/day protein and lipid to 3g/kg/day protein and lipid over 5 days.	with target energy and protein intake 133 to 150 kcal/kg/day and 4g/kg/day for the intervention group, and 133kcal/kg/day and 3.3g/kg/day for the control group. PN was discontinued once infants received >50% of their total fluid as milk. Occipitofrontal circumference was measured using a non-stretchable lasso tape (Child Growth Foundation, London UK), total body length was measured using a standard infant measuring mat (Child Growth Foundation), mid-arm circumference (MAC) was measured using a non-stretchable disposable measuring tape, weight gain was measured using digital scales (Seca 757 class III) and energy intake was estimated by subtracting actual cumulative energy	Hyperalimentation: -1 (1.2) Control: -0.8 (1.1) Outcome: Weight at 36 weeks' PMA (g) - mean (SD) Hyperalimentation: 2136 (345) Control: 2090 (293) Outcome: Weight SDS at 36 weeks' PMA - mean (SD) Hyperalimentation: -1.3 (0.9) Control: -1.4 (0.8) Outcome: Length at 36 weeks' PMA (cm) - mean (SD) Hyperalimentation: 42.9 (2.3) Control: 42.4 (2.1) Outcome: Length SDS at 36 weeks' PMA - mean (SD) Hyperalimentation: -2.3 (1.3) Control: -2.6 (1.2) Outcome: Lower leg length at 36 weeks' PMA (cm) - mean (SD) Hyperalimentation: 10.3 (0.7)	and personnel involved in administering PN could not be blinded for safety reasons, however the authors report this would unlikely effect clinical care. Detection bias Blinding of outcome assessment: Unclear risk. Trained observers measured the primary outcome (occipitofrontal circumference) were blind to assignment. All other outcomes were measured by author. No details provided if blinded. Attrition bias Incomplete outcome data: High risk (20% of participants either died or lost at follow up). Reporting bias Selective reporting: Low risk. All outcomes reported. Other bias Other sources of bias: Low risk. No other sources of bias. Other information Study underpowered to show a significant difference in OFC.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			intake from recommended intake. Statistical analysis: Analysis was conducted in SPSS 12 using student's t tests, chi-squared tests, Mann-Whitney U tests, ANOVA and bivariate correlations.	Control: 10.3 (0.7) <u>Outcome: Mid-arm circumference at 36 weeks' PMA (cm) - mean (SD)</u> Hyperalimentation: 8.6 (0.8) Control: 8.5 (0.8) <u>Outcome: Energy intake at 4 weeks (kcal/kg) - mean (SD)</u> Hyperalimentation group (n=55): 2766 (233) Control group (n=59): 2621 (191)	
Full citation Zlotkin, S. H., Bryan, M. H., Anderson, G. H., Intravenous nitrogen and energy intakes required to duplicate in utero nitrogen accretion in prematurely born human infants, The Journal of pediatrics, 99, 115-20, 1981 Ref Id 690255	Sample size N = 22 Low energy, medium nitrogen: n = 6 Low energy, high nitrogen: n = 6 High energy, low nitrogen: n = 5 High energy, medium nitrogen: n = 8 High energy, high nitrogen: n = 5 Characteristics <u>Gestational age (weeks) - mean (range)</u> 29.2 (25 to 33)	Interventions Infants with hyperbilirubinaemia were assigned to low energy PN and infants without hyperbilirubinaemia were assigned to high energy PN. Infants within these groups were then randomised to low (high energy only), moderate or high nitrogen intake, forming 5 groups. Low energy, medium nitrogen: Non-protein intake of 50kcal/kg/day	Details All infants received the same amino acid mixture (Aminosyn) in 10% dextrose with a fluid intake of 160ml/kg/day. Feeding periods lasted 6 days and only PN was received during this time. Statistical analyses: Analysis of variance or covariance were used to compare group means. Simple and multiple regression	Results <u>Nitrogen retention (mg/kg/day) - mean (SE)</u> Low energy, medium nitrogen: 274 (11) Low energy, high nitrogen: 256 (20) High energy, low nitrogen: 432 (21) High energy, medium nitrogen: 320 (8) High energy, high nitrogen: 185 (24) <u>Nitrogen retention (%) - mean (SE)</u>	Limitations Quality of study assessed using ROBINS-I Confounding bias: High risk. Babies in the low energy groups all had hyperbilirubinaemia. Selection of participants' bias: High risk. 8 babies were included in more than one group. Classification of interventions bias: Low risk. Intervention groups clearly defined. Deviations from intended interventions bias: Unclear risk. Protocol violations, if any occurred, are not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Canada Study type Observational study (Trial with randomised and non-randomised assignment [non-randomised component of interest for current review question]) Aim of the study To assess the individual and combined effects of energy and nitrogen intake on nitrogen retention and growth in premature babies. Study dates Not stated. Source of funding Medical Research Council of Canada; Abbott Laboratories	<u>Postnatal age (days) - mean (range)</u> 18.7 (4 to 55) <u>Necrotising enterocolitis - number (%)</u> 19 (86) <u>Duodenal atresia - number (%)</u> 2 (9) <u>Diaphragmatic hernia - number (%)</u> 1 (5) Inclusion criteria Premature, appropriate size for gestational age infants. Exclusion criteria Infants aged less than 4 days (due to major changes in hydration status interfering with interpretation of weight change).	received from dextrose; 480mg/kg/day nitrogen. Low energy, high nitrogen: Non-protein intake of 50kcal/kg/day received from dextrose; 640mg/kg/day nitrogen. High energy, low nitrogen: Non-protein intake of 80kcal/kg/day received from a combination of dextrose (15g/kg/day) and lipids (2.7g/kg/day); 320mg/kg/day nitrogen. High energy, medium nitrogen: Non-protein intake of 80kcal/kg/day received from a combination of dextrose (15g/kg/day) and lipids (2.7g/kg/day); 480mg/kg/day nitrogen. High energy, high nitrogen: Non-protein intake of 80kcal/kg/day received from a combination of dextrose (15g/kg/day) and lipids (2.7g/kg/day); 640mg/kg/day nitrogen.	analyses were used to assess the relationship between energy and nitrogen intake on nitrogen retention and weight change.	Low energy, medium nitrogen: 42 (1) Low energy, high nitrogen: 52 (4) High energy, low nitrogen: 68 (3) High energy, medium nitrogen: 67 (2) High energy, high nitrogen: 60 (7) <u>Weight gain (g/kg/day) - mean (SE)</u> Low energy, medium nitrogen: 1.5 (3.2) Low energy, high nitrogen: 2.2 (4.0) High energy, low nitrogen: 15.6 (1.9) High energy, medium nitrogen: 16.2 (2.4) High energy, high nitrogen: 5.2 (3.1) <u>Length gain (cm/6 day) - mean (SE)</u> Low energy, medium nitrogen: 0.6 (0.2) Low energy, high nitrogen: 0.3 (0.1) High energy, low nitrogen: 0.7 (0.2) High energy, medium nitrogen: 1.0 (0.2) High energy, high nitrogen: not reported.	Missing data bias: Low risk. No missing data. Measurement of outcomes bias: Low risk. Unlikely that outcome assessors were blind to intervention for safety reasons but all outcomes are objective. Selection of the reported results bias: Moderate risk. Insufficient reporting of head circumference and length gain was not reported for the high energy, high nitrogen group. Other information 8 infants were included in more than one group. A low energy, low nitrogen group was not included due to risk of very poor nitrogen retention and growth (demonstrated in other studies). Three infants died from respiratory and/or haemorrhagic complications after completion of the study period; assigned treatment groups were not stated but the infants were all from different groups. The low, medium and high nitrogen groups were combined for the purpose of analysis in order to compare high energy and low energy groups.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Energy intake (kcal/kg/day) - mean Low energy, medium nitrogen: 55 Low energy, high nitrogen: 50 High energy, low nitrogen: 80 High energy, medium nitrogen: 80 High energy, high nitrogen: 83	

