National Institute for Health and Care Excellence

Draft for consultation

Neonatal parenteral nutrition

[D2] Amino acids

NICE guideline tbc

Evidence reviews

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Draft for Consultation

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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Contents

Optimal target dose and approach for amino acids

Review questions

This evidence report contains information on two questions conducted as one review relating to the individual constituents (amino acids) in parenteral nutrition for preterm and term babies.

- D2a. What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?
- D2b. What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Introduction

Amino acids are the building blocks of proteins which are components of all cells in the body. They fulfil structural and functional roles in the body. If preterm babies, critically ill preterm, or term babies do not receive sufficient amino acids, to the level they would receive in the womb, they are at risk of nutritional deficits or failure to grow as expected. Elevated levels of amino acids could lead to side effects such as acidosis or high serum urea. It is therefore important to find the optimal target dose and how this would best be reached. For amino acids to be used effectively by the body they need to be delivered alongside sufficient non-nitrogen energy (carbohydrates and lipids). This allows the amino acids to fulfil their important structural and functional roles in the body as opposed to being consumed as a primary energy source.

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	Optimal target dose: • Target dose of amino acid (g/kg/d) to be achieved Optimal way to achieve this: • Starting dose • Rate of increase in amino acids
Comparison	Optimal target dose: • None • Each other Optimal way to achieve this: • Different starting doses • Different increases • Different regimens
Outcomes	**Critical** • Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale) • Growth/Anthropometric measures:

	○ Weight gain (g/kg/d) ○ Linear growth ○ Head circumference (mm) • Body composition (measured as Lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion) • Adverse effects of amino acids: ○ Infection including sepsis ○ Acidosis ○ High serum urea ○ Hypercalcaemia/Hypophosphataemia ○ Hypokalaemia ○ Re-feeding syndrome **Important** • Mortality • Duration of hospital stay • Nutritional intake (g/kg/d) (prescribed amino acids actually received)

For further details see the review protocol in appendix A.

Clinical evidence

Included studies

Nineteen studies were identified for this review (Balakrishnan 2018, Balasubramanian 2013, Blanco 2008, Blanco 2012, Bulbul 2012, Burattini 2013, Can 2012, Can 2013, Clark 2007, Heimler 2010, Ibrahim 2004, Morgan 2014, Pappoe 2009, Roelants 2018, Scattolin 2013, Tan 2008, Uthaya 2016, van den Akker 2014, Vlaardingerbroek 2013).

Optimal target dose

Ten randomised controlled trials (RCTs) addressed the optimal target dose review question (review question D2a) and compared high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake (Blanco 2008, Blanco 2012, Burattini 2013, Clark 2007, Morgan 2014, Roelants 2018, Scattolin 2013, Tan 2008, Uthaya 2016, Vlaardingerbroek 2013). Stratified analysis were performed for this comparison based on high or low amino acid intake at commencement.

The studies were grouped according to being above or below a maintenance dose of 3g/kg/day (referred to as maximal intake) as this was the mid-point of what the included studies reported. In addition this was consistent with a recent Cochrane review (Osborn 2018), on amino acids intake in neonates where the categories changed from what was considered low to high maintenance intake.

Six studies started with an intake of amino acids that was ≤2 g/kg/d (Blanco 2008, Blanco 2012, Clark 2007, Morgan 2014, Scattolin 2013, Tan 2008), 2 studies started with an intake of amino acids >2 g/kg/d (Roelants 2018, Vlaardingerbroek 2013), and 2 studies started with an intake of ≤2 g/kg/d of amino acids in one arm and an intake of >2 g/kg/d amino acids in the other arm (Burattini 2013, Uthaya 2016). Given the differences in starting dosages these were analysed separately with a value of at or below 2 g/kg/day described as ‘low commencement’ and when the starting dose of amino acids was above 2 g/kg/day as ‘high commencement’.

This was done because both the final maintenance level as well as the starting could have potentially caused differences in outcomes.

How to achieve target dose

Nine RCTs addressed the optimal way to achieve the target dose (review question D2b); 3 RCTs compared early amino acid intake to delayed amino acid intake (Heimler 2010, Ibrahim 2004, van den Akker 2014) and 6 RCTs compared high amino acids (≥2 g/kg/d) to low amino acids (<2 g/kg/d) intake at commencement (Balakrishnan 2018, Balasubramanian 2013, Bulbul 2012, Can 2012, Can 2013, Pappoe 2009). High and low intake at commencement meant that amino acids were started at a different dose in each group but reached the same maintenance dose.

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, forest plots in appendix E, 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. The labels used for the intervention and comparison arms reflect those used in the comparisons described above and the analyses. These differ from those used by the study authors, which are included in the full evidence tables in appendix D. This was done because the names of the interventions and comparisons given by the authors of the studies were not necessarily the same as in the analysis of this review (for example, what studies referred to as 'standard' amino acid may be classified either as high or as low depending on the respective dosage as described in the categories above).

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Balakrishnan 2018 RCT USA	N=168 Babies with birth weight between 400g and 1250g and gestational age between 24^{+0} and 30^{+6} weeks' gestation Mean GA 26.8 weeks Mean BW 882g	High AA at commencement (n=85) 4g/kg/day on first day of life	Low AA at commencement (n=83) 1-2g/kg/day AA on first day of life and advanced by 0.5g/kg/day until 4g/kg/day	• Neurodevelopmental outcomes • Weight • Length • Head circumference • Sepsis • Mortality	Higher proportion of small for gestational age babies in high AA arm, despite randomisation
Balasubramanian 2013 RCT	N=123 Babies with birth weight	High AA at commencement (n=60)	Low AA at commencement (n=63)	• Weight gain • Linear growth	Lipids, multivitamin and trace elements

Study	Population	Intervention	Comparison	Outcomes	Comments
India	between 900g and 1250g Mean GA 31.9 weeks Mean BW 1098g	3 g/kg/d of parenteral AA on day 1 and dose increased to 4 g/kg/d the next day	1 g/kg/d of parenteral AA on day 1, and increased by 1 g/kg every day to maximum intake of 4 g/kg/d.	• Head circumference • Sepsis • Duration of hospital stay	were not routinely provided
Blanco 2008 RCT US	N=61 Babies at least 24 weeks' gestation, weighing <1000g enrolled in the first 12 hours of life Mean GA 26 weeks Mean BW 776g	High AA at maximal intake (n=30) 2.0 g/kg/day of IV AA starting within the first 24 hours of life, increasing by 1.0 g/kg/day every 24 hours to a maximum of 4.0 g/kg/day on day 7.	Low AA at maximal intake (n=31) 0.5 g/kg/day IV AA starting 24 to 36 hours of life, increasing by 0.5 g/kg/day every 24 hours to a maximum of 3.0 g/kg/day on day 7.	• Hyperkalaemia	Lipids, glucose, minerals, trace elements and vitamins were prescribed according to nursery protocol Groups had similar lipid from day 1 (approx. 0.5 to 2.7 g/kg/d over 7 days)
Blanco 2012 RCT US	N=43 Babies at least 24 weeks' gestation, weighing <1000g enrolled in the first 12 hours of life Mean GA 26.4 weeks Mean BW 812g	High AA at maximal intake (n=21) 2.0 g/kg/day of IV AA soon after enrolment and within the first 24 hours of life with increases of 1 g/kg/day every 24 hours to a maximum of 4.0 g/kg/day on day 7.	Low AA at maximal intake (n=22) 0.5 g/kg/day IV AA starting 24 to 36 hours of life with increases of 0.5 g/kg/day every 24 hours to a maximum of 3.0 g/kg/day on day 7.	• Neurodevelopmental outcomes • Weight gain • Sepsis • Mortality • Duration of hospital stay	Lipids, glucose, minerals, trace elements and vitamins were prescribed according to nursery protocol and as tolerated Infants were maintained on TPN with AA dosage at 3.5 g/kg/day until sufficient enteral feedings were established
Bulbul 2012 RCT Turkey	N=44 Pre-term infants who were appropriatel	High AA at commencement PN (n=22)	Low AA at commencement (n=22) PN with 1.0 g/kg/d AA on day 1,	• Weight gain • Head circumference • Sepsis	Target non protein calorie intakes (glucose plus lipid) were 35–40

Study	Population	Intervention	Comparison	Outcomes	Comments
	y sized for GA of <32 weeks Mean GA 29.3 weeks Mean BW 1336g	PN with 3.0 g/kg/d AA on day 1. 3.0 g/kg/d lipid on day 1.	increasing by 1.0 g/kg/day, to a maximum intake of 3.0 g/kg/d AA on day 3. 1.0 g/kg/d lipid day 1 increasing by 1.0 g/kg/day to 3.0 g/kg/d on day 3.	• Duration of hospital stay	kcal/kg/d on day 1 and 70–80 kcal/kg on day 3. BG maintained between 80–100 mg/dl
Burattini 2013 RCT Italy	N=114 Birth weight between 500 and 1249 g Mean GA 28.7 weeks Mean BW 984g	High AA at maximal intake (n=56) 2.5 g/kg/day on day 1, to maximum of 4 g/kg/day on day 4.	Low AA at maximal intake (n=58) 1.5 g/kg/day on day 1, increasing by 0.5 g/kg/day to a maximum of 2.5 g/kg/day on day 3.	• Neurodevelopmental outcomes • Weight gain • Linear growth • Head circumference • Sepsis • Mortality	Non-protein energy, minerals, and micronutrients were identical for the two groups. Lipids from 0.5 g/kg/d day 1, increasing to 2.5 g/kg/d on day 5.
Can 2012 RCT Turkey	N=50 Preterm infants born between 27 and 33 weeks appropriate for GA Mean GA 31.4 weeks Mean BW 1610g	High AA at commencement (n=25) PN with 3.0 g/kg/day AA on day 1, increasing by 1.0 g/kg/day to a maximal of 4.0 g/kg/day on day 2. Received lipids at 2.0 g/kg/day on day 1, increasing by 1.0 g/kg/day to a maximum of 3.0 g/kg/day on day 2.	Low AA at commencement (n=25) PN with 1.5 g/kg/day AA on day 1, increasing by 1.0 g/kg/day to a maximum of 4.0 g/kg/day AA on day 3. Received lipids at 1.0 g/kg/day on day 1, increasing by 1.0 g/kg/day to a maximum of 3.0 g/kg/day on day 3.	• Weight gain • Linear growth • Head circumference • Mortality • Duration of hospital stay • Nutritional intake (AA)	Fluid, glucose and electrolytes were ordered by the neonatologist and not dictated by the protocol. BG maintained between 80–100 mg/dL
Can 2013 RCT Turkey	N=75 Preterm infants appropriately sized for GA <32 weeks	High AA at commencement (n=40) PN with 3.0 g/kg/day AA on day 1, increasing by 1.0 g/kg/day to a maximum of 4.0	Low AA at commencement (n=35) PN with 1.5 g/kg/day AA on day 1, increasing by 1.0 g/kg/day to a maximum of 4.0	• Weight gain • Nutritional intake (AA)	BG maintained between 80–100 mg/dL

Study	Population	Intervention	Comparison	Outcomes	Comments
	Mean GA 28.8 weeks Mean BW 1242g	g/kg/day on day 2. Received lipids at 2.0 g/kg/day on day 1, increasing by 1.0 g/kg/day to a maximum of 3.0 g/kg/day on day 2.	g/kg/day on day 3. Received lipids at 1.0 g/kg/d on day 1, increasing by 1.0 g/kg/day to a maximum of 3.0 g/kg/d on day 3.		
Clark 2007 RCT US	N=122 Inborn infants with GA between 23 weeks 0 days and 29 weeks 6 days Median GA 3.5g/kg/day – 27 weeks; 2.5g/kg/day – 27 weeks Median BW 3.5g/kg/day – 961g; 2.5g/kg/day – 918g	High AA at maximal intake (n=64) 1.5 g/kg/day AA, increasing by 1.0 g/kg/day to a maximum of 3.5 g/kg/day on day 3.	Low AA at maximal intake (n=58) 1.0 g/kg/day AA, increasing by 0.5 g/kg/day to a maximum of 2.5 g/kg/day on day 4.	• Weight gain • Linear growth • Head circumference • Mortality	Similar early lipid from day 1 at 0.5 g/kg/day, increasing by 0.5 g/kg/day to a maximum of 3.5 g/kg/day.
Heimler 2010 RCT US	N=17 Preterm infants <34 weeks gestation requiring respiratory support and intravenous nutrition Mean GA 29.9 weeks Mean BW 1218g	Early AA intake (n=8) 1.5 g/kg/day AA between 8-24 hours, increasing by 0.5 g/kg/day to a maximum of 2.5g/kg/day by day 3.	Delayed AA intake (n=9) 1.0 g/kg/day AA between 72-88 hours, increasing by 0.5 g/kg/day to a maximum of 2.5 g/kg/day by day 7.	• Weight gain • Head circumference	Both groups received phosphate, trace elements and lipids at 0.5 g/kg/day from day 4. Serum glucose levels were maintained between 2.5 and 8.5 mmol/L, (45–150 mg/dL).
Ibrahim 2004 RCT US	N=32 Preterm infants with a birth	Early AA intake (n=16)	Delayed AA intake (n=16) 2.0 g/kg/day AA after 48 hours,	• Sepsis • Mortality	The nonprotein calorie to nitrogen ratio was 100:1 in

Study	Population	Intervention	Comparison	Outcomes	Comments
	weight between 501 to 1250g, and gestational age between 24 to 32 weeks who required mechanical ventilation for respiratory distress syndrome Mean GA 26.9 weeks Mean BW 907g	3.5 g/kg/day AA within 2 hours after birth. Received lipids at 3.0 g/kg/day on day 1.	increasing by AA 0.5g /kg/day to a maximum of 3.5 g/kg/day. Received lipids after 48 hours at 0.5 g/kg/day, increasing by 0.5 g/kg/day to a maximum of 3.0 g/kg/day. Lipids at 0.5 g/kg/d on day 3.		the treatment group, while no AA were supplied to the control group during the first 48 hours of life
Morgan 2014 RCT UK	N=150 Babies born at <29 weeks gestation, birth weight <1200g, admitted to NICU within 48 hours of birth Mean GA 26.7 weeks Mean BW 892g	High AA at maximal intake (n=74) 1.8 g/kg/day AA on day 1 to 2, increasing to 2.9 g/kg/day on day 3 to 4, and to 3.8 g/kg/day on day 5. Received lipids at 1.0 g/kg/day on day 1 to 2, increasing to 1.9 g/kg/day on day 3 to 4, 2.8 g/kg/day on day 5 to 6, and 3.8 g/kg/day on day 7.	Low AA at maximal intake (n=76) 1.8 g/kg/day AA on day 1 to 2, increasing to 2.4 g/kg/day on day 3 to 4, and to 2.8 g/kg/day by day 5. Received lipids at 1.0 g/kg/day on day 1 to 2, increasing to 1.9 g/kg/day on day 3 to 4, 2.8 g/kg/day on day 5 (similar lipids until day 7).	• Weight gain • Head circumference • Sepsis • Mortality	Micronutrients, vitamins, and electrolytes were the same.
Pappoe 2009 RCT US	N=43 Infants 600-1200g without life threatening illness or significant congenital malformations Mean GA	High AA at commencement (n=24) 2.0 g/kg/day AA on day 1 increasing to 3.0 g/kg/day on day 2 and 3.5 g/kg/day on day 3. Received 2.0 g/kg/day lipids	Low AA at commencement (n=19) 1.0 g/kg/day AA on day 1 increasing by 0.5 g/kg/day to a maximum of 3.5 g/kg/day on day 6. Received 1.0 g/kg/day lipids	• Weight gain • Mortality • Duration of hospital stay • Nutritional intake (AA)	If BUN concentrations exceeded 40 mg/dl, the amount of protein was decreased by 1.0 g/kg/day. Fluid and electrolytes were similar across groups.

Study	Population	Intervention	Comparison	Outcomes	Comments
	26.8 weeks Mean BW 880g	from day 1, increasing to 3.0 g/kg/day on day 2 and 3.5 g/kg/day from day 3.	increasing by 0.5 g/kg/day to a maximum of 3.5 g/kg/day.		
Roelants 2018 RCT Netherlands	N=90 Inborn babies with birthweight <1500g Mean GA Not reported Mean BW Not reported	High AA at maximal intake (n=45) 3.6g/kg/day AA on first day of life	Low AA at maximal intake (n=45) 2.4g/kg/day AA on first day of life	• Neurodevelopmental outcomes	Long-term follow-up of Vlaardingerbroek 2013. Study underpowered and intervention may have been too short to produce lasting differences in neurodevelopmental outcomes.
Scattolin 2013 RCT Italy	N=115 Infants with a birth weight <1250g Mean GA 27.7 weeks Mean BW 935.9g	High AA at maximal intake (n=60) 2.0 g/kg/day AA, increasing by 1.0 g/kg/day to a maximum of 4.0 g/kg/day on day 4.	Low AA at maximal intake (n=55) 1.5 g/kg/day AA, increasing by 0.5 g/kg/day to a maximum of 3.0 g/kg/day on day 4.	• Weight gain • Linear growth • Head circumference • Sepsis • Mortality • Duration of hospital stay	Lipid intake not reported but infants had the same non protein intake.
Tan 2008 RCT UK	N=114 Infants born before 29 weeks' gestation Mean GA 26.1 weeks Mean BW 913g	High AA at maximal intake (n=55) 20% more energy (117 kcal/kg/day) 1.0 g/kg/day AA on day 1, increasing stepwise to 4.0 g/kg/day by day 7. Received 1.0 g/kg/day lipids, increasing stepwise to 4.0	Low AA at maximal intake (n=59) 93 kcal/kg/day 1.0 g/kg/day AA on day 1, increasing stepwise to 3.0 g/kg/day by day 5. Received 1.0 g/kg/day lipids, increasing stepwise to 3.0 g/kg/day by day 5.	• Weight gain • Linear growth • Head circumference Mortality • Duration of hospital stay	Standard PN was in line with ESPGHAN guidelines.