ANOVA: analysis of variance; CGA: correct for gestational age; MAC: mid arm circumference; NICU: neonatal intensive care unit; OFC: occipital frontal circumference; PMA: post menstrual age; PN: parenteral nutrition; ROBINS-I: risk of bias in non-randomised studies of interventions; SCAMP: standardised, concentrated, additional macronutrients, parenteral nutrition; SD: standard deviation; SDS: standard deviation score: SE: standard error; UK: United Kingdom.

Appendix E – Forest plots

Forest plots for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Figure 2: Forest plot for comparison high energy intake versus low energy intake: Nitrogen retention (%)

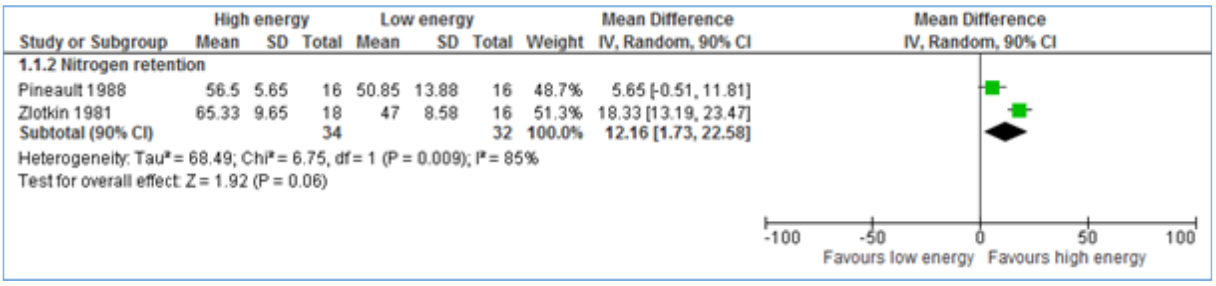


Figure 3: Forest plot for comparison high energy intake versus low energy intake: Nitrogen balance

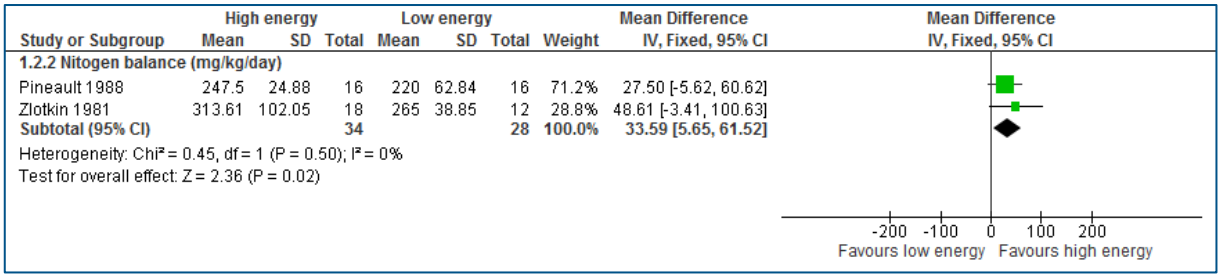


Figure 4: Forest plot for comparison high energy intake versus low energy intake: Weight (g)

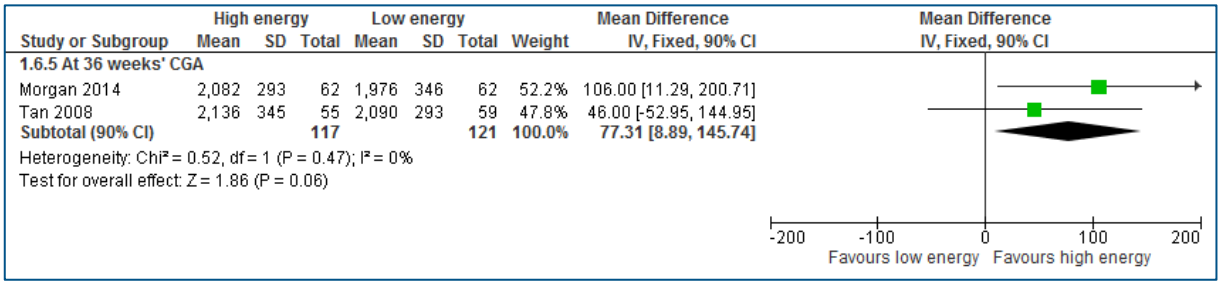


Figure 5: Forest plot for comparison high energy intake versus low energy intake: Weight gain

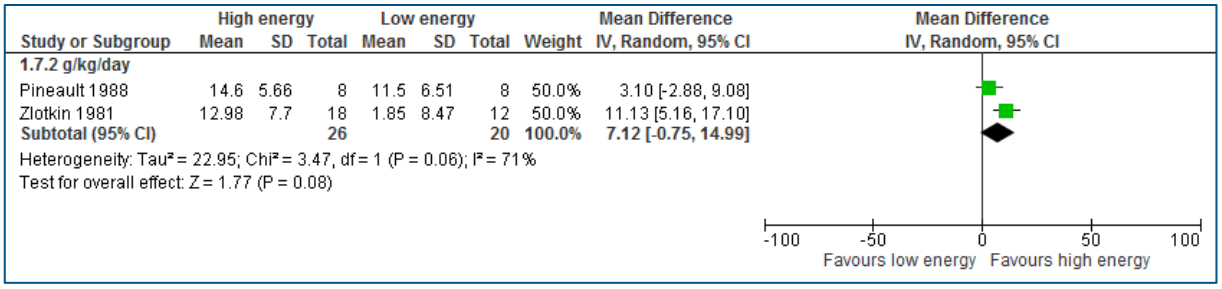


Figure 6: Forest plot for comparison high energy intake versus low energy intake: Length gain (cm/week)

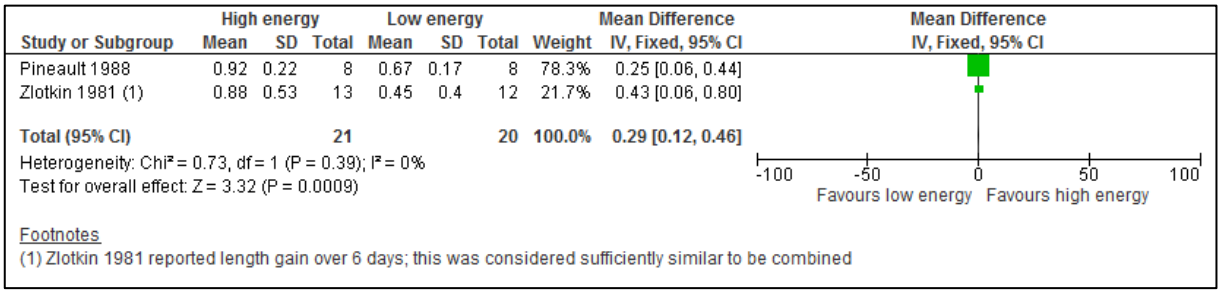
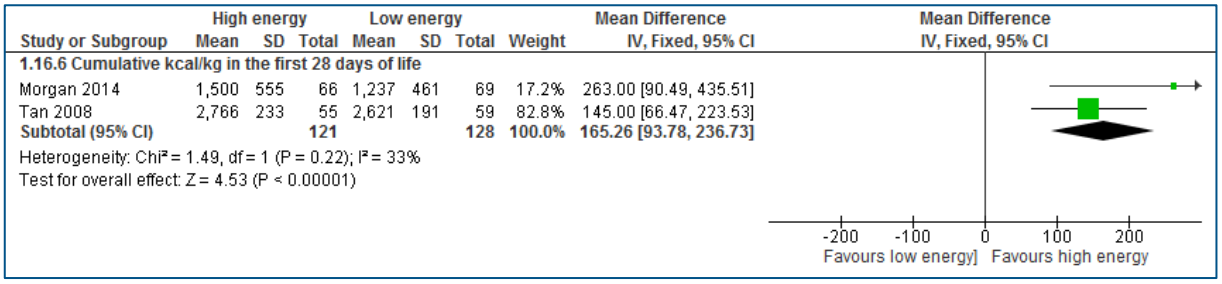


Figure 7: Forest plot for comparison high energy intake versus low energy intake: Energy intake



Appendix F – GRADE tables

GRADE tables for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Table 4: Clinical evidence profile for high energy intake versus low energy intake