Study	Population	Intervention	Comparison	Outcomes	Comments
		g/kg/day by day 7.			
Uthaya 2016 RCT UK	N=168 Preterm infants born at 31 weeks gestation (≤30 weeks plus 6 days) Mean GA 27.8 weeks Mean BW 1.05kg	High AA at maximal intake (n=84) 3.6 g/kg/day AA from day 1.	Low AA at maximal intake (n=84) 1.7 g/kg/day AA on day 1, increasing to 2.1 g/kg/day on day 2 to a maximum of 2.7 g/kg/day from day 3	• Weight gain • Linear growth • Head circumference • Body composition • Sepsis • Mortality • Duration of hospital stay	Participants were randomised into 4 groups according to AA and lipid intake (Inc-AA/Intralipid, vs. Inc-AA/SMOFlipid, vs. Imm-RDI/Intralipid, vs. Imm-RDI/SMOFlipid). Data was combined into 2 groups (Imm-RDI versus Inc-AA). Groups received 2g/kg/day lipids on day 1, increasing to 3.0 g/kg/day from day 2 onwards.
Van den Akker 2014 RCT Netherlands	N=111 Infants born with a birth weight less than 1500g before 32 weeks' gestation Mean BW 1.02kg	Early AA intake (n=54) 2.4 g/kg/day AA within 2 hours following birth for the first 3 days.	Delayed AA intake (n=57) 1.2 g/kg/day AA, 24-48 hours after birth, increasing to 2.4 g/kg/day 24 hours later.	• Neurodevelopment outcomes • Weight gain • Head circumference	Groups received the same nutritional protocol after day 3. Lipids described in previous study (Te Braake 2005) as 1.4 g/kg/day on day 2, increasing to 2.8 g/kg/day on day 3 and 4.
Vlaardingerbroek 2013 RCT Netherlands	N=96 Inborn very low birth weight infants	High AA at maximal intake (n=47) 3.6 g/kg/day AA from birth onwards.	Low AA at maximal intake (n=49) 2.4 g/kg/day AA during the first 2 days	• Weight gain • Linear growth • Head circumference	Participants randomised to 3 groups: Control vs. AA + lipids, vs. high AA + lipids. Data collected for

Study	Population	Intervention	Comparison	Outcomes	Comments
	weighing <1500g Mean GA 27.2 weeks Mean BW 872g			• Sepsis • Mortality • Duration of hospital stay	2 groups only (AA + lipids and high AA + lipids) Both groups received 2.0 g/kg/day lipids on day 1, increasing to 3.0 g/kg/day on day 2.

AA: amino acid; BG: blood glucose; BUN: blood urea nitrogen; BW: birthweight; ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition; GA: gestational age; Imm-RDI: immediate recommended daily intake; Inc-AA: incremental introduction of amino acids; IV: intravenous; PN: parenteral nutrition; RCT: randomised controlled trial; TPN: total parenteral nutrition; UK: United Kingdom; US: United States.

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 these review questions. 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 these review questions.

Summary of studies included in the economic evidence review

No economic evaluations were identified which were applicable to these review questions.

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

High amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake

Where there is no division into different groups in the evidence statement this indicates that only the maximal intake differed. However, as described above there were sometimes different starting doses of amino acid used in studies informing this comparison. These were analysed as subgroups. When the starting dose of amino acids was at or below 2 g/kg/day

this is described as 'low commencement' and when the starting dose of amino acids was above 2 g/kg/day this was described as 'high commencement' in the evidence statements in this section.

Neurodevelopment outcomes

Bayley II Mental Development Index at 2 years

- Low quality evidence from 1 RCT (n=32) showed no clinically important difference in Bayley II mental development index scores at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: Mean difference (MD) -6.00 (95% CI -14.34 to 2.34).

Bayley III Mental Development Index at 2 years

- Low quality evidence from 1 RCT (n=100) showed no clinically important difference in Bayley III mental development index scores at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 3.00 (95% CI -2.52 to 8.52).

Bayley III Motor Score <70 at 2 years

- Very low quality evidence from 1 RCT (n=90) showed a clinically important difference in the rate of Bayley III Motor scores less than 70 at 2 years, with more babies scoring less than 70, indicating worse outcome, in the group who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was high uncertainty around the effect: Relative risk (RR) 2.00 (95% CI 0.19 to 21.28).

Bayley III Psychomotor Score <70 at 2 years

- Very low quality evidence from 1 RCT (n=90) showed no clinically important difference in the rate of Bayley III Psychomotor scores less than 70 at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was high uncertainty around the effect: RR 1.00 (95% CI 0.06 to 15.50).

Psychomotor Development Index at 2 years

- Very low quality evidence from 1 RCT (n=32) showed no clinically important difference in Psychomotor Development Index scores at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was high uncertainty around the effect: MD 3.00 (95% CI -6.41 to 12.41).

Weight gain

Weight gain (g/kg/day) at 1 month

- Low quality evidence from 2 RCTs (n=128) showed no clinically important difference in weight gain at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD -1.10g/kg/day (95% CI -3.21to 1.00).
    - Low quality evidence from 1 RCT (n=96) showed no clinically important difference in weight gain at 1 month in mixed birthweight babies who received high amino acid intake at commencement and maximal intake compared with high amino acid intake at commencement and low amino acid at maximal intake. However, there was uncertainty around the effect: MD -1.10g/kg/day (95% CI -3.22 to 1.02).
    - Very low quality evidence from 1 RCT (n=32) showed no clinically important difference in weight gain at 1 month in extremely low birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was high uncertainty around the effect: MD -1.40g/kg/day (95% CI -22.10 to 19.30).

Weight gain (g/kg/day) at discharge

- Moderate quality evidence from 2 RCTs (n=210) showed no clinically important difference in weight gain at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.77g/kg/day (95% CI -0.11 to 1.65).
    - Low quality evidence from 1 RCT (n=96) showed no clinically important difference in weight gain at discharge in babies who received high amino acid intake at commencement and maximal intake compared with high amino acid intake at commencement and low amino acid at maximal intake. However, there was uncertainty around the effect: MD 2.00g/kg/day (95% CI -0.54 to 4.54).
    - Low quality evidence from 1 RCT (n=114) showed no clinically important difference in weight gain at discharge in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: MD 0.60g/kg/day (95% CI -0.34 to 1.54).

Weight (g) at 1 month

- Moderate quality evidence from 1 RCT (n=135) showed no clinically important difference in weight at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 57.00g (95% CI -21.29 to 135.29).

Weight (g) at discharge

- Low quality evidence from 5 RCTs (n=600) showed no clinically important difference in weight at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 92.60g (95% CI 36.84 to 148.35).
    - Very low quality evidence from 3 RCTs (n=353) showed no clinically important difference in weight at discharge in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximum intake. However, there was uncertainty around the effect: MD 113.67g (95% CI 49.73 to 177.61).
    - Moderate quality evidence from 2 RCTs (n=247) showed no clinically important difference in weight at discharge in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximum intake: MD 25.74g (95% CI -88.15 to 139.63).

Weight (g) post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in weight at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD -129.00g (95% CI -821.46 to 563.46).

Days to regain birth weight

- Very low quality evidence from 3 RCTs (n=343) showed no clinically important difference in the number of days taken to regain birth weight in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD -1.47 days (95% CI -2.61 to -0.33).
    - Very low quality evidence from 2 RCTs (n=229) showed no clinically important difference in the number of days taken to regain birth weight in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: MD -2.53 days (95% CI -4.18 to -0.87).
    - Low quality evidence from 1 RCT (n=114) showed no clinically important difference in the number of days taken to regain birth weight in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: -0.50 days (95% CI -2.08 to 1.08).

Percentage weight loss

- Low quality evidence from 2 RCTs (n=229) showed no clinically important difference in percentage weight loss in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.22% (95% CI -1.20, 1.64).
    - High quality evidence from 1 RCT (n=115) showed no clinically important difference in percentage weight loss in babies who received low amino acid intake at commencement and high amino acid intake at maximal intake compared with low amino acid intake at commencement and maximal intake: MD 0.51% (95% CI -1.66 to 2.68).
    - Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in percentage weight loss in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake: MD 0.00% (95% CI -1.87 to 1.87).

Weight change in z-score at 1 month

- Low quality evidence from 1 RCT (n=96) showed no clinically important difference in weight change in z-score at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD -0.20 (95% CI -0.62 to 0.22).

Weight change in z-score at discharge

- Low quality evidence from 1 RCT (n=96) showed no clinically important difference in weight change in z-score at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 0.27 (95% CI -0.23 to 0.77).

Weight z-score at 1 month

- Moderate quality evidence from 1 RCT (n=135) showed no clinically important difference in weight z-score at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 0.14 (95% CI -0.11 to 0.39).

Weight z-score at discharge

- Low quality evidence from 3 RCTs (n=352) showed no clinically important difference in weight z-score at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.16 (95% CI -0.02 to 0.33)
    - Low quality evidence from 2 RCTs (n=238) showed no clinically important difference in weight z-score at discharge in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake: MD 0.19 (95% CI -0.02 to 0,40).
    - Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in weight z-score at discharge in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake: MD 0.07 (95% CI -0.25 to 0.39).

Weight z-score post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in weight z-score at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD -0.05 (95% CI -0.53 to 0.43).

Linear growth

Length (cm) at discharge

- Low quality evidence from 4 RCTs (n=476) showed no clinically important difference in length at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake:, MD 0.54cm (95% CI 0.11 to 0.98).
    - Very low quality evidence from 2 RCTs (n=229) showed no clinically important difference in length at discharge in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: MD 0.77cm (95% CI 0.20 to 1.34).
    - Moderate quality evidence from 2 RCTs (n=247) showed no clinically important difference in length at discharge in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake: MD 0.22cm (95% CI -0.46 to 0.90).

Length (cm) post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in length at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD -0.10cm (95% CI -1.81 to 1.61).

Length z-score at discharge

- Low quality evidence from 2 RCTs (n=228) showed no clinically important difference in length z-score at discharge in babies who received mixed amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid at commencement and maximal intake: MD 0.12 (95% CI -0.14 to 0.38).

Length z-score post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference length z-score at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.04 (95% CI -0.43 to 0.51).

Lower leg length gain (mm/day) at 1 month

- Moderate quality evidence from 1 RCT (n=96) showed no clinically important difference in lower leg length gain at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.01mm/day (95% CI -0.05 to 0.07).

Lower leg length (mm) at 1 month

- Moderate quality evidence from 1 RCT (n=115) showed no clinically important difference in lower leg length at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 3.62mm (95% CI 0.60 to 6.64).

Lower leg length (mm) at discharge

- Very low quality evidence from 2 RCTs (n=229) showed no clinically important difference in lower leg length at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 2.28mm (95% CI -2.16 to 6.72).

Head circumference

Head circumference growth (cm/week) at 1 month

- Very low quality evidence from 2 RCTs (n=231) showed no clinically important difference in head circumference growth at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 0.08cm/week (95% CI -0.02 to 0.18).

- Moderate quality evidence from 1 RCT (n=139) showed a clinically important difference in head circumference growth at 1 month, with greater growth in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: MD 0.13cm/week (95% CI 0.05 to 0.20).
- Moderate quality evidence from 1 RCT (n=96) showed no clinically important difference in head circumference growth at 1 month in babies who received high amino acid intake at commencement and maximal intake compared with high amino acid intake at commencement and low amino acid at maximal intake: MD 0.02cm/week (95% CI -0.09 to 0.13).

Head circumference growth (cm/week) at discharge

- Low quality evidence from 1 RCT (n=96) showed no clinically important difference in head circumference growth at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 0.03cm/week (95% CI -0.03 to 0.09).

Head circumference (cm) at 1 month

- Moderate quality evidence from 1 RCT (n=135) showed no clinically important difference in head circumference at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.60cm (95% CI 0.04 to 1.16).

Head circumference (cm) at discharge

- Very low quality evidence from 5 RCTs (n=602) showed no clinically important difference in head circumference at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD -0.04cm (95% CI -0.41 to 0.33).
  - Very low quality evidence from 3 RCTs (n=355) showed no clinically important difference in head circumference at discharge in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake: MD 0.12cm (95% CI -0.37 to 0.60).
  - Moderate quality evidence from 2 RCTs (n=247) showed no clinically important difference in head circumference at discharge in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake: MD -0.27cm (95% -0.68 to 0.15).

Head circumference (cm) post discharge (2 years)

- Low quality evidence from 1 RCT (n=100) showed no clinically important difference in head circumference at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD -0.30cm (95% CI -0.99 to 0.39).

Head circumference z-score at 1 month

- Moderate quality evidence from 1 RCT (n=135) showed no clinically important difference in head circumference z-score at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 0.30 (95% CI 0.01 to 0.59).

Head circumference z-score at discharge

- Very low quality evidence from 3 RCTs (n=354) showed no clinically important difference in head circumference z-score at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.04 (95% CI -0.29 to 0.38).

- Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in head circumference z-score at discharge in babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake: MD -0.06 (95% CI -0.39 to 0.27).
- Very low quality evidence from 2 RCTs (n=240) showed no clinically important difference in head circumference z-score at discharge in babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: MD 0.10 (95% -0.48 to 0.68).

Head circumference z-score post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=100) showed no clinically important difference in head circumference z-score at 2 years in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD -0.01 (95% CI -0.50 to 0.48).

Head circumference change in z-score at 1 month

- Moderate quality evidence from 1 RCT (n=96) showed no clinically important difference in head circumference change in z-score at 1 month in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake: MD 0.00 (95% CI -0.36 to 0.36).

Head circumference change in z-score at discharge

- Low quality evidence from 1 RCT (n=96) showed no clinically important difference in head circumference change in z-score at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was uncertainty around the effect: MD 0.40 (95% CI -0.02 to 0.82).

Body composition

- High quality evidence from 1 RCT (n=133) showed no clinically important difference in non-adipose (lean) body mass at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake:, MD 18.51g (95% CI -202.96 to 239.98).

Late onset sepsis

- Very low quality evidence from 6 RCTs (n=671) showed no clinically important difference in rate of late onset sepsis in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was high uncertainty around the effect: RR 0.97 (95% CI 0.75 to 1.25).
  - Low quality evidence from 2 RCTs (n=242) showed no clinically important difference in the rate of late onset sepsis in mixed birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was high uncertainty around the effect: RR 0.94 (95% CI 0.65 to 1.36).
  - Very low quality evidence from 1 RCT (n=96) showed no clinically important difference in the rate of late onset sepsis in mixed birthweight babies who received high amino acid intake at commencement and maximal intake compared with high amino acid intake at commencement and low amino acid at maximal intake. However, there was high uncertainty around the effect: RR 0.98 (95% CI 0.56 to 1.71).
  - Very low quality evidence from 2 RCTs (n=282) showed no clinically important difference in the rate of late onset sepsis in mixed birthweight babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was high uncertainty around the effect: RR 0.97 (95% 0.59 to 1.50).

- Very low quality evidence from 1 RCT (n=51) showed no clinically important difference in the rate of late onset sepsis in extremely low birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid at commencement and maximal intake. However, there was high uncertainty around the effect: RR 1.12 (95% CI 0.32 to 4.01).

Hyperkalaemia

- Very low quality evidence from 1 RCT (n=61) showed a clinically important difference in rate of hyperkalaemia between babies who received high amino acid at maximal intake compared with low amino acid at maximal intake, with more babies with hyperkalaemia associated with low amino acid at maximal intake. However, there was high uncertainty around the effect: RR 0.62 (95% CI 0.16 to 2.37).

Mortality

- Very low quality evidence from 8 RCTs (n=985) showed no clinically important difference in rate of mortality at discharge in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However, there was high uncertainty around the effect: RR 0.85 (95% CI 0.60 to 1.20).
  - Very low quality evidence from 4 RCTs (n=529) showed no clinically important difference in rate of mortality at discharge in mixed birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake. However, there was high uncertainty around the effect: RR 0.94 (95% CI 0.58 to 1.52).
  - Very low quality evidence from 1 RCT (n=96) showed a clinically important difference in rate of mortality at discharge between mixed birthweight babies who received high amino acid intake at commencement and maximal intake compared with high amino acid intake at commencement and low amino acid at maximal intake, with a higher mortality rate associated with babies who received high amino acid intake at commencement and low amino acid at maximal intake. However, there was high uncertainty around the effect: RR 0.73 (95% CI 0.30 to 1.76).
  - Very low quality evidence form 2 RCTs (n=299) showed a clinically important difference in rate of mortality at discharge between mixed birthweight babies who received high amino acid intake at commencement and maximal intake compared with low amino acid intake at commencement and maximal intake, with a higher mortality rate associated with babies who received low amino acid intake at commencement and maximal intake. However, there was high uncertainty around the effect: RR 0.57 (95% CI 0.26 to 1.25).
  - Very low quality evidence from 1 RCT (n=61) showed a clinically important difference in rate of mortality at discharge between extremely low birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid intake at commencement and maximal intake, with a higher mortality rate associated with babies who received low amino acid intake at commencement and maximal intake. However, there was high uncertainty around the effect: RR 1.55 (95% CI 0.49 to 4.95).

Duration of hospital stay

- Very low quality evidence from 3 RCTs (n=243) showed no clinically important difference in duration of hospital stay in babies who received high amino acid at maximal intake compared with low amino acid at maximal intake. However there was uncertainty around the effect: MD 1.43 days (95% CI -10.05 to 12.91).
  - Moderate quality evidence from 21 RCT (n=129) showed no clinically important difference in duration of hospital stay in mixed birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared

with low amino acid intake at commencement and maximal intake. However, there was uncertainty around the effect: MD -8.95 days (95% CI -17.90 to 0.00).

- Low quality evidence from 1 RCT (n=96) showed no clinically important difference in duration of hospital stay in mixed birthweight babies who received high amino acid intake at commencement and maximal intake compared with high amino acid intake at commencement and low amino acid at maximal intake. However, there was uncertainty around the effect: MD 7.80 days (95% CI -4.30 to 19.90).
- Low quality evidence from 1 RCT (n=32) showed a clinically important difference in duration of hospital stay between extremely low birthweight babies who received low amino acid intake at commencement and high amino acid at maximal intake compared with low amino acid at commencement and maximal intake, with longer duration of hospital stay associated with babies who received low amino acid intake at commencement and high amino acid at maximal intake. However, there was uncertainty around the effect: MD 7.00 days (95% CI -4.01 to 18.01).