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High energy intake	Low energy intake	Relative (95% CI)	Absolute	Quality	Importance
Nitrogen retention (%) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12	12	-	14 higher (4.52 to 23.48 higher)	⊕⊕OO LOW	CRITICAL
Nitrogen retention (%) (Better indicated by higher values)												
2	observational studies	very serious[3]	very serious[4]	no serious indirectness	serious[5]	none	34*	32*	-	12.16 higher (1.73 to 22.58 higher)	⊕OOO VERY LOW	CRITICAL
Nitrogen balance - Nitrogen balance (mg/kg/day) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	12	12	-	MD 66 higher (14.98 to 117.02 higher)	⊕⊕OO LOW	CRITICAL
Nitrogen balance - Nitrogen balance (mg/kg/day) (Better indicated by higher values)												
2	observational studies	very serious[3]	no serious inconsistency	no serious indirectness	serious[7]	none	34*	28*	-	MD 33.59 higher (5.65 to 61.52 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference (mm) - Day 7 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	69	-	MD 1 higher (3.39 lower to 5.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Head circumference (mm) - Day 14 (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High energy intake	Low energy intake	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	69	-	MD 2 higher (2.39 lower to 6.39 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Head circumference (mm) - Day 21 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[8]	none	66	69	-	MD 4 higher (1.07 lower to 9.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference (mm) - Day 28 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	none	66	69	-	MD 6 higher (0.43 to 11.57 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference (mm) - At 36 weeks' CGA (Better indicated by higher values)												
2	randomised trials	serious[10]	serious[11]	no serious indirectness	serious[12]	none	118	122	-	MD 1.04 higher (6.8 lower to 8.88 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference z-score at 36 weeks' CGA (Better indicated by higher values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[13]	none	55	59	-	MD 0.2 lower (0.62 lower to 0.22 higher)	⊕⊕OO LOW	CRITICAL
Head circumference gain (cm/week) (Better indicated by higher values)												
1	observational studies	serious[14]	no serious inconsistency	no serious indirectness	serious[15]	none	7	8	-	MD 0.40 higher (0.02 to 0.78 higher)	⊕OOO VERY LOW	CRITICAL
Weight (g) - Day 7 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	69	-	31 higher (8.22 lower to 70.22 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Weight (g) - Day 14 (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High energy intake	Low energy intake	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[16]	none	66	69	-	55 higher (9.24 to 100.76 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight (g) - Day 21 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[17]	none	66	69	-	75 higher (20.78 to 129.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight (g) - Day 28 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[18]	none	66	69	-	57 higher (8.7 lower to 122.7 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight (g) - At 36 weeks' CGA (Better indicated by higher values)												
2	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117	121	-	77.31 higher (8.89 to 145.74 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight gain - g/day (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[19]	none	12	12	-	MD 10 higher (21.7 lower to 41.7 higher)	⊕OOO VERY LOW	CRITICAL
Weight gain - g/kg/day (Better indicated by higher values)												
2	observational studies	very serious[3]	serious[11]	no serious indirectness	serious[20]	none	26	20	-	MD 7.12 higher (0.75 lower to 14.99 higher)	⊕OOO VERY LOW	CRITICAL
Weight z-score at 36 weeks' CGA (Better indicated by higher values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[21]	none	55	59	-	MD 0.1 higher (0.21 lower to 0.41 higher)	⊕⊕OO LOW	CRITICAL
Mid-arm circumference (cm) at 36 weeks' CGA (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High energy intake	Low energy intake	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	59	-	mean 0.10 higher (0.19 lower to 0.39 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length (cm) at 36 weeks' CGA (Better indicated by higher values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[22]	none	55	59	-	MD 0.5 higher (0.31 lower to 1.31 higher)	⊕⊕OO LOW	CRITICAL
Length gain (cm/week) (Better indicated by higher values)												
2	observational studies	very serious[3]	no serious inconsistency	no serious indirectness	serious[23]	none	21	20	-	MD 0.29 higher (0.12 to 0.46 higher)	⊕OOO VERY LOW	CRITICAL
Length z-score at 36 weeks' CGA (Better indicated by higher values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[24]	none	55	59	-	MD 0.3 higher (0.16 lower to 0.76 higher)	⊕⊕OO LOW	CRITICAL
Lower leg length (cm) at 36 weeks' CGA (Better indicated by higher values)												
1	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	59	-	MD 0 higher (0.26 lower to 0.26 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mortality - Day 28												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[25]	none	8/74 (10.8%)	7/76 (9.2%)	RR 1.17 (0.45 to 3.07)	16 more per 1000 (from 51 fewer to 191 more)	⊕⊕OO LOW	IMPORTANT
Mortality - At 36 weeks' CGA												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[25]	none	11/63 (17.5%)	12/64 (18.8%)	RR 0.93 (0.44 to 1.95)	13 fewer per 1000 (from 105 fewer to 178 more)	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High energy intake	Low energy intake	Relative (95% CI)	Absolute	Quality	Importance
Conjugated hyperbilirubinaemia (conjugated bilirubin > 50 mmol/L) - Day 28												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[25]	none	6/66 (9.1%)	8/69 (11.6%)	RR 0.78 (0.29 to 2.14)	26 fewer per 1000 (from 82 fewer to 132 more)	⊕⊕OO LOW	IMPORTANT
Conjugated hyperbilirubinaemia (conjugated bilirubin > 50 mmol/L) - At 36 weeks' CGA												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[25]	none	13/63 (20.6%)	12/64 (18.8%)	RR 1.1 (0.54 to 2.22)	19 more per 1000 (from 86 fewer to 229 more)	⊕⊕OO LOW	IMPORTANT
Energy intake - kcal/kg/d in the first 48 hours of life (Better indicated by higher values)												
1	randomised trials	serious[26]	no serious inconsistency	no serious indirectness	serious[27]	none	20[f]	20[f]	-	MD 15.3 higher (4.07 to 26.53 higher)	⊕⊕OO LOW	IMPORTANT
Energy intake - kcal/kg/d at week 1 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	69	-	MD 7 higher (4.61 to 9.39 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Energy intake - kcal/kg/d at week 2 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	69	-	MD 17 higher (9.87 to 24.13 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Energy intake - kcal/kg/d at week 3 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[28]	none	66	69	-	MD 9 higher (2.35 lower to 20.35 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Energy intake - kcal/kg/d at week 4 (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[29]	none	66	69	-	MD 5 higher (5.24 lower to 15.24 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High energy intake	Low energy intake	Relative (95% CI)	Absolute	Quality	Importance
Energy intake - Cumulative kcal/kg in the first 28 days of life (Better indicated by higher values)												
2	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[30]	none	121	128	-	MD 165.26 higher (93.78 to 236.73 higher)	⊕⊕OO LOW	IMPORTANT
Energy intake (kcal/kg/day) - timeframe unclear (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12	12	-	MD 25 higher (18.58 to 31.42 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Energy intake (kcal/kg/day) - timeframe unclear (Better indicated by higher values)												
1	observational studies	serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	8	8	-	MD 18.2 higher (15.65 to 20.75 higher)	⊕OOO VERY LOW	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio.
[1] Evidence was downgraded by 1 due to unclear risk of selection bias
[2] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (8.28)
[3] Evidence was downgraded by 2 due to high risk of selection bias in one study and moderate risk of selective reporting bias
[4] Evidence was downgraded by 2 due to high heterogeneity
[5] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (5.62)
[6] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (32.95)
[7] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (26.35)
[8] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (8.00)
[9] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (8.50)
[10] Evidence was downgraded by 1 due to high risk of attrition bias in one of the studies
[11] Evidence was downgraded by 1 due to moderate heterogeneity
[12] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (7.02)
[13] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (-0.55)

[14] Evidence was downgraded by 1 due to moderate risk of selective reporting bias
[15] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (0.17)
[16] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (85.5)
[17] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (104.50)
[18] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (121.00)
[19] Evidence downgraded by 2 due to very serious imprecision; 95% confidence intervals cross 2 default MIDs for continuous variables, calculated as 0.5 of SD of low energy group at baseline (-15.05, 15.05)
[20] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (3.85)
[21] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (0.40)
[22] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (1.05)
[23] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (0.16)
[24] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (0.60)
[25] Evidence downgraded by 2 due to very serious imprecision; 95% confidence intervals cross 2 default MIDs for dichotomous outcomes (0.80, 1.25)
[26] Evidence was downgraded by 1 due to unclear risk of selection bias and high risk of other bias
[27] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (8.95)
[28] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (15.5)
[29] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (13.00)
[30] Evidence downgraded by 1 due to serious imprecision; 95% confidence intervals cross 1 default MID for continuous variables, calculated as 0.5 of SD of low energy group at baseline (168.36)
** 8 babies were included in each arm in Pineault 1988, but two nutrition phases were completed resulting in n=16 in each arm*
[ι] cross over study – 20 babies, acting as their own control

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

One global search was conducted for all review questions. See supplementary material D for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

No evidence was identified which was applicable to this review question.

Appendix I – Health economic evidence profiles

Economic evidence profiles for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

No evidence was identified which was applicable to this review question.

Appendix J – Health economic analysis

Economic evidence analysis for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

Clinical studies

Table 5: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
Bajaj, N., Preterm nutrition and neurodevelopment: An overview, Perinatology, 17, 153-162, 2017	Narrative review.
Balasubramanian, H., Nanavati, R. N., Kabra, N. S., Effect of two different doses of parenteral amino acid supplementation on postnatal growth of very low birth weight neonates - A randomized controlled trial, Indian Pediatrics, 50, 1131-6, 2013	Study intervention does not meet protocol eligibility criteria - study compares amino acid intakes.
Bell, E. F., Filer, L. J., Jr., Wong, A. P., Stegink, L. D., Effects of a parenteral nutrition regimen containing dicarboxylic amino acids on plasma, erythrocyte, and urinary amino acid concentrations of young infants, The American journal of clinical nutrition, 37, 99-107, 1983	Study intervention does not meet protocol eligibility criteria - both interventions receive the same calorie intake.
Ben, X. M., Nutritional management of newborn infants: Practical guidelines, World Journal of Gastroenterology, 14, 6133-6139, 2008	Study design does not meet protocol eligibility criteria - Guideline publication - references checked for relevant papers.
Blau, Jonathan, Sridhar, Shanthy, Mathieson, Susan, Chawla, Anupama, Effects of protein/nonprotein caloric intake on parenteral nutrition associated cholestasis in premature infants weighing 600-1000 grams, JPEN. Journal of parenteral and enteral nutrition, 31, 487-90, 2007	Study intervention does not meet protocol eligibility criteria - different kcal/kg/day not stated for each regimen, only actual intakes reported for cholestasis vs non cholestasis infants.
Bockenkamp, B., Jouvet, P., Arsenault, V., Beausejour, M., Pelletier, V. A., Assessment of calories prescribed and delivered to critically ill children, e-SPEN, 4, e172-e175, 2009	Study intervention does not meet protocol eligibility criteria - Infants receive both parenteral and enteral nutrition.
Bolisetty, S., Pharande, P., Nirthanakumaran, L., Quy-Phong Do, T., Osborn, D., Smyth, J., Sinn, J., Lui, K., Improved nutrient intake following implementation of the consensus standardised parenteral nutrition formulations in preterm neonates a before-after intervention study, BMC Pediatrics, 14, 309, 2014	Study does not meet protocol eligibility criteria - a retrospective before and after cohort study. The intervention does not meet inclusion criteria - the study compares the effect of introducing a new management protocol and does not stated administered calorie levels.
Bonsante,F., Iacobelli,S., Chantegret,C., Martin,D., Gouyon,J.B., The effect of parenteral nitrogen and energy intake on electrolyte balance in the preterm infant, European Journal of Clinical Nutrition, 65, 1088-1093, 2011	Study design does not meet protocol eligibility criteria - non-comparative cohort study.
Brans, Y. W., Andrew, D. S., Carrillo, D. W., Dutton, E. P., Menchaca, E. M., Puleo-Scheppke, B. A., Tolerance of fat emulsions in very-low-birth-weight neonates, American journal of diseases of children (1960), 142, 145-52, 1988	Study intervention does not meet eligibility criteria - amount of administered kcal/kg/day not stated.

Study	Reason for Exclusion
Brener Dik, P. H., Galletti, M. F., Bacigalupo, L. T., Jonusas, S. F., Mariani, G. L., Hypercalcemia and hypophosphatemia among preterm infants receiving aggressive parenteral nutrition, Archivos Argentinos de Pediatria, 116, e371-e377, 2018	Intervention does not meet inclusion criteria - the study compares the effect of introducing a new nutrition protocol and does not state prescribed calorie levels.
Burattini, I., Bellagamba, M. P., Spagnoli, C., D'Ascenzo, R., Mazzoni, N., Peretti, A., Cogo, P. E., Carnielli, V. P., Targeting 2.5 versus 4 g/kg/day of amino acids for extremely low birth weight infants: A randomized clinical trial, Journal of Pediatrics, 163, 1278, 2013	Study intervention does not meet protocol eligibility criteria - energy provided was the same across intervention arms.
Burgess, L., Flanagan, B., Turner, M., Morgan, C., Elevated essential amino acid levels in very preterm infants receiving total parenteral nutrition, Journal of Pediatric Gastroenterology and Nutrition, 64, 797, 2017	Study intervention does not meet protocol eligibility criteria - amounts of energy administered not stated.
Burgess, Laura, Morgan, Colin, Mayes, Kelly, Tan, Maw, Plasma arginine levels and blood glucose control in very preterm infants receiving 2 different parenteral nutrition regimens, JPEN. Journal of parenteral and enteral nutrition, 38, 243-53, 2014	Study intervention does not meet protocol eligibility criteria - combination of PN and EN.
Butler, T. J., Szekely, L. J., Grow, J. L., A standardized nutrition approach for very low birth weight neonates improves outcomes, reduces cost and is not associated with increased rates of necrotizing enterocolitis, sepsis or mortality, Journal of Perinatology, 33, 851-7, 2013	Study intervention does not meet protocol eligibility criteria - the study is a before and after comparison of a standardised nutrition guidelines within a centre (which includes enteral feeding).
Calkins, K. L., Havranek, T., Kelley-Quon, L., Gibson, L., Venick, R., Shew, S., Low dose soybean oil for the prevention of parenteral nutrition associated cholestasis in neonates with congenital gastrointestinal disorders, Journal of Investigative Medicine, 61, 157-158, 2013	Study intervention does not meet protocol eligibility criteria- energy administered not stated and infants also received EN.
Can, E., Bulbul, A., Uslu, S., Comert, S., Bolat, F., Nuhoglu, A., Evaluation of two different types of parenteral nutrition on early growth of preterm infants, Early Human Development, 86, S85, 2010	Conference abstract.
Chessex, P., Gagne, G., Pineault, M., Vaucher, J., Bisaillon, S., Brisson, G., Metabolic and clinical consequences of changing from high-glucose to high-fat regimens in parenterally fed newborn infants, Journal of Pediatrics, 115, 992-997, 1989	Study intervention does not meet protocol eligibility criteria - calorie intake equal across interventions.
Choi, A. Y., Lee, Y. W., Chang, M. Y., Modification of nutrition strategy for improvement of postnatal growth in very low birth weight infants, Korean Journal of Pediatrics, 59, 165-173, 2016	Study intervention does not meet protocol eligibility criteria - change of protocol for parenteral and enteral feeding.
Collins, Carmel T., Chua, Mei Chien, Rajadurai, Victor S., McPhee, Andrew J., Miller, Lisa N., Gibson, Robert A., Makrides, Maria, Higher protein and energy intake is associated with increased weight gain in pre-term infants,	Study intervention does not meet protocol eligibility criteria - EN.