Early amino acid intake versus delayed amino acid intake

Neurodevelopment outcomes

- Low quality evidence from 1 RCT (n=73) showed no clinically important difference in Development Index scores at 2 years in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD -3.50 (95% CI -8.59 to 1.59).

Weight gain

Weight (g) at discharge (6 weeks)

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in weight at discharge in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD 155g (95% CI -139.86 to 449.86).

Weight (g) post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=111) showed no clinically important difference in weight at 2 years in babies who received early amino acid intake compared with delayed amino acid intake: MD 100g (95% CI -572 to 772).

Days to regain birth weight

- Very low quality evidence from 1 RCT (n=17) showed a clinically important difference in the number of days to regain birth weight, with shorter time taken to regain weight in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD -1.70 days (95% CI -4.53 to 1.13).

Percentage weight loss at 7 days

- Very low quality evidence from 1 RCT (n=17) showed no clinically important difference in percentage weight loss at 7 days in babies who received early amino acid intake compared with delayed amino acid intake. However, there was high uncertainty around the effect: MD 0.90% (95% CI -5.36 to 7.16).

Weight <10th percentile at 6 weeks

- Very low quality evidence from 1 RCT (n=111) showed a clinically important difference in rate of weight below the 10th percentile at 6 weeks in babies who received early amino acid intake compared with delayed amino acid intake, with more babies below the 10th percentile in the group of babies receiving delayed amino acids. However, there was high uncertainty around the effect: RR 0.75 (95% CI 0.44 to 1.30).

Weight <10th percentile at 2 years

- Very low quality evidence from 1 RCT (n=111) showed a clinically important difference in rate of weight below the 10th percentile at 2 years in babies who received early amino acid intake compared with delayed amino acid intake, with more babies below the 10th percentile in the group of babies receiving delayed amino acids. However, there was high uncertainty around the effect: RR 0.66 (95% CI 0.33 to 1.32).

Weight change in z-score at discharge (6 weeks)

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in weight change in z-score at discharge in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD -0.22 (95% CI -0.70 to 0.26).

Weight change in z-score post discharge (2 years)

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in weight change in z-score at 2 years in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD -0.17 (95% CI -0.75 to 0.41).

Head circumference

Head circumference increment (cm) at 2 weeks

- Very low quality evidence from 1 RCT (n=17) showed a clinically important difference in head circumference increment at 2 weeks in babies who received early amino acid intake compared with delayed amino acid intake, with greater head circumference increment in the group of babies receiving early amino acids. However, there was high uncertainty around the effect: MD 0.25cm (95% CI -0.14 to 0.64).

Head circumference (cm) at discharge (6 weeks)

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in head circumference at discharge in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD 0.10cm (95% CI -0.50 to 0.70).

Head circumference (cm) post discharge (2 years)

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in head circumference at 2 years in babies who received early amino acid intake compared with delayed amino acid intake. However, there was uncertainty around the effect: MD 0.20cm (95% CI -0.47 to 0.87).

Head circumference < 10th percentile at 6 weeks

- Very low quality evidence from 1 RCT (n=111) showed a clinically important difference in rate of head circumference below the 10th percentile at 6 weeks in babies who received early amino acid intake compared with delayed amino acid intake, with more babies below the 10th percentile in the group of babies receiving delayed amino acids. However, there was high uncertainty around the effect: RR 0.35 (95% CI 0.04 to 3.28).

Head circumference < 10th percentile at 2 years

- Very low quality evidence from 1 RCT (n=111) showed a clinically important difference in rate of head circumference below the 10th percentile at 2 years in babies who received early amino acid intake compared with delayed amino acid intake, with more babies below the 10th percentile in the group of babies receiving delayed amino acids. However, there was high uncertainty around the effect: RR 0.70 (95% CI 0.12 to 4.05).

Head circumference change in z-score at discharge (6 weeks)

- Moderate quality evidence from 1 RCT (n=111) showed no clinically important difference in head circumference change in z-score at discharge in babies who received early amino acid intake compared with delayed amino acid intake: MD -0.15 (95% CI -0.66 to 0.36).

Head circumference change in z-score post discharge (2 years)

- Moderate quality evidence from 1 RCT (n=111) showed no clinically important difference in head circumference change in z-score at 2 years in babies who received early amino acid intake compared with delayed amino acid intake: MD 0.03 (95% CI -0.46 to 0.52).

Late onset sepsis

- Very low quality evidence from 1 RCT (n=29) showed no clinically important difference in rate of late onset sepsis in babies who received early amino acid intake compared with delayed amino acid intake. However, there was high uncertainty around the effect: RR 0.92 (95% CI 0.41 to 2.07).

Mortality

- Very low quality evidence from 2 RCTs (n=167) showed a clinically important difference in rate of mortality in babies who received early amino acid intake compared with delayed amino acid intake. However, there was high uncertainty around the effect: RR 0.78 (95% CI 0.35 to 1.75).
    - Very low quality evidence from 1 RCT (n=135) showed no clinically important difference in rate of mortality in babies who received early amino acid intake compared with delayed amino acid intake when critical illness was unspecified. However, there was high uncertainty around the effect: RR 0.84 (95% CI 0.35 to 1.99).
    - Very low quality evidence from 1 RCT (n=32) showed a clinically important difference in rate of mortality in critically ill babies (requiring ventilation) who received early amino acid intake compared with delayed amino acid intake, with a greater mortality rate associated with babies receiving delayed amino acids. However, there was high uncertainty around the effect: RR 0.50 (95% CI 0.05 to 4.98).

High amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement to the same maximal intake

Neurodevelopmental outcomes

Bayley III cognitive composite score at 18 to 24 months

- Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in Bayley III cognitive composite scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD 0.40 (95% CI -3.86 to 4.66).

Bayley III language composite score at 18 to 24 months

- Low quality evidence from 1 RCT (n=113) showed no clinically important difference in Bayley III language composite scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD 2.30 (95% CI -3.20 to 7.85).

Bayley III receptive communication score at 18 to 24 months

- Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in Bayley III receptive communication scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD -0.20 (95% CI -1.83 to 1.43).

Bayley III expressive communication score at 18 to 24 months

- Low quality evidence from 1 RCT (n=112) showed no clinically important difference in Bayley III expressive communication scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD 0.60 (95% CI -0.33 to 1.53).

Bayley III motor composite score at 18 to 24 months

- Moderate quality evidence from 1 RCT (n=114) showed no clinically important difference in Bayley III motor composite scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD -0.10 (95% CI -4.89 to 4.69).

Bayley III fine motor score at 18 to 24 months

- Moderate quality evidence from 1 RCT (n=113) showed no clinically important difference in Bayley III fine motor scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD 0.10 (95% CI -0.66 to 0.86).

Bayley III gross motor score at 18 to 24 months

- Moderate quality evidence from 1 RCT (n=112) showed no clinically important difference in Bayley III gross motor scores at 18 to 24 months in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD -0.10 (95% CI -0.92 to 0.72).

Weight gain

Weight gain (g/kg/day) at 1 month

- High quality evidence from 1 RCT (n=123) showed a clinically important difference in weight gain at 1 month in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with greater weight gain in the group of babies receiving low amino acid intake at commencement: MD -4.48g/kg/day (95% CI -6.17 to -2.79).

Weight gain (g/kg/day) at discharge

- Very low quality evidence from 1 RCT (n=42) showed no clinically important difference in weight gain at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was high uncertainty around the effect: MD 0.40g/kg/day (95% CI -1.69 to 2.49).

Weight (g) at 1 month

- Moderate quality evidence from 1 RCT (n=123) showed a clinically important difference in weight at 1 month in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with greater weight gain in the group of babies receiving low amino acid intake at commencement. However, there was uncertainty around the effect: MD -123.12g (95% CI -198.61 to -47.63).

Weight (g) at 36 weeks postmenstrual age (PMA)

- Moderate quality evidence from 1 RCT (n=121) showed no clinically important difference in weight at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD -29.00g (95% CI -135.93 to 77.93).

Weight (g) at discharge

- Moderate quality evidence from 3 RCTs (n=212) showed no clinically important difference in weight at discharge in babies who received high amino acid intake at commencement

compared with low amino acid intake at commencement: MD 35.78g (95% CI -42.79 to 114.35).

Weight percentile at 36 weeks PMA

- Low quality evidence from 1 RCT (n=121) showed no clinically important difference in weight percentile at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -4.70 (95% CI -10.44 to 1.04).

Weight percentile at discharge

- Low quality evidence from 1 RCT (n=126) showed no clinically important difference in weight percentile at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -7.20 (95% CI -15.00 to 0.60).

Weight z-score at 36 weeks PMA

- Moderate quality evidence from 1 RCT (n=121) showed no clinically important difference in weight z-score at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD -0.06 (95% CI -0.31 to 0.19).

Weight z-score at discharge

- Low quality evidence from 1 RCT (n=126) showed no clinically important difference in weight z-score at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.18 (95% CI -0.46 to 0.10).

Days to regain birth weight

- Very low quality evidence from 3 RCTs (n=136) showed no clinically important difference in the number of days to regain birthweight in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.61 days (95% CI -2.54 to 1.33).
    - Moderate quality evidence from 1 RCT (n=50) showed a clinically important difference in the number of days to regain birthweight in mixed birthweight babies who received high amino acid and 2g/kg/day of lipids at commencement compared with low amino acid and 1g/kg/day of lipids at commencement, with fewer days to regain birthweight associated with the group of babies receiving high amino acid and 2g/kg/day of lipids. However, there was uncertainty around the effect: MD -1.50 days (95% CI -3.11 to 0.11).
    - Low quality evidence from 1 RCT (n=44) showed a clinically important difference in the number of days to regain birthweight in mixed birthweight babies who received high amino acid and 3g/kg/day of lipids at commencement compared with low amino acid and 1g/kg/day of lipids at commencement, with fewer days to regain birthweight associated with the group of babies receiving low amino acid and 1g/kg/day of lipids. However, there was uncertainty around the effect: MD 2.30 days (95% CI -0.48 to 5.08).
    - Very low quality evidence from 1 RCT (n=10) showed a clinically important difference in the number of days to regain birthweight in very low birthweight babies who received high amino acid and 2g/kg/day of lipids at commencement compared with low amino acid and 1g/kg/day of lipids at commencement, with fewer days to regain birthweight associated with the group of babies receiving high amino acid and 2g/kg/day of lipids. However, there was high uncertainty around the effect: MD -2.90 days (95% CI -8.31 to 2.51).
    - Low quality evidence from 1 RCT (n=32) showed a clinically important difference in the number of days to regain birthweight in extremely low birthweight babies who received

high amino acid and 2g/kg/day of lipids at commencement compared with low amino acid and 1g/kg/day of lipids at commencement, with fewer days to regain birthweight associated with the group of babies receiving high amino acid and 2g/kg/day of lipids. However, there was uncertainty around the effect: MD -1.17 days (95% CI -3.73 to 1.39).

Percentage weight loss

- Low quality evidence from 1 RCT (n=42) showed a clinically important difference in percentage weight loss in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with decreased weight loss associated with the group of babies receiving high amino acid intake. However, there was uncertainty around the effect: MD -3.80% (95% CI -7.20 to -0.40).

Weight < 10th percentile at discharge

- Very low quality evidence from 1 RCT (n=42) showed no clinically important difference in rate of weight below the 10th percentile in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement . However, there was high uncertainty around the effect: RR 0.95 (95% CI 0.62 to 1.46).

Length growth (cm/week) at 1 month

- Moderate quality evidence from 1 RCT (n=123) showed a clinically important difference in length growth at 1 month in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with greater length growth associated with the group of babies receiving low amino acid intake. However, there was uncertainty around the effect: MD -0.27cm/week (95% CI -0.40 to -0.14).

Length (cm) at 1 month

- Very low quality evidence from 2 RCTs (n=173) showed no clinically important difference in length at 1 month in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.67cm (95% CI -1.34 to 0.00).
    - Moderate quality evidence from 1 RCT (n=123) showed no clinically important difference in length at 1 month in babies who were not routinely provided with lipids who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -1.02cm (95% CI -1.76 to -0.28).
    - Moderate quality evidence from 1 RCT (n=50) showed no clinically important difference in length at 1 month in babies who received high amino acid intake and 2g/kg/day of lipids at commencement compared with low amino acid intake and 1g/kg/day of lipids at commencement. However, there was uncertainty around the effect: MD 1.10cm (95% CI -0.55 to 2.75).

Length (cm) at 36 weeks PMA

- Low quality evidence from 1 RCT (n=103) showed no clinically important difference in length at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.80 (95% CI -1.81 to 0.21).

Length (cm) at discharge

- Very low quality evidence from 2 RCTs (n=173) showed no clinically important difference in length at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD 0.42 (95% CI -0.62 to 1.46).
    - Low quality evidence from 1 RCT (n=123) showed no clinically important difference in length at discharge in babies with unspecified lipid intake who received high amino acid

intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.70 (95% CI -2.06 to 0.66).

- Moderate quality evidence from 1 RCT (n=50) showed a clinically important difference in length at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with greater length associated with the group of babies receiving high amino acid intake. However, there was uncertainty around the effect: MD 2.00cm (95% CI 0.38 to 3.62).

Length percentile at 36 weeks PMA

- Low quality evidence from 1 RCT (n=103) showed no clinically important difference in length percentile at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -5.20 (-11.74 to 1.34).

Length percentile at discharge

- Low quality evidence from 1 RCT (n=123) showed no clinically important difference in length percentile at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -7.80 (95% CI -16.50 to 0.90).

Length z-score at 36 weeks PMA

- Low quality evidence from 1 RCT (n=103) showed no clinically important difference in length z-score at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.35 (95% Ci -0.74 to 0.04).

Length z-score at discharge

- Low quality evidence from 1 RCT (n=123) showed no clinically important difference in length z-score at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.24 (95% CI -0.59 to 0.11).

Head circumference (cm) at 1 month

- Moderate quality evidence from 1 RCT (n=50) showed no clinically important difference in head circumference at 1 month in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD 0.50cm (95% CI -0.03 to 1.03).

Head circumference (cm) at 36 weeks PMA

- Moderate quality evidence from 1 RTC (n=111) showed no clinically important difference in head circumference at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD -0.20cm (95% CI -0.70 to 0.30).

Head circumference (cm) at discharge

- Very low quality evidence from 3 RCTs (n=94218) showed no clinically important difference in head circumference at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement: MD 0.45cm (95% CI -0.11 to 1.01).
  - Low quality evidence from 1 RCT (n=124) showed no clinically important difference in babies with unspecified lipid intake who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.60cm (95% CI -1.53 to 0.33).
  - Low quality evidence from 1 RCT (n=44) showed no clinically important difference in babies who received high amino acid intake and 3g/kg/day of lipids at commencement

compared with low amino acid intake and 1g/kg/day of lipids at commencement. However, there was uncertainty around the effect: MD 0.90cm (95% CI -0.40 to 2.20).

- Moderate quality evidence from 1 RCT (n=50) showed a clinically important difference in head circumference at discharge in babies who received high amino acid intake and 2g/kg/day of lipids at commencement compared with low amino acid intake and 1g/kg/day of lipids at commencement, with greater head circumference in the group of babies receiving high amino acid intake and 2g/kg/day of lipids. However, there was uncertainty around the effect: MD 1.10cm (95% Ci 0.27 to 1.93).

Head circumference percentile at 36 weeks PMA

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in head circumference percentile at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -7.10 (95% CI -15.59 to 1.39).

Head circumference percentile at discharge

- Low quality evidence from 1 RCT (n=124) showed no clinically important difference in head circumference percentile at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -9.00 (95% CI -17.24 to -0.76).

Head circumference z-score at 36 weeks PMA

- Low quality evidence from 1 RCT (n=111) showed no clinically important difference in head circumference z-score at 36 weeks PMA in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.19 (95% CI -0.49 to 0.11).

Head circumference z-score at discharge

- Low quality evidence from 1 RCT (n=124) showed no clinically important difference in head circumference z-score at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was uncertainty around the effect: MD -0.30 (95% CI -0.57 to -0.03).

Late onset sepsis

- Low quality evidence from 3 RCTs (n=316) showed a clinically important difference in rate of late onset sepsis in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with more babies with sepsis associated with low amino acid intake. However, there was high uncertainty around the effect: RR 0.70 (95% CI 0.44 to 1.11).

Mortality

- Very low quality evidence from 3 RCTs (n=263) showed no clinically important difference in rate of mortality in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement. However, there was high uncertainty around the effect: RR 0.89 (95% CI 0.42 to 1.88).

Duration of hospital stay

- Moderate quality evidence from 3 RCTs (n=136) showed no clinically important difference in duration of hospital stay in babies who received high amino acid intake at commencement compared with low amino acid intake at : MD -1.69 days (95% CI -7.90 to 4.53).

Nutritional intake

Amino acid intake (g/kg/day) to first 7 days

- Very low quality evidence from 2 RCTs (n=92) showed a clinically important difference in amino acid intake in the first 7 days in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with greater amino acid intake associated with the group of babies receiving high amino acid intake. However, there was uncertainty around the effect: MD 0.54g/kg/day (95% CI 0.05 to 1.03).

Amino acid intake (g/kg/day) at discharge

- Low quality evidence from 1 RCT (n=75) showed a clinically important difference in amino acid intake at discharge in babies who received high amino acid intake at commencement compared with low amino acid intake at commencement, with greater amino acid intake associated with the group of babies receiving high amino acid intake. However, there was uncertainty around the effect: MD 0.32g/kg/day (95% CI 0.05 to 0.59).

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 discussed the importance and relevance of various outcomes when assessing the effectiveness of amino acids for PN in neonates. The committee agreed the critical outcomes are neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale), growth/anthropometric measures (weight gain, linear growth and head circumference), body composition (measured as lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion), and adverse effects of lipids (sepsis, acidosis, high serum urea, hypercalcaemia/hypophosphataemia, hypokalaemia, re-feeding syndrome). The critical roles of amino acids in protein synthesis, cellular structure and function is important for brain development; which is why neurodevelopmental outcomes and growth, especially head growth, were selected as critical outcomes. Adequate amino acid provision supported by appropriate non-nitrogen energy (carbohydrates and lipids) may lead to increased lean mass as opposed to a greater adiposity that may occur through growth driven by non-nitrogen energy. Mortality and duration of hospital stay, (defined as the proportion of prescribed amino acids actually received) were selected as important outcomes because they may be more a consequence of complications of being born preterm. Nutritional intake was also considered to be an important outcome because even though babies receiving higher amino acids would also have a higher intake, not all that is given is actually used by the baby and therefore a higher dose may need to be considered so that the baby receives all that is intended.

The quality of the evidence

The studies included in this review were assessed for quality using GRADE methodology. The quality of the evidence ranged from very low to high quality. Evidence was mainly downgraded due to imprecision around the effects but there was also bias in included studies due to lack of blinding, uncertainty surrounding the methods of randomisation and whether allocation concealment was performed, attrition and selective reporting of outcomes. There was some heterogeneity but this was mainly explained through subgroup analysis. Outcomes were reported in various ways across included studies. Therefore, we extracted data for each outcome as reported. For example, for weight the following outcomes were extracted: weight gain (g/kg/day), weight (g), weight z-score, change in weight z-score,

weight percentile and weight <10th percentile. The differences in how outcomes were reported across included studies limited the evidence that could be pooled.

There was no evidence for acidosis, high serum urea, hypercalcaemia/hypophosphataemia, hypokalaemia or re-feeding syndrome. Few studies reported the actual amount of amino acids delivered to the babies. This is an important factor in order to ascertain the effectiveness of the intervention, for instance, a high dose intervention may not have achieved its target dose and any benefit detected in fact be in response to a lower dose. Further, some of the included studies reported total amino acid intake from all sources (parenteral and enteral nutrition) rather than just amino acid intake derived from PN.

Benefits and harms

The committee were presented with substantial evidence relating to amino acid intake; however, the evidence was not entirely consistent and ranged in the level of quality as assessed by GRADE methodology. The committee used this evidence alongside their experience and expertise to make the recommendations by informal consensus.

Starting amino acids

There was some evidence that starting amino acids early (on the first day of life) compared with later improved growth and reduced mortality. Therefore, the committee agreed that there was no reason to delay starting amino acids, and they should be included immediately when starting PN.

The evidence comparing growth outcomes based on higher (≥2g/kg/day) and lower (<2g/kg/day) amino acid intake was inconsistent with some outcomes favouring higher intake and some outcomes favouring lower intake. There was no difference in mortality or duration of hospital stay based on amino acid intake at the start but there was some evidence of lower rates of sepsis with higher amino acid intake at start. The committee agreed that the evidence appeared to favour a higher starting dose. The committee also noted that one of the studies which favoured starting at a lower dose did not routinely provide lipids, multivitamins or trace elements as part of PN and, therefore, may not be representative of current clinical practice in the UK. However, there was more consistent evidence of benefit for growth outcomes with 2g/kg/day of amino acids compared with lower intake than 3g/kg/day of amino acids compared with lower intake. Therefore, the committee recommended 2g/kg/day as the upper end of the starting range. The committee also discussed that in their experience, an amino acid intake below 1.5g/kg/day results in a negative nitrogen balance; therefore, by informal consensus, the committee recommended this as the lower threshold for the starting range of amino acids.

For preterm babies, 1.5 g/kg/day was chosen as the lower starting dose threshold, because less than this can result in a negative nitrogen balance. The committee did not look for evidence on how different amino acid doses affect nitrogen balance, but used their knowledge of metabolic studies, which are widely used to estimate the minimum amount of amino acids needed to prevent negative nitrogen balance. The upper starting dose threshold of 2 g/kg/day was selected because there was some evidence (even if a bit inconsistent) of better growth at a starting dose of 2 g/kg/day of amino acids compared with less than 2 g/kg/day, but these benefits did not persist at higher amino acid starting doses (3 g/kg/day).

No direct evidence on term babies was found. Based on their knowledge and experience the committee agreed a lower a lower starting dose could be prescribed for term babies (1-2g/kg/day) as term babies generally lose less protein than preterm babies.

Maintaining amino acids

The evidence comparing higher (>3g/kg/day) and lower (≤3g/kg/day) amino acid intake at a maximum dose, showed no difference in growth outcomes or body composition, with the exception of greater head circumference growth in babies who received higher compared

with lower amino acid intake at maximum, (and who had low amino acid intake at start). There was some evidence of improved outcomes with higher amino acid intake showing reduced hyperkalaemia and mortality. The exception to this was extremely low birthweight babies who showed higher mortality and a longer duration of stay with higher compared with lower amino acid intake. However, the evidence was low quality and underpowered to detect differences in mortality. The committee also noted that the energy intake in this study was low and, based on their knowledge and expertise, thought that the adverse outcomes may not have occurred if energy intake was sufficient to utilise a higher amount of amino acids. Therefore, they discussed the importance of ensuring that PN regimens adhere to the ratios recommended in this guideline. There was also some evidence that babies were more likely to have Bayley III motor scores less than 70 with higher amino acid intake at start, but this study was underpowered and there were no differences between groups for other neurodevelopmental outcomes.

The committee discussed the lower limit of the maintenance range at length. They agreed that differences beyond amino acid intake between studies, such as energy and lipid intake, made it difficult to draw conclusions about effect of amino acid intake. For preterm babies a lower limit of 3g/kg/day was selected because the meta-analysis which included an overall ten studies across different outcomes suggested that amino acids provision above 3g/kg/day was associated with some better outcomes (for example the rate of mortality was lower in babies receiving higher amino acids) . There was some evidence of appropriate growth at a maximal intake of 2.7 g/kg/day, but this was supported by early (within the first 24 hours) and progressive enteral feeding. The committee noted that some babies receiving neonatal PN will be on no, or minimal enteral feeds or will be unable to increase enteral feeding in a timely manner. This, combined with the weak evidence of improved growth at 3 g/kg/day or more, meant that 3 g/kg/day was selected as the lower end of the maintenance range. However, the committee were split on this point so a majority decision was taken.

The committee agreed by informal consensus, and based on their expertise that high amino acids can be associated with certain adverse events, which were not reported in the included evidence (such as acidosis, high serum urea, hypercalcaemia or hypophosphataemia, hypokalaemia and re-feeding syndrome). In order to minimise the risk of such adverse outcomes, the committee agreed that it was important to provide a maintenance range that should not be exceeded.

The maximum amino acid intake in the studies reviewed was 4 g/kg/day. The committee looked for adverse effects across all the studies in the evidence review, including those using maximum amounts of over 3.5 g/kg/day, and found no clear evidence of harm. However, the committee were concerned that the absence of evidence of harm is not the same as evidence of absence. It was noted that higher amino acid intakes need to be supported by sufficient non-nitrogen energy. The committee followed the evidence in agreeing an upper maintenance range limit of 4 g/kg/day for preterm babies. They suggested being more vigilant for adverse effects through appropriate monitoring when using the top half of this maintenance range.

No direct evidence on term babies was found. The committee noted that physiologically, term babies lose less protein than preterm babies so a maintenance dose can be prescribed. A maintenance range of 2.5-3 g/kg/day was recommended based on the committee's knowledge of nitrogen balance studies and the amount of amino acids needed to achieve a similar weight gain as full term infants who are milk fed.

The committee discussed that, whilst some of the included studies started amino acid intake at the maximum intended dose, most of the included studies incremented amino acid intake over 2 to 7 days. Therefore, the committee agreed that amino acid intake should be gradually increased from the starting range to the maintenance range. There was not enough evidence to specify the number of days over which intake should be increased, but the committee suggested 4 days as an example as this is approximately how long it would take to reach the

maintenance range if incrementing from the starting range at rates similar to those used in the included studies.

No evidence was found on babies who do not start PN from birth. The committee discussed, based on knowledge and experience that babies starting PN after the first 4 days after birth should start PN based on the recommended maintenance range. Babies starting PN after this time point may have already made progress with incrementing up to the maintenance levels of macronutrients required for growth from their enteral nutrition. If that enteral nutrition has to be stopped (for example, due to development of necrotising enterocolitis) and PN started the committee felt that returning to starting doses of macronutrients would likely lead to nutritional deficit. Alternatively, babies may be starting PN after this time point as they have not made sufficient progress with enteral fees within the first 72 hours after birth. However, the committee agreed, based on their expertise, that the quantity of macronutrients that can be tolerated is closely linked to the postnatal age of the baby, with older babies able to tolerate greater nutritional intake. Therefore, the committee agreed by informal consensus that starting on the maintenance range would be appropriate even if progress has not been made with enteral feeds. The committee agreed to use the same approach for other constituents whenever there is an absence of evidence.

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 target dosage of amino acids in preterm and term babies who are receiving PN and the optimal way of achieving this target dosage would not incur extra resource implications to the health care system.

The committee noted that getting the amount of amino acids right for neonatal PN may result in avoiding additional costs associated with adverse effects to the NHS given that incorrect relative amounts of amino acids can result in adverse events, for example acidosis, high serum urea, hypercalcaemia or hypophosphataemia, hypokalaemia and re-feeding syndrome which in turn may result in longer stays in neonatal intensive care and high associated costs.

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 questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Field (based on PRISMA-P)	Content
Review question	D2a. What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care? D2b. What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?
Type of review question	Intervention
Objective of the review	Where provision of parenteral nutrition (PN) support has been agreed, the optimal target dose and approach for amino acids is important.
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)	D2a. Target dose of amino acid (g/kg/d) to be achieved D2b. Starting dose Rate of increase in amino acids
Eligibility criteria – comparator(s)/control or reference (gold) standard	D2a. Each other D2b. Different starting doses Different increases Different regimens

Field (based on PRISMA-P)	Content

Outcomes and prioritisation	**Critical**
	• Neurodevelopmental outcomes (general cognitive abilities at two years corrected age as measured by a validated scale)
	• Growth/anthropometric measures:
	  ○ Weight gain (g/kg/d)
	  ○ Linear growth
	  ○ Head circumference (mm)
	  ○ Infection (including sepsis)
	• Body composition (measured as
	  ○ lean mass, fat-free mass, fat mass, adipose tissue, nitrogen accretion)
	• Adverse effects of IV amino acids:
	  ○ Infection including sepsis
	  ○ Acidosis
	  ○ High serum urea
	  ○ Hypercalcaemia/Hypophosphataemia
	  ○ Hypokalaemia
	  ○ Re-feeding syndrome
	
	Important
	• Mortality
	• Duration of hospital stay
	• Nutritional intake (g/kg/d) (prescribed amino acids actually received)

Eligibility criteria – study design	Systematic reviews of RCT RCTs Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making). Non-comparative studies (only for critical outcomes if no evidence from RCTs or comparative cohort studies are available or there is limited data available to inform decision making) The decision to include comparative cohort studies and non-comparative studies will be determined for each parameter according to available RCTs data 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

Field (based on PRISMA-P)	Content
	No date restriction Low income countries will be downgraded for indirectness
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) Babies who are critically ill or need surgery Where evidence exists, consideration will be given to the specific needs of population subgroups: Age of baby (first 2 weeks vs. later) Preterm (Extremely preterm <28 weeks' GA; very preterm: 28-31 weeks' GA; moderately preterm: 32-36 weeks' GA) Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Birthweight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) First week of life and after first week of life Critically ill babies or those requiring surgery (for example, inotropic support, therapeutic hypothermia or fluid restriction) Possible equality considerations Mothers aged 17 or below Parents or carers whose first language is not English Parents or carers who have learning difficulties or disabilities Important confounders (when comparative observational studies are included for interventional reviews): Age of baby (first 2 weeks vs. later) Preterm (Very early <28 weeks GA; 28-31 weeks GA; 32-36 weeks GA) Birth weight: Low birth weight (< 2500g); very low birth weight (< 1500g) and extremely low birth weight (< 1000g) Actual dose received Sex of baby

Field (based on PRISMA-P)	Content
	Hyperglycaemia Gestation (pre-term vs. term) For neurodevelopmental outcomes: Biological (sex, small for gestational age, ethnicity) Neonatal (PVL, IVH, infarct, sepsis, ROP, NEC, antenatal/postnatal steroids, BPD at 36 weeks) Social (SES, substance abuse, alcohol abuse, multiple pregnancy, chorioamnionitis, neglect, maternal age, maternal mental health disorder) Postnatal (epilepsy, age of establishing feeding)
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. A random sample of the references 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 will be resolved by discussion between the two reviewers. The senior systematic reviewer or guideline lead will act as arbiter where necessary.
Data management (software)	Pairwise meta-analyses, if possible, will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. Low income countries will be downgraded for indirectness. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists (ROBIS (systematic reviews and meta-analyses); Cochrane risk of bias tool (RCTs or comparative cohort studies); Cochrane risk of bias tool (Non-randomised studies).
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 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.

Field (based on PRISMA-P)	Content
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
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	This review is not registered with PROSPERO

BPD: bronchopulmonary dysplasia; CCTR: Cochrane controlled trials register; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GA: Gestational age; GRADE: Grading of Recommendations Assessment, Development and Evaluation;

HTA: Health Technology Assessment; IVH: Intraventricular haemorrhage; NEC: Necrotising enterocolitis; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NIHR: National Institute for Health Research; PROSPERO: International prospective register of systematic reviews; PVL: Periventricular leukomalacia; RCT: randomised controlled trial; ROBIS: risk of bias in systematic reviews; ROP: Retinopathy of prematurity; SES: Socioeconomic status

Appendix B – Literature search strategies

Literature search strategies for review questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

One combined search was conducted for the research questions.

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	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.

#	Searches
27	(g adj3 kg adj3 (d or day) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
29	(g adj3 kg adj3 (d or day) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.

#	Searches
30	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
31	(g adj3 kg adj3 (d or day) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or

#	Searches
	Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
32	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 macronutrient?).mp.
33	exp AMINO ACIDS/ad [Administration & Dosage]
34	exp LIPIDS/ad [Administration & Dosage]
35	exp PROSTAGLANDINS/ad [Administration & Dosage]
36	34 not 35
37	exp CARBOHYDRATES/ad [Administration & Dosage]
38	exp HEPARIN/ad [Administration & Dosage]
39	exp GLYCOPEPTIDES/ad [Administration & Dosage]
40	exp AMINOGLYCOSIDES/ad [Administration & Dosage]
41	or/38-40
42	37 not 41
43	FAT EMULSIONS, INTRAVENOUS/
44	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 36 or 42
45	14 and 25 and 44
46	14 and 43
47	45 or 46
48	limit 47 to english language
49	LETTER/
50	EDITORIAL/
51	NEWS/
52	exp HISTORICAL ARTICLE/
53	ANECDOTES AS TOPIC/
54	COMMENT/
55	CASE REPORT/
56	(letter or comment*).ti.
57	or/49-56
58	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
59	57 not 58
60	ANIMALS/ not HUMANS/
61	exp ANIMALS, LABORATORY/
62	exp ANIMAL EXPERIMENTATION/
63	exp MODELS, ANIMAL/
64	exp RODENTIA/
65	(rat or rats or mouse or mice).ti.
66	or/59-65
67	48 not 66

1 Database: Embase

#	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.

#	Searches
22	((peripheral$ or central$) adj3 (line? or catheter$)).ti,ab.
23	drip?.ti,ab.
24	or/14-23
25	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
26	(g adj3 kg adj3 (d or day) adj5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)).mp.
27	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or

#	Searches
	Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
28	(g adj3 kg adj3 (d or day) adj5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)).mp.
29	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
30	(g adj3 kg adj3 (d or day) adj5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or

#	Searches
	Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM$ Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)).mp.
31	((Dose? or Dosage? or Regimen? or Amount? or Optimal$ or Optimis$ or Requir$ or Target? or Rate? or Increment$ or Safe$ or Efficacy or Initiat$ or Start$ or Introduc$ or Receiv$ or Administer$) adj5 macronutrient?).mp.
32	exp AMINO ACIDS/do [Drug Dose]
33	exp LIPID/do [Drug Dose]
34	exp PROSTAGLANDIN/do [Drug Dose]
35	33 not 34
36	exp CARBOHYDRATE/do [Drug Dose]
37	exp HEPARIN/do [Drug Dose]
38	exp GLYCOPEPTIDE/do [Drug Dose]
39	exp AMINOGLYCOSIDE/do [Drug Dose]
40	or/37-39
41	36 not 40
42	exp AMINO ACIDS/
43	exp LIPID/
44	exp PROSTAGLANDIN/
45	43 not 44
46	exp CARBOHYDRATE/
47	exp HEPARIN/
48	exp GLYCOPEPTIDE/
49	exp AMINOGLYCOSIDE/
50	or/47-49
51	46 not 50
52	OPTIMAL DRUG DOSE/
53	RECOMMENDED DRUG DOSE/
54	DRUG DOSE REGIMEN/
55	DOSE CALCULATION/
56	DRUG DOSE COMPARISON/
57	DRUG DOSE ESCALATION/
58	DRUG DOSE INCREASE/
59	DRUG DOSE INTENSIFICATION/
60	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 35 or 41
61	42 or 45 or 51
62	52 or 53 or 54 or 55 or 56 or 57 or 58 or 59
63	13 and 24 and 60
64	13 and 24 and 61 and 62
65	or/63-64
66	limit 65 to english language

#	Searches
67	letter.pt. or LETTER/
68	note.pt.
69	editorial.pt.
70	CASE REPORT/ or CASE STUDY/
71	(letter or comment*).ti.
72	or/67-71
73	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
74	72 not 73
75	ANIMAL/ not HUMAN/
76	NONHUMAN/
77	exp ANIMAL EXPERIMENT/
78	exp EXPERIMENTAL ANIMAL/
79	ANIMAL MODEL/
80	exp RODENT/
81	(rat or rats or mouse or mice).ti.
82	or/74-81
83	66 not 82

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)):ti,ab
5	MeSH descriptor: [INFANT, PREMATURE] explode all trees
6	((preterm* or pre-term* or prematur* or pre-matur*) near/5 infan*):ti,ab
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	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or