Study	Reason for Exclusion
Journal of Paediatrics and Child Health, 46, 96-102, 2010	
Cooke, R. J., Zee, P., Yeh, Y. Y., Safflower oil emulsion administration during parenteral nutrition in the preterm infant. 1. Effect on essential fatty acid status, Journal of pediatric gastroenterology and nutrition, 4, 799-803, 1985	Study intervention does not meet protocol eligibility criteria - energy administered not stated.
De Lima, A. M., Goulart, A. L., Bortoluzzo, A. B., Kopelman, B. I., Nutritional practices and postnatal growth restriction in preterm newborns, Revista da Associacao Medica Brasileira, 61, 500-506, 2015	Study design and intervention do not meet protocol eligibility criteria - retrospective cohort; infants received both PN and EN.
Deprettere, A. J., Van Acker, K. J., Van Reempts, P. J., De Leeuw, I., Inadequate intravenous feeding in sick neonates: a retrospective study, Clinical nutrition (Edinburgh, Scotland), 13, 161-5, 1994	Study design and intervention do not meet inclusion criteria - retrospective study; infants received PN and EN.
Dinerstein, A., Nieto, R. M., Solana, C. L., Perez, G. P., Otheguy, L. E., Larguia, A. M., Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants, Journal of Perinatology, 26, 436-42, 2006	Study intervention does not meet protocol eligibility criteria - EN and PN.
Feng, Y., Hong, L., Pan, L., Li, J., Chang, P., Cumulative energy intakes in the first two weeks of life are associated with hospital outcomes in birth weight less than 1500 g infants, Journal of Pediatric Gastroenterology and Nutrition, 66 (Supplement 2), 1068, 2018	Abstract only
Fenton, T. R., McMillan, D. D., Sauve, R. S., Nutrition and growth analysis of very low birth weight infants, Pediatrics, 86, 378-83, 1990	Study design does not meet protocol eligibility criteria - prospective cohort; energy administered not stated.
Fischer, Celine Julie, Maucort-Boulch, Delphine, Essomo Megnier-Mbo, Christine Murielle, Remontet, Laurent, Claris, Olivier, Early parenteral lipids and growth velocity in extremely-low-birth-weight infants, Clinical nutrition (Edinburgh, Scotland), 33, 502-8, 2014	Study intervention does not meet protocol eligibility criteria - amounts of energy administered not stated. Infants receive human milk.
Georgieff, M. K., Hoffman, J. S., Pereira, G. R., Bernbaum, J., Hoffman-Williamson, M., Effect of neonatal caloric deprivation on head growth and 1-year developmental status in preterm infants, The Journal of pediatrics, 107, 581-7, 1985	Study intervention does not meet protocol eligibility criteria - parenteral and enteral feeding.
Georgieva, R. W., Van De Lagemaat, M., Lafeber, H. N., Schaafsma, A., Are current ESPGHAN recommendations for enteral nutrient supply for preterm infants also applicable for late preterm infants?, Journal of Pediatric Gastroenterology and Nutrition, 62, 837-838, 2016	Study intervention does not meet protocol eligibility criteria - energy intake is equal across interventions.
Guellec, Isabelle, Gascoin, Geraldine, Beuchee, Alain, Boubred, Farid, Tourneux, Pierre, Ramful, Duksha, Zana-Taieb, Elodie, Baud, Olivier, Biological Impact of Recent Guidelines on Parenteral Nutrition in Preterm Infants, Journal of pediatric gastroenterology and nutrition, 61, 605-9, 2015	Narrative review.

Study	Reason for Exclusion
Guzman,J.M., Jaraba,M.P., De La Torre,M.J., Ruiz-Gonzalez,M.D., Huertas,M.D., Alvarez,R., Zapatero,M., Parenteral nutrition and immature neonates. Comparative study of neonates weighing under 1000 and 1000-1250 g at birth, Early Human Development, 65 Suppl, S133-S144, 2001	Study intervention does not meet protocol eligibility criteria - similar energy administered for all infants.
Hay, W. W., Fetal nutrition-what can we learn to better nourish the preterm infant?, Archives of Disease in Childhood, 97, A28, 2012	Conference abstract.
Heird, W. C., Hay, W., Helms, R. A., Storm, M. C., Kashyap, S., Dell, R. B., Pediatric parenteral amino acid mixture in low birth weight infants, Pediatrics, 81, 41-50, 1988	Study intervention does not meet protocol eligibility criteria - babies receive both PN and EN.
Hentschel, R., Homburg, A., Franck, P., Kunze, M., Impact of early aggressive nutrition on very low birth weight infants on weight, length and head circumference. A retrospective study, Journal of Neonatal-Perinatal Medicine, 10, 221, 2017	Abstract only.
Herrmann, K. R., Early parenteral nutrition and successful postnatal growth of premature infants, Nutrition in Clinical Practice, 25, 69-75, 2010	Study intervention does not meet protocol eligibility criteria - includes EN; PN energy administered not stated.
Janeiro, P., Cunha, M., Marques, A., Moura, M., Barroso, R., Carreiro, H., Caloric intake and weight gain in a neonatal intensive care unit, European Journal of Pediatrics, 169, 99-105, 2010	Study intervention does not meet protocol eligibility criteria - unclear if babies in different time periods received different energy intakes; and infants received EN.
Jones, M. O., Pierro, A., Garlick, P. J., McNurlan, M. A., Donnell, S. C., Lloyd, D. A., Protein metabolism kinetics in neonates: effect of intravenous carbohydrate and fat, Journal of pediatric surgery, 30, 458-62, 1995	Study intervention does not meet protocol eligibility criteria - both groups received equal calorie intake.
Jones, M. O., Pierro, A., Hammond, P., Nunn, A., Lloyd, D. A., Glucose utilization in the surgical newborn infant receiving total parenteral nutrition, Journal of pediatric surgery, 28, 1121-5, 1993	Study intervention does not meet protocol eligibility criteria - unclear if energy administered differed across groups as this information was not stated.
Kamarudin, Nor Aini, Manan, Mohamed Mansor, Zulkifly, Hanis Hanum, Neoh, Chin Fen, Ali, Salmiah Mohd, Ming, Long Chiau, Amino acid dosing in parenteral nutrition for very low birth weight preterm neonates: an outcome assessment, Asia Pacific Journal of Clinical Nutrition, 25, 53-61, 2016	Study design does not meet protocol eligibility criteria - retrospective chart review; energy administered not stated.
Kofler, M., Beer, R., Marinoni, S., Schiefecker, A. J., Sohm, F., Pfausler, B., Thome, C., Schmutzhard, E., Helbok, R., Nutrition in aneurysmal subarachnoid hemorrhage patients, Neurocritical Care, 23, S216, 2015	Conference abstract.
Lai, N. M., Rajadurai, S. V., Tan, K. H., Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/ chronic lung disease, Cochrane database of systematic reviews (Online), 3, CD005093, 2006	Cochrane systematic review - references checked for inclusion (EN only).

Study	Reason for Exclusion
Leow, L. Y. C., Oh, C. C., Neo, S. L., Chua, M. C., Role of standardized parenteral nutrition bags for neonates, Journal of Perinatal Medicine, 41, 2013	Conference abstract.
Levit, O. L., Calkins, K. L., Gibson, L. C., Kelley-Quon, L., Robinson, D. T., Elashoff, D. A., Grogan, T. R., Li, N., Bizzarro, M. J., Ehrenkranz, R. A., Low-dose intravenous soybean oil emulsion for prevention of cholestasis in preterm neonates, Journal of Parenteral and Enteral Nutrition, 40, 374-382, 2016	Study intervention does not meet protocol eligibility criteria- study compares different does of fat emulsions. Study does not state energy administered per group.
Loys, C. M., Maucort-Boulch, D., Guy, B., Putet, G., Picaud, J. C., Hays, S., Extremely low birthweight infants: how neonatal intensive care unit teams can reduce postnatal malnutrition and prevent growth retardation, Acta Paediatrica, 102, 242-8, 2013	Study intervention does not meet protocol eligibility criteria - parenteral and enteral feeding.
Marchildon, M. B., Parenteral 20% safflower oil emulsion safety and effectiveness as a caloric source in newborn infants, JPEN. Journal of parenteral and enteral nutrition, 6, 25-9, 1982	Study design does not meet protocol eligibility criteria- case series.
Meurling, S., Grotte, G., Complete parenteral nutrition in the surgery of the newborn infant, Acta chirurgica Scandinavica, 147, 465-73, 1981	Study design does not meet protocol eligibility criteria - case series.
Moltu, S. J., Blakstad, E. W., Strommen, K., Almaas, A. N., Nakstad, B., Ronnestad, A., Braekke, K., Veierod, M. B., Drevon, C. A., Iversen, P. O., Westerberg, A. C., Enhanced feeding and diminished postnatal growth failure in very-low-birth-weight infants, Journal of Pediatric Gastroenterology & Nutrition, 58, 344-51, 2014	Study intervention does not meet protocol eligibility criteria - EN and PN.
Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome at 2.5 years in very preterm infants randomised to receive two different parenteral nutrition regimens at birth: The SCAMP nutrition study, Journal of Pediatric Gastroenterology and Nutrition, 64, 764, 2017	Conference abstract.
Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome in very preterm infants randomized to receive two different parenteral nutrition regimens: The scamp nutrition study, Journal of Neonatal-Perinatal Medicine, 10, 220-221, 2017	Abstract only.
Morgan, J. B., Nutrition of the very low birthweight infant, Care of the Critically Ill, 8, 122-124, 1992	Narrative review.
Pharande, P., Nirthanakumaran, L., Do, T., Smyth, J., Lui, K., Sinn, J., Bolisetty, S., Implementation of consensus neonatal parenteral nutrition formulations and improved nutrient intakes in preterm neonates, Journal of Paediatrics and Child Health, 50, 56, 2014	Conference abstract.
Pineault, M., Chessex, P., Bisaillon, S., Lepage, D., Dallaire, L., Total parenteral nutrition in the newborn: amino acids-energy interrelationships,	Study outcomes do not meet protocol eligibility criteria - no relevant outcomes reported.

Study	Reason for Exclusion
American Journal of Clinical Nutrition, 48, 1065-9, 1988	
Pineault, M., Chessex, P., Piedboeuf, B., Bisaillon, S., Beneficial effect of coinfusing a lipid emulsion on venous patency, Journal of Parenteral and Enteral Nutrition, 13, 637-640, 1989	Study outcomes do not meet protocol eligibility criteria - No relevant outcomes reported.
Pineault, M., Lepage, G., Bisaillon, S., Roy, C. C., Chessex, P., Total parenteral nutrition in the newborn: Energy substrates and plasma total fatty acids, Pediatric Research, 26, 290-293, 1989	Study outcomes do not meet protocol eligibility criteria - No relevant outcomes reported.
Ribed Sanchez, A., Romero Jimenez, R. M., Sanchez De Orgaz, M. C., De Juan, A., Tovar Pozo, M., Diaz Garzon, J., Sanjurjo Saez, M., Early aggressive parenteral nutrition in preterm infants, International Journal of Clinical Pharmacy, 35, 983, 2013	Conference abstract.
Rizzi, G., Gaio, P., Meneghelli, M., Tessari, A., Pasinato, A., Fantinato, M., Valerio, E., Verlato, G., Parenteral nutrition in preterm infants of birth weight <1250 G: Possible influences on growth and bone status, Journal of Maternal-Fetal and Neonatal Medicine, 27, 333-334, 2014	Conference abstract - not an RCT.
Rochow,N., Fusch,G., Muhlinghaus,A., Niesytto,C., Straube,S., Utzig,N., Fusch,C., A nutritional program to improve outcome of very low birth weight infants, Clinical Nutrition, 31, 124-131, 2012	Study intervention does not meet protocol eligibility criteria - EN and PN.
Roggero, Paola, Gianni, Maria L., Orsi, Anna, Amato, Orsola, Piemontese, Pasqua, Liotto, Nadia, Morlacchi, Laura, Taroni, Francesca, Garavaglia, Elisa, Bracco, Beatrice, Agosti, Massimo, Mosca, Fabio, Implementation of nutritional strategies decreases postnatal growth restriction in preterm infants, PloS one, 7, e51166, 2012	Study intervention does not meet protocol eligibility criteria - EN and PN.
Romero, R., Kleinman, R. E., Feeding the very low-birth-weight infant, Pediatrics in review, 14, 123-32, 1993	Narrative review.
Rook, D., Schierbeek, H., Vlaardingerbroek, H., Dorst, K., Vermeulen, M. J., Van Goudoever, J. B., Increased energy intake directly following birth does not increase gsh synthesis rates in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 52, E78-E79, 2011	Conference abstract; outcomes do not meet protocol eligibility criteria.
Rubecz, I., Energy metabolism, substrate utilization, metabolite and hormone levels in infants fed various parenteral solutions, Acta paediatrica Academiae Scientiarum Hungaricae, 23, 59-68, 1982	Study design does not meet protocol eligibility criteria - case series.
Rubecz, I., Mestyan, J., Varga, P., Klujber, L., Energy metabolism, substrate utilization, and nitrogen balance in parenterally fed postoperative neonates and infants. The effect of glucose, glucose + amino acids, lipid + amino	Study intervention does not meet protocol eligibility criteria - energy administered similar across groups.