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	Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)) :ti,ab
27	(g adj3 kg adj3 (d or day) near/5 (amino acid? or Alanine or Pantothenic Acid or Lysinoalanine or Mimosine or Chloromethyl Ketone? or Aspartic Acid or Isoaspartic Acid or N-Methylaspartate or Potassium Magnesium Aspartate or Glutamate? or 1-Carboxyglutamic Acid or Glutamic Acid or Sodium Glutamate or Pemetrexed or Polyglutamic Acid or Pyrrolidonecarboxylic Acid or Arginine or Argininosuccinic Acid or Benzoylarginine-2-Naphthylamide or Benzoylarginine Nitroanilide or Homoarginine or Nitroarginine or omega-N-Methylarginine or Tosylarginine Methyl Ester or Asparagine or Glutamine or Proglumide or Lysine or Hydroxylysine or Polylysine or Ornithine or Eflornithine or Aminoisobutyric Acids or Isoleucine or Leucine or Valine or 2-Amino-5-phosphonovalerate or Valsartan or Dextrothyroxine or Phenylalanine or Dihydroxyphenylalanine or Cysteinyldopa or Levodopa or Methyldopa or Fenclonine or N-Formylmethionine or p-Fluorophenylalanine or Thyroxine or Thyronine? or Diiodothyronine? or Triiodothyronine or Tryptophan or 5-Hydroxytryptophan or Tyrosine or Betalain? or Betacyanin? or Diiodotyrosine or Melanin? or Methyltyrosine? or Monoiodotyrosine or Phosphotyrosine or Cycloleucine or Desmosine or Histidine or Ergothioneine or Methylhistidine? or Imino Acid? or Azetidinecarboxylic Acid or Proline or Captopril or Fosinopril or Hydroxyproline or Technetium Tc 99m or Isodesmosine or NG-Nitroarginine Methyl Ester or Citrulline or Cystathionine or Cystine or Diaminopimelic Acid or Homocystine or 2-Aminoadipic Acid or Carbocysteine or Methionine or Racemethionine or Threonine or Phosphothreonine or Cysteine or Serine or Azaserine or Droxidopa or Enterobactin or Phosphoserine or Cysteic Acid or Acetylcysteine or Selenocysteine or Ethionine or Homocysteine or S-Adenosylhomocysteine or S-Adenosylmethionine or Buthionine Sulfoximine or Selenomethionine or Vitamin U or Penicillamine or S-Nitroso-N-Acetylpenicillamine or Thiorphan or Tiopronin or Aminobutyrate? or gamma-Aminobutyric Acid or Pregabalin or Vigabatrin or Aminocaproate? or Aminocaproic Acid or Norleucine or Diazooxonorleucine or Aminolevulinic Acid or Canavanine or Creatine or Phosphocreatine or Glycine? or Allylglycine or Glycocholic Acid or Glycodeoxycholic Acid or Glycochenodeoxycholic Acid or Sarcosine or Homoserine or Kynurenine or Oxamic Acid or Phosphoamino Acid? or Quisqualic Acid)) :ti,ab
28	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)) :ti,ab
29	(g adj3 kg adj3 (d or day) near/5 (Lipid? or intralipid? or Ceroid or Fat? or Cholesterol? or Oil? or Fatty Acid? or Omega-3 or Omega-6 or Linolenic Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or Ricinoleic Acid? or Triolein or Caprylate? or Decanoic Acid? or Decanoate? or Eicosanoic Acid? or Endocannabinoid? or Eicosanoid? or Arachidonic Acid? or Hydroxyeicosatetraenoic Acid? or eicosatetraenoic Acid? or Isoprostane? or Neuroprostane? or Leukotriene? or SRS-A or Thromboxane? or Eicosatetraynoic Acid? or Eicosatrienoic Acid? or Lipoxin? or Linoleic Acid? or Lubiprostone or Capsaicin or Erucic Acid? or Oleic Acid? or Undecylenic Acid? or Gefarnate or Ionomycin or Oxylipin? or Sorbic Acid? or Heptanoic Acid? or Atorvastatin Calcium or Heptanoate? or Lauric Acid? or Laurate? or Mupirocin or Mycolic Acid? or Mycophenolic Acid? or Myristic Acid? or Myristate? or Palmitic Acid? or Palmitate? or Palmitoyl Coenzyme A or Prostanoic Acid? or Sodium Morrhuate or Stearic Acid? or Stearate? or Thioctic Acid? or Glyceride? or Diglyceride? or Monoglyceride? or Triglyceride? or Triacetin or Glycolipid? or Cord Factor? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Polyisoprenyl Phosphate Sugar? or Polyisoprenyl Phosphate Monosaccharide? or Polyisoprenyl Phosphate Oligosaccharide? or Lipofuscin or Lipopolysaccharide? or O Antigen? or Lipoprotein? or Apolipoprotein? or ATP Binding Cassette Transporter Sub-Family G Member 5 or ATP Binding Cassette Transporter Sub-Family G Member 8 or Chylomicron? or Apoprotein or Phospholipid? or Glycerophosphate? or Phosphatidic Acid? or Glycerophospholipid? or Glycerylphosphorylcholine or Phosphatidylcholine? or Dimyristoylphosphatidylcholine or Dipalmitoylphosphatidylcholine or Lecithin? or Phosphatidylethanolamine? or Phosphatidylglycerol? or Cardiolipin? or Phosphatidylinositol? or Phosphatidylserine? or Phospholipid Ether? or Plasmalogen? or Platelet Activating Factor or Lysophospholipid? or Lysophosphatidylcholine? or Sphingomyelin? or Proteolipid? or Sphingolipid? or Sterol? or Adosterol or Cholecalciferol or Hydroxycholecalciferol? or Calcifediol or Dihydroxycholecalciferol? or Calcitriol or Dihydroxyvitamin D3 or Azacosterol or Cholestanol or Dehydrocholesterol? or Desmosterol or 19-Iodocholesterol or Oxysterol? or Hydroxycholesterol? or Ketocholesterol? or Ergocalciferol? or 25-Hydroxyvitamin D2 or

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	Dihydrotachysterol or Lanosterol or Phytosterol? or Brassinosteroid? or Ecdysteroid? or Sitosterol? or Stigmasterol or Withanolide? or Solanine or Polyhydroxyalkanoate?)) :ti,ab
30	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM* Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)) :ti,ab
31	(g adj3 kg adj3 (d or day) near/5 (Carbohydrate? or Amino Sugar? or Hexosamine? or Fructosamine or Galactosamine or Acetylgalactosamine or Glucosamine or Acetylglucosamine or Muramic Acid? or Acetylmuramyl-Alanyl-Isoglutamine or Neuraminic Acid? or Sialic Acid? or N-Acetylneuraminic Acid or Deoxy Sugar? or Deoxyglucose or Fluorodeoxyglucose F18 or Deoxyribose or Fucose or Rhamnose or Sucrose or High Fructose Corn Syrup or Glycoconjugate? or Glycolipid? or Galactolipid? or Glycosphingolipid? or Ganglioside? or Sulfoglycosphingolipid? or Ceramide? or Cerebroside? or Galactosylceramide? or Glucosylceramide? or Globoside? or Lactosylceramide? or Trihexosylceramide? or Sphingomyelin? or Psychosine or Glycosylphosphatidylinositol? or Glycopeptide? or Peplomycin or Phleomycin? or Peptidoglycan or Ristocetin or Glycoprotein? or AC133 Antigen or ADAM* Protein? or Fertilin? or Cholesterol Ester Transfer Protein? or Fibrillin? or Lipopolysaccharide? or Glycoside? or Anthocyanin? or Atractyloside or Digitonin or Acetyldigitoxin? or Acetyldigoxin? or Medigoxin or Lanatoside? or Deslanoside or Proscillaridin or Strophanthin? or Cymarine or Ouabain or Chromomycin? or Galactoside? or Methylgalactoside? or Nitrophenylgalactoside? or Thiogalactoside? or Glucoside? or Amygdalin or Arbutin or Canagliflozin or Chloralose or Esculin or Methylglucoside? or 3-O-Methylglucose or Thioglucoside? or Glucosinolate? or Glycosylated Hemoglobin A or Lincosamide? or Mannoside? or Methylmannoside? or Methylglycoside? or Novobiocin or Nucleoside? Nucleotide? or Adenosine Diphosphate or O-Acetyl-ADP-Ribose or Cyclic ADP-Ribose or Cytidine Diphosphate Diglyceride? or Guanosine Diphosphate or Uridine Diphosphate or Olivomycin? or Phlorhizin or Saponin? or Escin or Ginsenoside? or Holothurin or Quillaja Saponin? or Solanine or Teichoic Acid? or Thioglycoside? or Tomatine or Monosaccharide? or Carbasugar? or Heptose? or Mannoheptulose or Hexose? or Fructose or Galactose or Glucose or Mannose or Sorbose or Imino Sugar? or Imino Furanose? or Imino Pyranose? or 1-Deoxynojirimycin or Ketose? or Dihydroxyacetone or Xylulose or Pentose? or Arabinose or Ribose or Xylose or Tetrose? or Thiosugar? or Triose? or Glyceraldehyde or Polysaccharide? or Alginate? or Carrageenan or Chitin or Chitosan or Ficoll or Fructan? or Inulin or Galactan? or Agar or Glucan? or Lentinan or Sizofiran or Zymosan or Cellulose or Cellobiose or Hypromellose Derivative? or Methylcellulose or Carboxymethylcellulose Sodium or Dextran? or Glycogen or Isomaltose or Maltose or Starch or Amylopectin or Amylose or Dextrin? or Cyclodextrin? or Hydroxyethyl Starch Derivative? or Trehalose or Glycosaminoglycan? or Chondroitin or Dermatan Sulfate or Heparitin Sulfate or Hyaluronic Acid or Keratan Sulfate or Mannan? or Oligosaccharide? or Disaccharide? or Lactose or Lactulose or Melibiose or Sucralfate or Oligosaccharide? or Trisaccharide? or Acarbose or Raffinose or Pectin? or Pentosan Sulfuric Polyester or Bambermycin? or Lipid A or O Antigen? or Prebiotic? or Prodigiozan or Proteoglycan? or Aggrecan? or CD44 Antigen? or Versican? or Heparan Sulfate Proteoglycan? or Small Leucine-Rich Proteoglycan? or Biglycan or Decorin or Fibromodulin or Lumican or Sepharose or Xylan? or Sugar Acid? or Ascorbic Acid or Dehydroascorbic Acid or Diketogulonic Acid or Glucaric Acid or Gluconate? or Glyceric Acid? or Diphosphoglyceric Acid? or Diphosphoglycerate or Tartrate? or Tartronate? or Uronic

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	Acid? or Glucuronate? or Glucuronic Acid or Hexuronic Acid? or Iduronic Acid or Sugar Alcohol? or Dithioerythritol or Dithiothreitol or Erythritol or Erythrityl Tetranitrate or Galactitol or Dianhydrogalactitol or Mitolactol or Glycerol or Inositol or Phytic Acid or Mitobronitol or Ribitol or Sorbitol or Isosorbide or Xylitol or Sugar Phosphate? or Dihydroxyacetone Phosphate or Glycerophosphate? or Glycerylphosphorylcholine or Hexosephosphate? or Fructosephosphate? or Fructosediphosphate? or Galactosephosphate? or Glucosephosphate? or Glucose-6-Phosphate or Hexosediphosphate? or Mannosephosphate? or Pentosephosphate? or Phosphoribosyl Pyrophosphate or Ribosemonophosphate? or Ribulosephosphate? or Polyisoprenyl Phosphate or Dolichol Monophosphate Mannose)) :ti,ab
32	((Dose? or Dosage? or Regimen? or Amount? or Optimal* or Optimis* or Requir* or Target? or Rate? or Increment* or Safe* or Efficacy or Initiat* or Start* or Introduc* or Receiv* or Administer*) near/5 macronutrient?) :ti,ab
33	MeSH descriptor: [AMINO ACIDS] explode all trees and with qualifier(s): [Administration & dosage - AD]
34	MeSH descriptor: [LIPIDS] explode all trees and with qualifier(s): [Administration & dosage - AD]
35	MeSH descriptor: [PROSTAGLANDINS] explode all trees and with qualifier(s): [Administration & dosage - AD]
36	#34 not #35
37	MeSH descriptor: [CARBOHYDRATES] explode all trees and with qualifier(s): [Administration & dosage - AD]
38	MeSH descriptor: [HEPARIN] explode all trees and with qualifier(s): [Administration & dosage - AD]
39	MeSH descriptor: [GLYCOPEPTIDES] explode all trees and with qualifier(s): [Administration & dosage - AD]
40	MeSH descriptor: [AMINOGLYCOSIDES] explode all trees and with qualifier(s): [Administration & dosage - AD]
41	#38 or #39 or #40
42	#37 not #41
43	MeSH descriptor: [FAT EMULSIONS, INTRAVENOUS] this term only
44	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #36 or #42
45	#14 and #25 and #44
46	#14 and #43
47	#45 or #46

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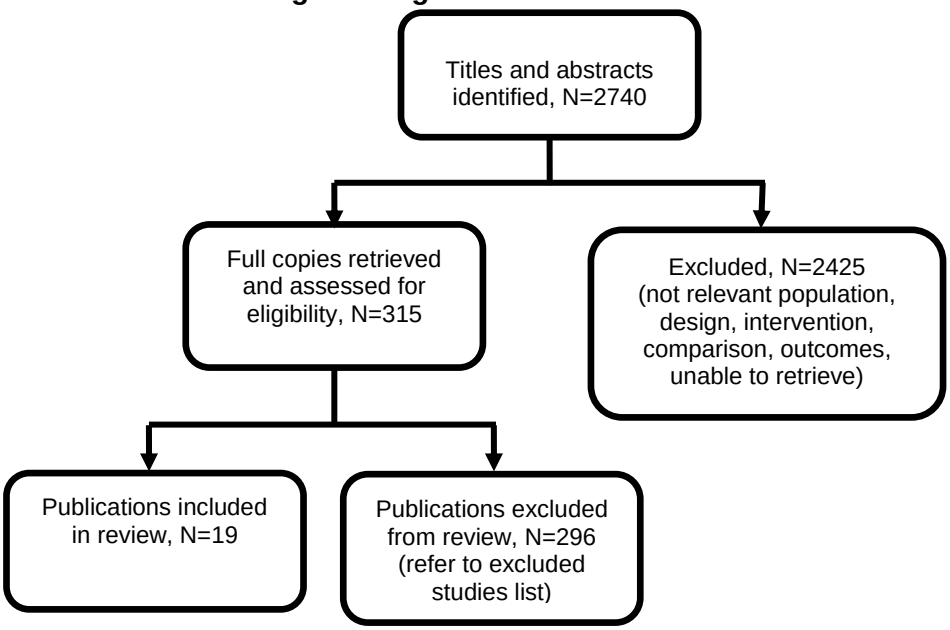
Appendix C – Clinical evidence study selection

Clinical study selection for review questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Figure 1: PRISMA Flow chart of clinical article selection for review question, What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care? and What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?



Appendix D – Clinical evidence tables

Clinical evidence tables for review questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Table 3: Clinical evidence table for included studies

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Balakrishnan, M., Jennings, A., Przystac, L., Phornphutkul, C., Tucker, R., Vohr, B., Stephens, B. E., Bliss, J. M., Growth and Neurodevelopmental Outcomes of Early, High-Dose Parenteral Amino Acid Intake in Very Low Birth Weight Infants: A Randomized Controlled Trial, Journal of Parenteral and Enteral Nutrition, 42, 597-606, 2018	Sample size N = 467 screened (n=102 declined participation, n=65 parents unavailable for consent within 18 hours, n=90 research staff unavailable, n=9 congenital anomaly, n=24 unlikely to survive longer than 72 hours) N = 168 enrolled and randomised (n=83 standard AA; n=85 high AA) Characteristics Standard AA vs. High AA Mean gestational age, weeks (range): 26.6 (24-30) vs. 26.9 (24-30)	Interventions Standard AA: received 1-2g/kg/day AA on first day of life and advanced by 0.5g/kg/day until 4g/kg/day High AA: received 4g/kg/day on first day of life	Details All babies were started on a standard hyperalimentation solution containing 2g/100ml Premasol, resulting in 1-2g/kg/day AA depending on volume of fluid given. Standard solution also contained 10% dextrose, 60mg/kg/day calcium gluconate and an approximate ratio of 14% chloride: 86% acetate. All babies also received IV lipids but the amount is not reported (although authors report it was similar between groups). Babies in the high AA group were switched to	Results Bayley Scale of Infant and Toddler Development III (BSID-III) cognitive composite score at 18-24 months - mean (SD) Standard AA (n=59): 90.2 (10.3) High AA (n=55): 90.6 (12.7) BSID-III language composite score at 18-24 months - mean (SD) Standard AA (n=58): 88.0 (13.4)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - Computer-generated randomised sequences stratified by birth weight Allocation concealment: Unclear risk - No information provided about allocation concealment Performance bias Blinding of participants and personnel: Low risk - Clinical team caring for study babies were blind to treatment assignment Detection bias

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 1008621 Country/ies where the study was carried out USA Study type RCT Aim of the study To determine the effect of high amino acid shortly after birth on growth and neurodevelopmental outcomes Study dates November 2008 to November 2012 Source of funding No sources of funding reported	Mean birth weight, grams (range): 888 (400-1250) vs. 877 (495-1243) Mean birth length, cm (range): 34.1 (25-40) vs. 34.1 (28-42) Mean birth head circumference, cm (range): 24.0 (19-28) vs. 24.2 (20-28) No. male (%): 46 (55) vs. 39 (46) No. small for gestational age: 10 (12) vs. 17 (20) Inclusion criteria Babies with birthweight 400-1250g born between 24^{+0} and 30^{+6} weeks' gestation; informed consent obtained within 18 hours of birth Exclusion criteria Chromosomal, structural, metabolic, endocrine or renal abnormality; considered unlikely to survive longer than 72 hours		4g/100ml Premasol within 1 hour of randomisation. Authors report that this group was started on 3-4g/kg/day, presumably based on volume of fluid given, but that this was advanced to 4g/kg/day on first fay of life. The PN solution between groups was otherwise identical. The study protocol specified that the attending neonatologist could decrease the amount of AA administered if there was evidence of metabolic acidosis, oliguria or serum urea nitrogen/bicarbonate value greater than 2 standard deviations above or below the mean, respectively, for the patients' birth weight. Decisions about enteral nutrition were made at clinicians' discretion. Power analysis showed that 50 babies in each group would be required to detect an 8.5 point difference in Bayley Cognitive Composite scores at 18-	High AA (n=55): 90.3 (16.2) BSID-III receptive communication scale at 18-24 months - mean (SD) Standard AA (n=59): 8.3 (5.6) High AA (n=55): 8.1 (3.0) BSID-III expressive communication scale at 18-24 months - mean (SD) Standard AA (n=58): 8.2 (2.4) High AA (n=54): 8.8 (2.6) BSID-III motor composite score at 18-24 months - mean (SD) Standard AA (n=59): 93.1 (12.3) High AA (n=55): 93.0 (13.7) BSID-III fine motor scale at 18-24	Blinding of outcome assessment: Low risk - Unclear if study investigators assessing growth outcomes were blind to treatment assignment but outcomes are objective; psychologists conducting neurodevelopmental assessments were blind to treatment allocation Attrition bias Incomplete outcome data: Unclear risk - 2% and 11% loss to follow-up in the standard and high AA groups, respectively, due to mortality. Other reasons/numbers lost to follow-up are not reported (higher rates of missing data for neurodevelopmental outcomes) Reporting bias Selective reporting: High risk - nutritional intake, days taken to regain birthweight and achieve full feeds and length of stay were not reported in sufficient detail for analysis Other bias Other sources of bias: Low risk Other information The high AA groups was classified as received 4g/kg/day

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
			24 months. T tests and repeated measures were used for continuous variable and chi-squared tests were used for categorical variables.	months - mean (SD) Standard AA (n=58): 9.7 (2.0) High AA (n=55): 9.8 (2.1) BSID-III gross motor scale at 18-24 months - mean (SD) Standard AA (n=58): 8.3 (2.1) High AA (n=54): 8.2 (2.3) Weight (g) - mean (SD) At 36 weeks postmenstrual age (PMA) - Standard AA (n=61): 2267 (350) vs. High AA (n=60): 2238 (241) At discharge - Standard AA (n=66): 3012 (971) vs. High AA (n=60): 2885 (848) Weight percentile - mean (SD) At 36 weeks PMA - Standard AA (n=61): 19.6 (19.3)	of AA at start for the purpose of analysis as babies received this on the first day of life, within 1 hour of randomisation. Note. Despite randomisation, there were a higher proportion of small for gestational age survivors in the high AA arm compared with the standard AA arm, which may have contributed to differences in growth outcomes. Additional analyses were undertaken excluding small for gestational age babies and then the only significant differences on growth outcomes between arms was for head circumference percentile and z score at discharge.

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				vs. High AA (n=60): 14.9 (12.2) At discharge - Standard AA (n=66): 31.8 (26.1) vs. High AA (n=60): 24.6 (18.2) Weight z score - mean (SD) At 36 weeks PMA - Standard AA (n=61): -1.10 (0.79) vs. High AA (n=60): -1.16 (0.61) At discharge - Standard AA (n=66): -0.65 (0.92) vs. High AA (n=60): -0.83 (0.67) Length (cm) - mean (SD) At 36 weeks PMA - Standard AA (n=55): 44.0 (2.5) vs. High AA (n=48): 43.2 (2.7) At discharge - Standard AA (n=64): 47.9 (3.8) vs. High AA (n=59): 47.2 (3.9)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Length percentile - mean (SD) At 36 weeks PMA - Standard AA (n=55): 20.1 (21.0) vs. High AA (n=48): 14.9 (12.2) At discharge - Standard AA (n=64): 28.3 (27.9) vs. High AA (n=59): 20.5 (21.1) Length z score - mean (SD) At 36 weeks PMA - Standard AA (n=55): -1.13 (0.97) vs. High AA (n=48): -1.48 (1.06) At discharge - Standard AA (n=64): -0.84 (1.11) vs. High AA (n=59): -1.08 (0.87) Head circumference (cm) - mean (SD) At 36 weeks PMA - Standard AA (n=60): 31.7 (1.5) vs. High AA (n=51): 31.5 (1.18)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				At discharge - Standard AA (n=64): 34.0 (2.6) vs. High AA (n=60): 33.4 (2.7) Head circumference percentile - mean (SD) At 36 weeks PMA - Standard AA (n=60): 33.1 (25.5) vs. High AA (n=51): 26.0 (20.1) At discharge - Standard AA (n=64): 41.6 (25.7) vs. High AA (n=60): 32.6 (21.0) Head circumference z score - mean (SD) At 36 weeks PMA - Standard AA (n=60): -0.56 (0.89) vs. High AA (n=51): -0.75 (0.73) At discharge - Standard AA (n=64): -0.26 (0.84) vs. High AA (n=60): -0.56 (0.72)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Sepsis - n/N Standard AA: 24/73 High AA: 16/76 Mortality - n/N Standard AA: 10/83 High AA: 9/85	
Full citation 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 Ref Id 393321 Country/ies where the study was carried out India	Sample size n = 150 enrolled n = 123 analysed Characteristics Low AA group (n = 75) vs. High AA group (n = 75) Mean gestational age, weeks (SD) 32.12 (2.3) vs. 31.65 (1.97) Mean birthweight, g (SD) 1092.4 (105.5) vs. 1103.5 (110.1) Male gender 35 (46.6) vs. 26 (34.6) Inclusion criteria Babies with birth weight 900 to 1250kg from a level 3 NICU in Mumbai. Exclusion criteria	Interventions The low AA group received 1 g/kg/d of parenteral amino acids on day 1 and dose increased by 1 g/kg/d of parenteral amino acids on day 1 and dose increased by 1 g/kg every day till maximum of 4 g/kg/d. The high AA group received 3 g/kg/d of parenteral amino acids on day 1 and dose increased to 4 g/kg/d on the next day.	Details All babies started on trophic feeds (10 mL/kg/d) on day 1 and feeds were not advanced for the first 4 days. Subsequent feeds were advanced at the rate of 10-15 mL/kg/d if babies tolerated feeds and were haemodynamically stable.	Results Low AA Group (n=63) vs. High AA Group (n=60) Mean weight gain at 28 days, g/kg/d (SD): 13.15 (5.25) vs. 8.67 (4.28) Mean weight in g at 28 days (SD): 1494.7 (22.4) vs. 1371.58 (202.64) Mean length in cm at 28 days (SD): 40.21 (2.34) vs. 39.19 (1.8) Mean length gain, cm/week (SD): 0.63 (0.36) vs. 0.36 (0.348)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk. A random number sequence was generated in a variable block size of two or four each using a "Random Allocation Software" computer program. Allocation concealment: Low risk. The random allocation of sequence was generated by a statistician who was not part of the study, using serially numbered, opaque, sealed and identical envelopes. Performance bias Blinding of participants and personnel: Low risk. Blinding of clinicians.

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Study type RCT Aim of the study To investigate the effects of two different doses of parenteral amino acid supplementation on postnatal growth in very low birth weight (VLBW) infants receiving partial parenteral nutrition (PPN). Study dates February 2008 to February 2010 Source of funding Authors report no funding was received	Babies missed out in the first 24 hours of life, having obvious congenital anomalies affecting growth and requiring surgical intervention.			No. of early onset sepsis (%): 28 (44.4) vs. 19 (31.6) No. of late onset sepsis (%): 9 (14.3) vs. 7 (11.6) No. of necrotising enterocolitis (%): 6 (9.5) vs. 8 (13.3) No. of hypoglycaemia (%): 10 (15.8) vs. 16 (26.6)	Detection bias Blinding of outcome assessment: Low risk. Judicial assessors of outcomes blinded. Attrition bias Incomplete outcome data: Low risk. Reasons for loss to follow up provided. Reporting bias Selective reporting: Low risk. All outcomes reported on. Other bias Other sources of bias: Unclear risk. Partial parenteral nutrition with inadequate calories, short term assessment of postnatal growth, and absence of biochemical evidence of protein accretion to support clinical evidence. Other information Higher initial parenteral AA supplementation in settings where partial parenteral nutrition is administered resulted in poor growth in VLBW infants due to inadequate non-protein calorie intake.
Full citation	Sample size	Interventions	Details	Results	Limitations

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Blanco, C. L., Falck, A., Green, B. K., Cornell, J. E., Gong, A. K., Metabolic Responses to Early and High Protein Supplementation in a Randomized Trial Evaluating the Prevention of Hyperkalemia in Extremely Low Birth Weight Infants, Journal of Pediatrics, 153, 535-540, 2008 Ref Id 687529 Country/ies where the study was carried out USA Study type RCT Aim of the study To evaluate whether early and higher intravenous amino acid (EHAA) supplementation decreases hyperkalaemia in extremely low birth	n = 61 Characteristics Standard amino acid (SAA) vs. early and high amino acid (EHAA) Mean birth weight, (SD): 783 (140) vs. 768 (124) Mean gestational age, weeks (SD): 26.3 (2.0) vs. 25.7 (2.0) No. infants less than 24 weeks: 5 vs. 10 No. infants between 25-27 weeks: 17 vs. 13 No. infants between 28-32 weeks: 9 vs. 7 No. infants small for gestational age: 5 vs. 4 No. male infants: 17 vs. 20 CRIB score, mean (SD): 5.9 (4.5) vs. 6.4 (2.7) Prenatal steroids: 21 vs. 19	The standard group (SAA) infants received intravenous amino acid (AA) starting at 0.5 g/kg/day and increased by 0.5 g/kg/day every day to a maximum of 3 g/kg/day. The EHAA group received 2 g/kg/day of AA soon after birth and advanced by 1 g/kg/day to 4 g/kg/day.	SAA group started receiving AA between the first 24 to 36 hours of life. The EHAA received intravenous AA soon after enrolment and within the first 24 hours of life.	SAA (n=31) vs. EHAA (n=30) No. of Hyperkalaemia: 5 vs. 3 Mean AA intake, g/kg/day: 22.5 vs. 9.9	Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk. Infants were randomly allocated immediately after birth, however no details provided on how they were randomised. Allocation concealment: Low risk. Assigned to treatment group by the clinical pharmacist with cards in sealed sequential opaque envelopes. Performance bias Blinding of participants and personnel: Unclear risk. No details provided on blinding. Detection bias Blinding of outcome assessment: Low risk. Outcomes are objective. Attrition bias Incomplete outcome data: Low risk. Information provided on dropout. Reporting bias Selective reporting: Low risk. All outcomes reported on.

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
weight (ELBW) infants (<1000g) Study dates November 2002 to September 2005 Source of funding No sources of funding reported	Inclusion criteria BW < 1000g, age < 12 hours of life, GA ≥ 24 weeks. Exclusion criteria Major congenital anomalies, imminent death before enrolment, and previable infants, defined as infants who received no resuscitative measures because of extreme prematurity.				Other bias Other sources of bias: High risk. After the exclusion criteria of a GA ≥ 24 weeks was added, 1 subject < 24 weeks GA was inadvertently randomised. Other information Hyperkalaemia decreased significantly and was not affected by EHAA supplementation in the first week of life. AA infusion was discontinued early (mean 3.5 days) in 6 patients in the EHAA group due to high serum BUN levels or elevated serum ammonia
Full citation Blanco, Cynthia L., Gong, Alice K., Schoolfield, John, Green, Belinda K., Daniels, Wanda, Liechty, Edward A., Ramamurthy, Rajam, Impact of early and high amino acid supplementation on ELBW infants at 2 years, Journal of Pediatric Gastroenterology	Sample size N=61 (in the initial study), N=31 in standard group versus N=30 in the early and high AA group N=43 analysed at 6-12 months, N=22 in standard group versus N=21 in the early and high AA group N=32 analysed at 18-24 months, N=16 in	Interventions Standard AA protocol versus early and high AA protocol	Details Infants on the standard AA protocol received 0.5 g/kg/d amino acids starting in the first 24 to 36 hours of life with increases of 0.5 g/kg/d every 24 hours to a maximum of 3.0 g/kg/d and continued until day 7 of life. Infants on the early and high AA protocol received 2.0 g/kg/d amino acids soon after enrolment with increases of 1.0 g/kg/d	Results Outcomes of children examined at 19-24 months Weight gain by 28 days, g/kg/d, Mean (SD) Standard group: 12.2 (4.6) versus Early and high AA: 10.8 (42) TPN days, total hospital stay	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk. Allocation concealment: Low risk. Assigned to treatment group by the clinical pharmacist with cards in sealed sequential opaque envelopes. Performance bias Blinding of participants and personnel: Unclear risk.

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
and Nutrition, 54, 601-7, 2012 Ref Id 688550 Country/ies where the study was carried out USA Study type RCT (2-year follow-up) Aim of the study To determine the effects of early and high intravenous amino acids in extremely low birth weight infants throughout their first 2 years of life. Study dates Initial study commenced between November 2002 and September 2005 Follow-up occurred from February 2003 through July 2007	standard group versus N=16 in the early and high AA group Characteristics Demographics at discharge from survivors who completed follow-up, examined at 18-24 months Birth weight, g, Mean (SD) Standard group: 805 (145) versus Early and high AA: 820 (133), p=0.8 Gestational age, weeks, Mean (SD) Standard group: 26.3 (1.5) versus Early and high AA: 26.5 (1.9), p=0.8 Small for gestational age at birth Standard group: 2 versus Early and high AA: 3, p=0.6 White race Standard group: 1 versus Early and high AA: 0, p=1.0 Male sex		every 24 hours up to a maximum of 4 g/kg/d and continued until day 7 of life. Amino acids were given as Aminosyn PF; Abbott Laboratories, Chicago, IL, with 40 mg/kg/day of cysteine hydrochloride Lipids were given at Intralipid 20%. Glucose, minerals, trace elements and vitamins were given according to nursery protocol and as tolerated by the infant. After the study period, infants were maintained on total PN with amino acids at 3.5 g/kg/day until sufficient enteral feedings were accomplished and then weaned as total PN volume decreased (approximately at 2.0 g/kg/day on half of the total fluid intake and then 1.0 g/kg/day once less than one-third of fluid intake).	Standard group: 21 (12) versus Early and high AA: 28 (19) Mental Developmental Index, 24 months corrected gestational age Standard group: 63 (13) versus Early and high AA: 57 (11) Psychomotor Developmental Index, 24 months corrected gestational age Standard group: 64 (12) versus Early and high AA: 67 (15) Mortality, No Standard group: 4 versus Early and high AA: 6 Outcomes at discharge from survivors who completed follow-up, examined at 18-24 months	Detection bias Blinding of outcome assessment: Low risk. Attrition bias Incomplete outcome data: Low risk. Information provided on numbers dropout and those analysed Reporting bias Selective reporting: Low risk. Other bias Other sources of bias: High risk. Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding No sources of funding reported	Standard group: 8 versus Early and high AA: 10, p=0.5 Antenatal steroids Standard group: 10 versus Early and high AA: 11, p=0.6 CRIB score Standard group: 5.1 (3.6) versus Early and high AA: 5.3 (2.7), p=0.8 IVH (3 and 4) Standard group: 1 versus Early and high AA: 3, p=0.6 ROP, threshold Standard group: 2 versus Early and high AA: 3, p=1.0 BPD Standard group: 4 versus Early and high AA: 10, p=0.07 Maternal education, elementary school Standard group: 0 versus Early and high AA: 1, p=0.7			Length of stay, days, Mean (SD) Standard group: 74 (20) versus Early and high AA: 84 (22) NEC, No Standard group: 2 versus Early and high AA: 1 Sepsis, No Standard group: 2 versus Early and high AA: 3	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Maternal education, high school Standard group: 10 versus Early and high AA: 11, p=0.8 Maternal education, college education Standard group: 6 versus Early and high AA: 4, p=0.3 Inclusion criteria Infants within their first 12 hours of life, with a birth weight less than 1000g and at greater than 24 weeks gestational age. Exclusion criteria Infants with any major congenital abnormalities or imminent death				
Full citation Bulbul, A., Okan, F., Bulbul, L., Nuhoglu, A., Effect of low versus high early parenteral nutrition on plasma amino acid profiles in very	Sample size N=44 infants N=22 (group 1): early low dose PN N= 22 (group 2) early high dose PN	Interventions Low-dose parenteral nutrition (Group 1) versus early high-dose parenteral nutrition (Group 2)	Details Clinically stable infants were administered PN via a central venous catheter. Group 1 infants received PN starting with 1.0 g/kg/d amino acids and 1.0 g/kg/d lipid postnatal day	Results Group 1: early low dose PN Mean (SD) Body weight on day 14 (g): 1490 (292)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - Computer-generated randomisation table by independent researcher