Study	Reason for Exclusion
acids infused in isocaloric amounts, Journal of Pediatrics, 98, 42-46, 1981	
Rubecz, I., Mestyan, J., Varga, P., Soltesz, G., Metabolic and hormonal responses of low birthweight infants to intravenously infused calories not exceeding the maintenance energy expenditure, Archives of disease in childhood, 54, 499-505, 1979	Study design does not meet protocol eligibility criteria - case series.
Salas-Salvado, J., Molina, J., Figueras, J., Masso, J., Marti-Henneberg, C., Jimenez, R., Effect of the quality of infused energy on substrate utilization in the newborn receiving total parenteral nutrition, Pediatric research, 33, 112-7, 1993	Study intervention does not meet protocol eligibility criteria - energy administered not stated.
Schwalbe-Terilli, Courtney R., Hartman, Diane H., Nagle, Monica L., Gallagher, Paul R., Ittenbach, Richard F., Burnham, Nancy B., Gaynor, J. William, Ravishankar, Chitra, Enteral feeding and caloric intake in neonates after cardiac surgery, American journal of critical care : an official publication, American Association of Critical-Care Nurses, 18, 52-7, 2009	Study intervention does not meet protocol eligibility criteria - EN.
Senterre, T., Habibi,, Rigo, F. J., Postnatal growth restriction may be limited in very-low-birthweight infants, Journal of Maternal-Fetal and Neonatal Medicine, 23, 325-326, 2010	Conference abstract - not an RCT.
Sjostrom, E. S., Lundgren, P., Ohlund, I., Holmstrom, G., Hellstrom, A., Domellof, M., Low energy intake during the first 4 weeks of life increases the risk for severe retinopathy of prematurity in extremely preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 101, F108-F113, 2016	Study intervention does not meet protocol eligibility criteria - EN and PN.
Spath, Cornelia, Zamir, Itay, Sjostrom, Elisabeth Stoltz, Domellof, Magnus, Use of Concentrated Parenteral Nutrition Solutions Is Associated With Improved Nutrient Intakes and Postnatal Growth in Very Low-Birth-Weight Infants, JPEN. Journal of parenteral and enteral nutrition, 2019	Intervention does not meet inclusion criteria - the study compares the effect of introducing a new PN regimen and does not state prescribed calorie levels.
Stephens, Bonnie E., Walden, Rachel V., Gargus, Regina A., Tucker, Richard, McKinley, Leslie, Mance, Martha, Nye, Julie, Vohr, Betty R., First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants, Pediatrics, 123, 1337-43, 2009	Study intervention does not meet protocol eligibility criteria - EN and PN.
Stoltz Sjostrom, E., Zamir, I., Spath, C., Domellof, M., A more concentrated parenteral nutrition solution improves nutrient intakes and postnatal weight gain in very low birth weight infants, European Journal of Pediatrics, 175, 1732, 2016	Conference abstract - not an RCT.
Sun, J., Liu, D., Bei, F., Aggressive parenteral nutrition support in premature low birth weight infants, Pediatric Critical Care Medicine, 12, A148, 2011	Conference abstract - not an RCT.

Study	Reason for Exclusion
Tagare, A., Walawalkar, M., Vaidya, U., Aggressive parenteral nutrition in sick very low birth weight babies: A randomized controlled trial, Indian Pediatrics, 50, 954-956, 2013	Study intervention does not meet protocol eligibility criteria - energy administered not stated.
Tan, M., Parry, S., Morgan, C., Neurodevelopmental outcome in very preterm infants randomised to receive two different parenteral nutrition regimens: The SCAMP nutrition study, Archives of Disease in Childhood, 101, A5, 2016	Conference abstract - energy administered not stated.
Terui, Keita, Usui, Noriaki, Tazuke, Yuko, Nagata, Kouji, Ito, Miharu, Okuyama, Hiroomi, Hayakawa, Masahiro, Taguchi, Tomoaki, Sato, Yasunori, Yoshida, Hideo, The Impact of Nutrition in the Congenital Diaphragmatic Hernia Treatment, Pediatrics international : official journal of the Japan Pediatric Society, 2019	Study intervention does not meet protocol eligibility criteria - grouped based on energy received, not prescribed regimens.
Tian, Tina, Coons, Joshua, Chang, Hong, Chwals, Walter J., Overfeeding-associated hyperglycemia and injury-response homeostasis in critically ill neonates, Journal of pediatric surgery, 53, 1688-1691, 2018	No relevant outcomes.
Tottman, A. C., Alsweiler, J. M., Bloomfield, F. H., Gamble, G. D., Jiang, Y., Leung, M., Poppe, T., Thompson, B., Wouldes, T. A., Harding, J. E., Neonatal nutritional intakes and neurodevelopment at school age in infants born preterm, Journal of Paediatrics and Child Health, 54, 50, 2018	Abstract only.
Tottman, A. C., Bloomfield, F. H., Cormack, B. E., Harding, J. E., Mohd Slim, M. A., Weston, A. F., Alsweiler, J. M., Relationships between Early Nutrition and Blood Glucose Concentrations in Very Preterm Infants, Journal of Pediatric Gastroenterology and Nutrition, 66, 960-966, 2018	Intervention does not meet inclusion criteria - the study compares the effect of introducing a new nutrition protocol and does not state prescribed calorie levels.
Urs, A. N., Somisetty, S. K., Hawkes, L., Paterson, M., Thethy, R. S., Evaluation of aggressive nutritional intervention in very low birth weight infants (VLBW) during the first 28 days of life, Paediatrics and Child Health, 20, 250, 2010	Conference abstract - energy administered not stated.
Vakrilova, L., Slancheva, B., Emilova, Z., Radulova, P., Hitrova, S., Petrova, G., Early parenteral nutrition of very low birth weight infants: Practical application, Intensive Care Medicine, 37, S398, 2011	Conference abstract - energy administered not stated; infants received EN.
Vakrilova, L., Slancheva, B., Emilova, Z., Yarakova, N., Early parenteral nutrition with very low and extremely low birth weight infants - Practical approach, Early Human Development, 86, S86-S87, 2010	Conference abstract - energy administered not stated.
Van Aerde, J. E., Sauer, P. J., Pencharz, P. B., Smith, J. M., Heim, T., Swyer, P. R., Metabolic consequences of increasing energy intake by adding lipid to parenteral nutrition in full-term	Study intervention does not meet protocol eligibility criteria.

Study	Reason for Exclusion
infants, The American journal of clinical nutrition, 59, 659-62, 1994	
Van Aerde, J. E., Sauer, P. J., Pencharz, P. B., Smith, J. M., Swyer, P. R., Effect of replacing glucose with lipid on the energy metabolism of newborn infants, Clinical science (London, England : 1979), 76, 581-8, 1989	Study intervention does not meet protocol eligibility criteria.
Weinstein, M. R., Haugen, K., Bauer, J. H., Hewitt, J., Finan, D., Intravenous energy and amino acids in the preterm newborn infant: effects on metabolic rate and potential mechanisms of action, The Journal of pediatrics, 111, 119-23, 1987	Study outcomes do not meet protocol eligibility criteria - outcomes of interest not measured.
Westin, Vera, Klevebro, Susanna, Domellof, Magnus, Vanpee, Mireille, Hallberg, Boubou, Stoltz Sjostrom, Elisabeth, Improved nutrition for extremely preterm infants - A population based observational study, Clinical nutrition ESPEN, 23, 245-251, 2018	Intervention does not meet inclusion criteria - prescribed calorie intake did not differ before and after implementation of nutrition interventions.

Economic studies

No economic evidence was identified for this review. See supplementary material D for further information.

Appendix L – Research recommendations

Research recommendations for review question: How many kcal/kg/day should be given to preterm and term babies receiving parenteral nutrition?

No research recommendations were made for this review question.