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
low birth-weight infants, Journal of Maternal-Fetal and Neonatal Medicine, 25, 770-776, 2012 Ref Id 688602 Country/ies where the study was carried out Turkey Study type RCT Aim of the study To compare the efficacy of early high doses of parenteral nutrition versus early low doses of parenteral nutrition with progressive increments in very low birth weight infants. Study dates Not reported Source of funding	Characteristics Group 1: early low dose PN Mean (SD) Gestational age (w): 29.4 (1.8) Birth weight (g): 1355 (237) Head circumference (cm): 27.7 (1.3) Male (%): 70 Vaginal delivery (%): 65 Antenatal steroids (%): 55 Apgar score 1 min: 5.6 (1.0) Apgar score 5 min: 7.2 (1.2) Clinical risk index score for babies: 5.2 (3.2) Age at start parenteral nutrition (h): 5.3 (2.5)		1. Increases were made by 1.0 g/ kg/day, with an aimed intake of 3.0 g/ kg/d amino acids and 3.o g/ kg/d lipid on postnatal day 3. Group 1 infants received PN starting with 3.0 g/kg/d amino acids and 3.0 g/kg/d lipids on postnatal day 1. Glucose started postnatal day 1 at 6–8 mg/kg/min and increased gradually to 12 mg/kg/min as needed to maintain the blood glucose concentration between 80–100 mg/dl but avoiding any hyperglycaemia. Target nonprotein calorie intakes (glucose plus lipid) were 35–40 kcal/kg/d on day 1 and 70–80 kcal/kg on day 3. To compensate for enteral protein intake, the maximum parenteral amino acid dosage was reduced by the percentage of total nutrition volume, represented by the patient's enteral feeding volume. Parenteral amino acid dosage was reduced	Body weight change, (g): 134 (74) Head circumference on day 14 (cm): 28.7 (1.3) Head circumference change (cm): 0.99 (0.66) Gestational age at discharge (w): 34.2 (10.1) Body weight at discharge (g): 2155 (180) Head circumference at discharge (cm): 31.2 (2.1) Proven sepsis: 1 Length of hospital stay (d): 33.5 (19.4) Necrotising enterocolitis, Stage 2: n=1	Allocation concealment: Low risk - Investigators, parents and nursing staff were unaware of treatment allocation. Performance bias Blinding of participants and personnel: Low risk Detection bias Blinding of outcome assessment: Low risk Attrition bias Incomplete outcome data: Unclear risk Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Authors report no funding was received	Age at finishing parenteral nutrition (d): 15 (5.2) Age of tolerating trophic feeding and increasing feeds (d): 3.4 (2.1) Age of decreasing parenteral nutrition (d): 7.8 (4.0) Age of starting full enteral nutrition (d): 17.1 (3.4) Age of body weight achieved to birth weight (d): 10.2 (3.9) Group 2: early high dose PN Mean (SD) Gestational age (w): 29.1 (1.1) Birth weight (g): 1316 (247) Head circumference (cm): 27.5 (1.3) Male (%): 52		when the enteral feedings supplied 0.5 g/kg/d protein and was stopped when enteral feedings supplied 75% of total nutrition volume. When infants were stable they were fed unfortified expressed breast milk or a preterm formula in addition to PN. Trophic enteral feeding started with in the first 24–48 h of life as 10 ml/kg/day in infants weighing less than 1250 g at birth, 15–20 ml/kg/day in infants weighing ≥1250 g at birth and slowly advanced (10–20 ml/kg/day) after feeding volumes are tolerated.	Group 2: early high dose PN Mean (SD) Body weight on day 14 (g): 1379 (280) Body weight change, (g): 62 (98) Head circumference on day 14 (cm): 28.6 (1.6) Head circumference change (cm): 1.0 (0.5) Gestational age at discharge (w): 34.9 (9.2) Body weight at discharge (g): 2210 (91) Head circumference at discharge (cm): 32.1 (2.3)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Vaginal delivery (%): 42 Antenatal steroids (%): 52 Apgar score 1 min: 5.5 (1.1) Apgar score 5 min: 7.3 (1.1) Clinical risk index score for babies: 6.3 (1.9) Age at start parenteral nutrition (h): 4.6 (2.2) Age at finishing parenteral nutrition (d): 15.1 (4.4) Age of tolerating trophic feeding and increasing feeds (d): 2.9 (2.0) Age of decreasing parenteral nutrition (d): 8.7 (3.9) Age of starting full enteral nutrition (d): 16.9 (3.1)			Proven sepsis: 1 Length of hospital stay (d): 34.4 (18.1) Necrotising enterocolitis, Stage 2: n=2	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Age of body weight achieved to birth weight (d): 12.5 (5.4) Inclusion criteria Pre-term infants who were appropriately sized for GA of <32 weeks Exclusion criteria Infants who were transferred to another hospital within 48 h after birth, or who had congenital (cardiac, pulmonary, or gastrointestinal) anomalies or metabolic abnormalities known to affect energy or nutrient metabolism. Severe asphyxia characterized by seizures or severe metabolic acidosis on the first day of life, evidence of infection, and infants of diabetic mothers.				
Full citation Burattini, I., Bellagamba, M. P., Spagnoli, C., D'Ascenzo, R., Mazzoni, N., Peretti, A., Cogo, P. E., Carnielli, V. P.,	Sample size n = 159 screened n = 131 enrolled n = 114 analysed Characteristics	Interventions The standard AA (SAA) group received 1.5 g/kg/day on day 1, followed by increments of 0.5 g/kg/day to a	Details PN was initiated immediately after birth as soon as vascular access was established. Duration of PN was different according to BW categories (24, 18 and 14	Results SAA (n = 58) vs. HAA (n = 56) Mean maximum weight loss, % (SD): 11.3 (5.0) vs. 11.3 (5.2)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - Random permuted blocks within strata protocol Allocation concealment: Low risk - Sealed envelopes used,

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
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 Ref Id 688607 Country/ies where the study was carried out Italy Study type RCT Aim of the study To compare the effect of 2.5 vs. 4 g/kg/day of amino acid (AA) in parenteral nutrition of extremely low birth weight (ELBW) infants on metabolic tolerance short-term grown and neurodevelopment Study dates	SAA (n = 58) vs. HAA (n = 56) Mean gestational age, days (SD): 201 (15) vs. 201 (14) Mean BW, g (SD): 994 (194) vs. 974 (182) No. male: 32 vs. 33 No. small for gestational age: 7 vs. 6 Any prenatal steroid: 48 (82.7%) vs. 46 (82.1%) Median Apgar 1 degree min, (IQR): 7 (6-7.25) vs. 6 (6-8) Median Apgar 5 degree min, (IQR): 8 (7-8) vs. 8 (7-9) Inclusion criteria BW between 500 and 1249 g. Exclusion criteria Admitted beyond 24 hours of age and patients with birth asphyxia, life expectancy shorter than 7 days, major congenital abnormalities, and congenital metabolic disorders, death before discharge, necrotising	maximum of 2.5 g/kg/day on the third day of life. The high AA (HAA) group received 2.5 g/kg/day on day 1 and a maximum of 4 g/kg/day on day 4.	days for babies weighing 500-749g, 750-999g, and from 1000-1249g)	Mean age at regained BW, days (SD): 11.7 (4.1) vs. 11.2 (4.5) Mean age at 1800 g, days (SD): 50.7 (15.1) vs. 51.1 (12.1) Mean weight gain from birth to 1800 g, g/kg/days (SD): 12.1 (2.0) vs. 12.1 (2.0) Mean weight gain from regained BW to 1800 g, g/kg/days (SD): 16.4 (2.5) vs. 16.4 (2.5) Mean weight gain from regained BW to 36 week PMA, g/kg/days (SD): 16.0 (2.7) vs. 16.6 (2.4) Hyperglycaemia: 20 (345) vs. 6 (11%) At 36 weeks, Mean (SD):	although caregivers were aware of the PN group assignment Performance bias Blinding of participants and personnel: High risk - Caregivers were aware of the PN group assignment. Detection bias Blinding of outcome assessment: Low risk - Neurodevelopment were assessed by personnel blinded to treatment assignment. Attrition bias Incomplete outcome data: Low risk - Information provided on number of dropouts and infants analysed. Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk. Other information An extra 8g/kg of AA over the first 10 days of life did not improve growth and neurodevelopment.

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
December 2006 to August 2009 Source of funding No sources of funding reported	enterocolitis and gastrointestinal surgery			Weight, g: 1847 (322) vs. 1865 (387) Weight Z Score: -1.95 (0.80) vs. -1.88 (0.93) Length, cm: 42.7 (1.9) vs. 42.7 (2.4) Length z-score: -1.86 (0.76) vs. -1.82 (0.91) Head circumference, cm: 30.6 (1.3) vs. 30.5 (1.4) Head circumference Z score: -1.53 (0.90) vs. -1.59 (0.88) At 2 years, Mean (SD): SAA group, N=52 vs. HAA group, N=48 Weight, g: 11822 (1661) vs. 11693 (1856) Weight Z Score: -0.17 (1.12) vs. -0.22 (1.31)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Length, cm: 87.4 (4.1) vs. 87.3 (4.6) Length z-score: 0.57 (1.12) vs. 0.61 (1.25) Head circumference, cm: 48.4 (1.6) vs. 48.1 (1.9) Head circumference Z score: -0.56 (1.3) vs. -0.57 (1.2) Bayley III Score: 94 (13) vs. 97 (15) Severe mental retardation: 1 vs. 3 Death: 5 vs. 4 Necrotising enterocolitis: 2 vs. 2	
Full citation Can, E., Bulbul, A., Uslu,S., Comert,S., Bolat,F., Nuhoglu,A., Effects of aggressive parenteral nutrition on growth and clinical outcome in	Sample size N=53 N=50 completed study and included in the analysis Characteristics	Interventions Aggressive PN (group 1) versus conventional PN (group 2)	Details As soon as the infant was clinically stabilised, PN was given through an indwelling central venous catheter. Group 1 (Aggressive PN) received PN starting day 1	Results Amino acid (g/kg per day) Mean (SD) Aggressive PN:	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - computer-generated randomisation table used by an independent researcher

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
preterm infants, Pediatrics International, 54, 869-874, 2012 Ref Id 325506 Country/ies where the study was carried out Turkey Study type RCT Aim of the study To compare aggressive PN with conventional PN in preterm infants Study dates Not reported Source of funding Authors report that no funding was received	Aggressive PN: mean (SD) Weeks of gestation [range]: 31.3 (1.5) [27–33] Birthweight (g): 1622.2 (276.2) Birth height (cm): 41.5 (2.6) Male, n (%): 16 (64) Caesarean section, n (%): 17 (68) Maternal steroids, n (%):17 (68) Time PN started (h): 2.1 (1.2) p=0.59 Age enteral feeds started (days): 2.1 (1.0) p=0.20 Parenteral nutrition time (days): 11.1 (5.5) p=0.49 Full enteral feeding time (days): 13.1 (6.8) p=0.52		at 3.0 g/kg per day AA with an increment of 1.0 g/kg per day to a target intake of 4.0 g/kg per day AA on day 2. Lipids started at 2.0 g/kg per day with an increment of 1.0 g/kg per to a target intake of 3.0 g/kg per day lipids on day 2. Group 2 (Conventional PN) received PN starting day 1 at 1.5 g/kg per day AA with an increment of 1.0 g/kg per day to a target intake of 4.0 g/kg per day AA on day 3. Lipids started at 1.0 g/kg per day on day 1 with an increment of 1.0 g/kg per day to a target intake of 3.0 g/kg per day lipids on day 3. Glucose infusion started day 1 at 6–8 mg/kg per min to maintain the blood glucose concentration between 80–100 mg/dL while avoiding any hyperglycaemia. Parenteral AA dosage was reduced when enteral feeding supplied 0.5g/kg per day protein and was	Week 1: 3.87 (0.7); Week 2: 3.5 (0.5) Conventional PN: Week 1: 3.07 (0.4); Week 2: 3.3 (0.6) Head circumference (cm) Mean (SD) Aggressive PN: Day 1: 29.3 (1.6); Week 1: 29.7 (1.7); Week 2: 30.7 (2.9); Week 3: 31.3 (0.8) Conventional PN: Day 1: 29.2 (2.5); Week 1: 29.5 (2.5); Week 2: 30.3 (2.2); Week 3: 30.8 (1.1) Weight (g) Mean (SD) Aggressive PN: Day 1: 1622 (276); Week 1: 1559 (291); Week 2: 1639 (447); Week 3: 1721 (489) Conventional PN:	Allocation concealment: Low risk - Investigators, parents and nursing staff were unaware of treatment allocation Performance bias Blinding of participants and personnel: Low risk - PN was prepared by the hospital pharmacy. Detection bias Blinding of outcome assessment: Low risk - The code of the batch numbers was broken after data analysis had been performed. Attrition bias Incomplete outcome data: Low risk Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Time to regain birthweight (days) 12.7 (2.2) p=0.09 Conventional PN: mean (SD) Weeks of gestation [range]: 31.4 (2.0) [27–33] Birthweight (g): 1598.2 (345.7) Birth height (cm): 40.3 (4.3) Male, n (%): 15 (60) Caesarean section, n (%): 19 (76) Maternal steroids, n (%): 19 (76) Time PN started (h): 2.3 (1.4) p=0.59 Age enteral feeds started (days): 2.5 (1.2) p=0.20 Parenteral nutrition time (days): 12.2 (5.5) p=0.49		terminated when enteral feeding supplied 75% of total nutrition volume. Infants were initially fed unfortified expressed breast milk in addition to PN when clinically stable	Day 1: 1598 (345); Week 1: 1528 (342); Week 2: 1617 (402); Week 3: 1710 (371) Length (cm) Mean (SD) Aggressive PN: Day 1: 41.5 (2.60); Week 1: 42.2 (2.5); Week 2: 42.8 (2.3); Week 3: 43.9 (2.6) Conventional PN: Day 1: 40.3 (4.3); Week 1: 41.3 (3.6); Week 2: 42.1 (3.7); Week 3: 42.8 (3.3) Hyperglycaemia 5 infants were found to be hyperglycaemic but group not specified NEC Aggressive PN: N=1 (4%) versus Conventional PN: n=2 (8%)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Full enteral feeding time (days): 14.2 (5.5) p=0.52 Time to regain birthweight (days) 14.1 (3.4) p=0.09 Inclusion criteria Appropriate for gestational age preterm born between 27 and 33 weeks of gestation Exclusion criteria Infants transferred to another hospital after birth, with major congenital anomalies (cardiac, pulmonary or gastrointestinal), metabolic abnormalities (severe asphyxia characterised by seizures or severe metabolic acidosis on the first day of life, evidence of infection and maternal diabetes) and neonates who were supported by formula due to inadequate breast milk.				
Full citation Can, E., Bulbul, A., Uslu, S., Bolat, F.,	Sample size	Interventions Early aggressive parenteral	Details Infants who received early aggressive parenteral	Results	Limitations Cochrane risk of bias tool

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Comert, S., Nuhoglu, A., Early aggressive parenteral nutrition induced high insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP3) levels can prevent risk of retinopathy of prematurity, Iranian Journal of Pediatrics, 23, 403-410, 2013 Ref Id 745003 Country/ies where the study was carried out Turkey Study type RCT Aim of the study To compare early aggressive parenteral nutrition to conservative nutrition in preterm infants. Study dates	N=75 (APN, n=40 vs. CPN, n=35) Characteristics APN vs. CPN Weeks of gestation, mean (SD): 28.7 (1.5) and range 25-31 vs. 29.0 (1.1) and range 25-31 Birth weight, g, mean (SD): 1210 (176.2) vs. 1278 (145.5) Birth height, cm, mean (SD): 41.1 (3.4) vs. 40.7 (3.2) Head circumference, cm, mean (SD): 29.4 (2.2) vs. 29.1 (2.0) Maternal age: 24.4 (3.6) vs. 23.1 (4.2) Caesarean section, n (%): 25.0 (68%) vs. 23.0 (76%) Maternal steroids, n (%): 27.0 (68%) vs. 25.0 (76%) Inclusion criteria Preterm infants aged less than 32 weeks and appropriately sized for age Exclusion criteria	nutrition (APN) vs. conventional parenteral nutrition (CPN)	nutrition (APN) received PN starting with 3.0 g/kg/d amino acids day 1 increasing by 1.0 g/kg/day to an aimed intake of 4.0 g/kg/d amino acids day 2. Lipids started at 2.0 g/kg/d lipids day 1 increasing by 1.0 g/kg/day to 3.0 g/kg/day lipids on day 2. Infants receiving conventional parenteral nutrition (CPN) received amino acids at 1.5 g/kg/d day 1 increasing by 1.0 g/kg/day to an aimed intake of 4.0 g/kg/day amino acids on day 3. Lipids started at 1.0 g/kg/d lipids day 1 increasing by 1.0 g/kg/day with an aimed intake of 3.0 g/kg/d lipids on day 3. Parenteral nutrition was given via central venous catheter. Amino acids were given as Primene 10%, Baxter/Clintec, Maurepance, France. Lipids were given as Intralipid 20%, Fresenius KABI, Uppsala, Sweden. Glucose infusion started day 1 at 6-8 mg/kg/min	APN (n=40) vs. CPN (n=35) Protein intake, g/kg, mean (SD): 3.52 (0.7) vs. 3.2 (0.5) Weight gain, g, mean (SD): 115 (75) vs. 100 (80)	Selection bias Random sequence generation: Low risk - A computer-generated randomisation table based on blocks of four Allocation concealment: Low risk - Parenteral nutrition prepared by pharmacy. Investigators, parents, and nursing staff were blinded to treatment allocation. Performance bias Blinding of participants and personnel: Low risk - Investigators, parents, and nursing staff were blinded Detection bias Blinding of outcome assessment: Low risk - Batch numbers used and the code of the batch numbers were broken after data analysis (analysis blinded) Attrition bias Incomplete outcome data: Low risk - Number of infants receiving intervention and analysed were reported Reporting bias Selective reporting: Unclear risk

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
April 2009 to December 2010 Source of funding Authors report that no funding was received	Infants transferred to another hospital within 48 hours of birth, with intrauterine growth retardation, small-for-gestational age and large-for-gestational age birth weights, congenital (cardiac, pulmonary, or gastrointestinal) anomalies or metabolic diseases known to affect energy or nutrient metabolism, severe asphyxia characterised by seizures or severe metabolic acidosis		and increased gradually to 12 mg/kg/min in order to maintain blood glucose concentration between 80-100 mg/dl. Infants were fed unfortified breast milk in addition to parenteral nutrition when clinically stable within day 1. Parenteral amino acids and lipids dosage was reduced when the enteral feedings supplied 0.5 g/kg/day protein and 1g/kg/day lipids and terminated when enteral feedings supplied 100-140 cc/kg/day total nutrition volume.		Other bias Other sources of bias: Low risk Other information Intakes of fluid, glucose and electrolytes was ordered by the attending neonatologist and not dictated by the experimental protocol.
Full citation Clark, R. H., Chace, D. H., Spitzer, A. R., Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: A randomized, controlled trial,	Sample size n = 230 screened n = 122 enrolled Characteristics Maximal dose of 3.5g/kg/day (n = 64) vs. Maximal dose of 2.5 g/kg/day (n = 58) Median EGA, wk (IQR): 27 (26-28) vs. 27 (25-28)	Interventions 2.5 g/kg per day group received amino acid supplementation started at 1.0 g/kg per day and advanced 0.5 g/kg per day to a maximum of 2.5 g/kg per day on day 4 of treatment. 3.5 g/kg per day group received amino acid	Details Amino acid supplementation was stopped when feedings reached 100 to 130 mL/kg per day.	Results Maximal dose of 3.5g/kg/day (n = 64) vs. Maximal dose of 2.5 g/kg/day (n = 58) At 28 days: Necrotising enterocolitis, medical: 5 (7.8) vs. 2 (3.4) Necrotising enterocolitis,	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk. Electronic system used to assign a randomised code. Allocation concealment: Low risk. Random assignment code used to determine the treatment assignment. Performance bias

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Pediatrics, 120, 1286-1296, 2007 Ref Id 688708 Country/ies where the study was carried out USA Study type RCT Aim of the study To measure the effects of 2 distinct strategies for parenteral nutrition on neonatal growth and blood amino acid profiles. Study dates September 2005 to June 2006 Source of funding Authors report that no funding was received	Median birth weight, g (IQR): 961 (780-1187) vs. 918 (788-1231) No. male gender (%): 38 (59.4) vs. 32 (55.2) Inclusion criteria Gestational age between 23 weeks and 0 days and 29 weeks and 6 days, inborn and parental consent to take part in the study. Exclusion criteria If > 48 hours of age or had a major congenital anomaly.	supplementation started at 1.5 g/kg per day and advanced 1 g/kg per day to a maximum of 3.5 g/kg per day on day 3 of treatment.		surgical: 2 (3.1) vs. 1 (1.) Number died at 28 days (%): 2 (3.1) vs. 1 (1.7) Total adverse events (N=99) to 35 patients: 18 vs. 17	Blinding of participants and personnel: Low risk. Blinding of clinicians. Detection bias Blinding of outcome assessment: Low risk. Judicial assessors of outcomes blinded. Attrition bias Incomplete outcome data: Low risk. Reasons for loss to follow up provided. Reporting bias Selective reporting: Low risk. All outcomes reported on. Other bias Other sources of bias: Low risk. Other information Higher doses of amino acid supplementation were not associated with improvements in neonatal growth.
Full citation Heimler, R., Bamberger, J. M.,	Sample size n = 17	Interventions Group A infants received 1.5 g/kg	Details Phosphate, trace elements and 20% intralipid (starting	Results Group A vs. Group G	Limitations Cochrane risk of bias tool Selection bias

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Sasidharan, P., The effects of early parenteral amino acids on sick premature infants, Indian Journal of Pediatrics, 77, 1395-1399, 2010 Ref Id 689096 Country/ies where the study was carried out USA Study type RCT Aim of the study To investigate the effects of early parenteral amino acid administration on body weight, fluid compartments and metabolic parameters during the first week of life in sick premature infants. Study dates Not reported.	Characteristics Group A (n = 8) vs. Group G (n = 9) Gestational age, week: 29.6 (2.3) vs. 30.2 (1.9) Birthweight, g: 1258 (339) vs. 1182 (214) Male, no: Not stated Inclusion criteria Gestational age < 34 weeks requiring respiratory support and intravenous nutrition. Exclusion criteria Infants with major congenital anomalies, or sepsis.	of amino acids at a mean age of 15 h (range 8-24 hour) with 40 mg of cysteine hydrochloride added per 1 g of amino acids and advanced by 0.5 g/kg per day up to 2.5 g/kg by day 3 and continued at 2.5 g/kg throughout the study. Group G infants received glucose solution with vitamins and calcium gluconate. They received amino acids (1 g/kg) starting at a mean age of 78 h (range 72-88 h), advanced by 0.5 g/kg per day up to a maximum of 2.5 g/kg by day 7.	at 0.5 g/kg per day) were introduced on day 4 in both groups.	7 day weight loss (% birth weight): 7.5 (5.1) vs. 6.6 (7.9) Return to birth weight (days): 12 (3.2) vs. 13.7 (27) Head circumference (OFC) increment first 2 weeks (cm): 0.5 (0.5) vs. 0.25 (0.27)	Random sequence generation: Unclear risk. No information provided on sequence generation. Allocation concealment: Unclear risk. Infants assigned by envelope but no further information Performance bias Blinding of participants and personnel: Unclear risk. No information provided on blinding. Detection bias Blinding of outcome assessment: Unclear risk. No information provided on blinding. Attrition bias Incomplete outcome data: High risk. No data on dropouts. Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk Other information No significant effect on body weight in infants receiving

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Children's Hospital of Wisconsin					amino acids during the first week of life.
Full citation Ibrahim,H.M., Jeroudi,M.A., Baier,R.J., Dhanireddy,R., Krouskop,R.W., Aggressive early total parental nutrition in low-birth-weight infants, Journal of Perinatology, 24, 482-486, 2004 Ref Id 208850 Country/ies where the study was carried out US Study type RCT Aim of the study To compare early aggressive PN versus late total PN in very low birth weight infants	Sample size N=32 N=16 (LTPN) N=16 (ETPN) Characteristics Infants were enrolled at 1 hour of age when clinical conditions seemed to preclude oral feedings for a period of at least 5 to 7 days ETPN group: Mean (SD) Gestational age (weeks): 27 (1.6) Birthweight (g): 846 (261) 5-minute Apgar score: 7 (3 to 8) Gender: (male : female) 10/6 Oxygen Index: 4.0 (0.7) Gestational age (weeks): p=0.65 Birthweight (g): p=0.25 5-minute Apgar score: p=0.76	Interventions Early aggressive PN (ETPN group) versus late total PN (LTPN group)	Details ETPN group received 3.5g/kg/day AA and 3g/kilo-day of 20% IL started within the first 2 hours after birth. LTPN group started on a solution containing 5% to 10% glucose during the first 48 hours of life. AA started after 48 hours at 2g/kg/day of AA and increased by 0.5g/kilo-day to a maximum of 3.5g/kilo/day AA. Lipids started after 48h at 0.5g/kilo-day increased by 0.5g/kilo-day to a maximum of 3g/kg/day. The nonprotein calorie to nitrogen ratio was 100:1 in the treatment group, while no AA were supplied to the control group during the first 48 hours of life.	Results Mortality ETPN: N=1 (day 34 due to necrotising enterocolitis complications) LTPN: N=2 (day 14 due to respiratory failure, and day 36 due to necrotising enterocolitis) Sepsis LTPN: N=7 ETPN: N=6 p=0.73	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk Allocation concealment: Low risk - Sealed envelopes used Performance bias Blinding of participants and personnel: High risk - Intake of water, glucose, and electrolytes were ordered by the attending physician and were not dictated by the experimental protocol Detection bias Blinding of outcome assessment: Unclear risk Attrition bias Incomplete outcome data: Unclear risk Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates July 2001 - April 1, 2002 Source of funding No sources of funding reported	Gender: (male : female) p=0.76 Oxygen Index: p=0.52 LTPN group: Mean (SD) Gestational age (weeks): 26.8 (1.5) Birthweight (g): 968 (244) 5-minute Apgar score: 6 (3 to 8) Gender: (male : female) 9/7 Oxygen Index: 4.72 (0.52) Inclusion criteria Preterm infants with a birth weight between 501 to 1250g, and gestational age between 24 to 32 weeks who required mechanical ventilation for respiratory distress syndrome Exclusion criteria Infants with major congenital anomalies, twin-to-twin transfusion (haemoglobin concentrations differ by more than 5g/dl), maternal diabetes				Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	treated with insulin, placenta previa, placenta abruption, or maternal history of drug abuse				
Full citation Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study, Pediatrics, 133, e120-8, 2014 Ref Id 378475 Country/ies where the study was carried out UK Study type RCT Aim of the study Comparison of standardised concentrated with added macronutrients	Sample size N=150 Characteristics Gestational age (mean GA weeks, SD): 26.7 (1.3) Birth weight (mean g, SD): 892 (170.5) Gender (male): 83/150 Age PN started (median, IQR): 3(2-7) Clinical Risk Index for Babies score (mean, SD): 10.8 (2.3) Inclusion criteria Babies born at <29 weeks gestation, birth weight <1200g, admitted to NICU within 48 hours of birth Exclusion criteria Babies who were not likely to survive, major congenital or chromosomal complications, parenchymal brain lesions at <48 hours age	Interventions SCAMP PN (12% glucose) plus 3.8g/kg/day protein/lipid Control PN (10% glucose) plus control regimen for protein/lipid	Details Babies were randomly assigned to 12% or 10% glucose PN within 6 hours of birth. Head circumference was measured weekly to the nearest millimetre using a standard tape measure during the study, to 28 days post treatment, and 36 weeks corrected age. Weight was also measured during the study, to 28 days post treatment, and 36 weeks corrected age	Results Critical outcomes Infection (late onset of sepsis >72 hours, n) at 28 days post treatment: 12% group: 21/74 10% group: 29/76 Infection (late onset of sepsis >72 hours, n) at 36 weeks GA: 12% group: 26/63 10% group: 28/64 Mortality at 28 days post treatment (n): 12% group: 8/74 10% group: 7/76 Mortality at 36 weeks GA (corrected age) (n): 12% group: 11/63 10% group: 12/64	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk Allocation concealment: Low risk Performance bias Blinding of participants and personnel: Low risk Detection bias Blinding of outcome assessment: Low risk Attrition bias Incomplete outcome data: Low risk Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
(SCAMP) parenteral nutrition with control PN to improve early head circumference growth in preterm infants Study dates Study date 2013 Source of funding Bliss via the Innovation in Care Programme; Newborn Appeal	measured by cranial ultrasound, no parental consent			Mean weight change at day 7 (mean g, SD): 12% group: 25 (103.137) 10% group: 5 (116.271) Mean weight change at day 14 (mean g, SD): 12% group: 135 (108.204) 10% group: 91 (121.272) Mean weight change at day 21 (mean g, SD): 12% group: 238 (116.97) 10% group: 174 (139.079) Mean weight change at day 28 post treatment (mean g, SD): 12% group: 360 (147.37) 10% group: 314 (160.304) Mean weight change at 36	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				weeks GA (Corrected age) (mean, g, SD): 12% group: 1173 (204.651) 10% group: 1078 (245.014) Mean head circumference change at 7 days (mean mm, SD): 12% group: 4 (8.485) 10% group: 3 (9.592) Mean head circumference change at 14 days (mean mm, SD): 12% group:12 (8.485) 10% group: 10 (9.592) Mean head circumference change at 21 days (mean mm, SD): 12% group: 21 (9.381) 10% group: 17 (10.63)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Mean head circumference change at 28 days post treatment (mean mm, SD): 12% group: 31 (10.583) 10% group: 25 (11.247) Mean head circumference change at 36 weeks GA corrected age (mean mm, SD) 12% group: 76 (8.888) 10% group: 71 (10.075) Protein intake, g/kg per day (Mean, SD) Total At week 1: 12% group: 2.8 (0.3) 10% group: 2.4 (0.3) Parenteral At week 1: 12% group: 2.7 (0.3) 10% group: 2.2 (1.5)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Total At week 2: 12% group: 3.6 (0.5) 10% group: 3.0 (0.2) Parenteral At week 2: 12% group: 3.0 (0.9) 10% group: 2.3 (0.6) Total At week 3: 12% group: 3.1 (0.6) 10% group: 3.0 (0.5) Parenteral At week 3: 12% group: 1.4 (1.3) 10% group: 1.1 (1.1) Total At week 4: 12% group: 3.2 (0.6) 10% group: 3.2 (0.7) Parenteral At week 4: 12% group: 0.8 (1.3) 10% group: 0.6 (0.9)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Cumulative Total: day 1-28 (g/kg per 28 days) 12% group: 89.4 (8.2) 10% group: 80.7 (8.0) Cumulative Parenteral: day 1-28 (g/kg per 28 days) 12% group: 54.8 (20.2) 10% group: 43.6 (15.7)	
Full citation Pappoe, T. A., Wu, S-Y., Pyati, S., A randomized controlled trial comparing an aggressive and a conventional parenteral nutrition regimen in very low birth weight infants, Journal of neonatal-perinatal medicine, 2, 149-156, 2009 Ref Id 714007	Sample size N=43 (N=24 Study group versus N=19 Control group) 1 infant from study group excluded from analysis Characteristics Mean (SD) Gestational age (weeks) Study group: 27 (1.8) versus Control group: 26.5 (1.7) Birth weight (g) Study group: 898 (156) versus Control group: 858 (138) Birth weight (g) 600-800g	Interventions Aggressive PN versus Conventional PN	Details For aggressive PN: Infants were started on AA at 2 g/kg/d on day 1 increased to 3.0 g/kg/d on day 2 and 3.5 kg/d day 3. Blood urea nitrogen was monitored daily on days two, three and four; if concentrations exceeded 40 mg/dl, the amount of protein was decreased by 1 g/kg/d. Lipids were provided from day 1 at 2 g/kg/d, increased to 3 g/kg/d on day 2 and to 3.5 g/kg/d from day 3. For conventional PN: Infants were started on 1.0 g/kg/day on day 1	Results Mean (SD) Amino acid intake (g/kg/day) Study group: 2.3 (0.4) versus Control group: 2.0 (0.4) Weight at day 7 (grams) Study group: 918.3 (168.7) versus Control group: 827 (142.7), p=0.07 Weight gain in 1st 7 days (g)	Limitations Cochrane Risk of bias tool for RCTs Selection Bias Random Sequence Generation: Unclear Risk Allocation concealment: Low risk - Opaque envelopes were prepared by one of the researchers. Performance Bias Blinding of participants and personnel: Unclear risk Detection Bias Blinding of outcome assessment: Unclear risk

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study To determine the effect of aggressive PN versus conventional PN in very low birth weight infants Study dates February 2005 to May 2006 Source of funding No sources of funding reported	Study group: 703 (61), n=6 versus Control group: 723 (53), n=8 Birth weight (g) 801-1000g Study group: 910 (96), n=10 versus Control group: 913 (78), n=8 Birth weight (g) 1001-1200g Study group: 1071 (59), n=7 versus Control group: 1030 (22), n=3 Prenatal steroids Study group: n=11 (48%) versus Control group: n=10 (53%) Male Study group: n=17 (74%) versus Control group: n=10 (58%) CRIB score > 5 Study group: n=9 (39%) versus Control group: n=7 (37%) 5 min, Apgar < 5		increasing by 0.5 g/kg/day to a max of 3.5 g/kg/day on day 6. Lipids were started on day 1 at 1g/kg/d and increased daily by 0.5 g/kg/d to a maximum of 3.5 g/kg/d	Study group: 19.7 (71.6) versus Control group: -30.3 (72), p=0.03 Weight gain in 1st 7 days (g) for infants 600-800g Study group: 60 (52.2) versus Control group: -16 (62), p=0.03 Weight gain in 1st 7 days (g) for infants 801-1000g Study group: 11.5 (78.4) versus Control group: -32 (48), p=0.54 Weight gain in 1st 7 days (g) for infants 1001-1200g Study group: 36.7 (55.6) versus Control group: -57 (119.5), p=0.13 No of infants reaching birth weight by day 7 (%) Study group: 14 (61%) versus	Attrition Bias Incomplete outcome data: Low risk Reporting Bias Selective reporting: Unclear risk Other Bias Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Study group: n=2 (9%) versus Control group: n=1 (5%) IUGR Study group: n=4 (17%) versus Control group: n=2 (11%) Inclusion criteria Infants with birth weight between 600-1200g without life threatening illness or significant congenital malformations Exclusion criteria Infants who died within 24 hours of admission, or infants with a life threatening illness such as pulmonary haemorrhage, severe hypotension with pressor use or intractable metabolic acidosis within 6 hours of admission.			Control group: -8 (42%), p=0.35 No of infants reaching birth weight by day 7 (%) 600-800g Study group: 5 (83%) versus Control group: 3 (38%), p=0.14 No of infants reaching birth weight by day 7 (%) 801-1000g Study group: 5 (45%) versus Control group: 3 (43%), p=0.66 No of infants reaching birth weight by day 7 (%) 1001-1200g Study group: 4 (67%) versus Control group: 2 (50%), p=1.0 days to birth weight Study group: 7 (4.0) versus Control group: 8.4 (3.5), p=0.22	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				days to birth weight 600-800g Study group: 5.2 (3.2) versus Control group: 7.8 (4.0), p=0.21 days to birth weight 801-1000g Study group: 8.2 (4.4) versus Control group: 8.7 (2.8), p=0.82 days to birth weight 1001-1200g Study group: 6.3 (3.5) versus Control group: 9.2 (4.2), p=0.27 Percentage weight loss Study group: 6.0 (4.9) versus Control group: 9.8 (6.1), p=0.03 Percentage weight loss 600-800g Study group: 3.2 (2.7) versus Control group: 9.1 (5.4), p=0.03	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Percentage weight loss 801-1000g Study group: 7.6 (5.9) versus Control group: 9.2 (4.4), p=0.57 Percentage weight loss 1001-1200g Study group: 5.8 (3.9) versus Control group: 12.4 (10.3), p=0.18 Average daily weight gain during hospitalisation (g) Study group: 20.4 (3.8) versus Control group: 20 (3.1), p=0.74 Hospital days Study group: 78.7 (21) versus Control group: 85.3 (31.3), p=0.48 Weight at discharge (g) Study group: 2490 (381) versus Control	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				group: 2551 (564), p=0.69 Weight < 10th percentile at discharge (10%) Study group: 65% versus Control group: 68%, p=1.00 Mortality (n) Study group: 2 versus Control 1, p=1.00 Hyperglycaemia Study group: n=16 (70%) versus Control: n=9 (47%) Hyperglycaemia requiring insulin Study group: n=12 (52%) versus Control: n=2 (10%), p<0.01 Hyperglycaemia requiring insulin (Infants 600-800g) Study group: n=4 (67%) versus	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Control: n=2 (25%), p=0.3 Hyperglycaemia requiring insulin (Infants 801-1000g) Study group: n=7 (64%) versus Control: n=0, p=0.01 Hyperglycaemia requiring insulin (Infants 1001-1200g) Study group: n=1 (29%) versus Control: n=0, p=1.00	
Full citation Roelants, Jorine A., Vlaardingerbroek, Hester, van den Akker, Chris H. P., de Jonge, Rogier C. J., van Goudoever, Johannes B., Vermeulen, Marijn J., Two-Year Follow-up of a Randomized Controlled Nutrition Intervention Trial in Very Low-Birth-Weight Infants, JPEN. Journal of	Sample size N=144 included in original trial (control group, n=48; AA plus lipids group, n=49; high AA plus lipids group, n=47 - control group not of interest for current review) N=134 included in follow-up (control group, n=44; AA plus lipids group, n=45; high AA plus lipids group, n=45; 2 infants excluded due to	Interventions AA plus lipids: 2.4g/kg/day on first day of life High AA plus lipids: 3.6g/kg/day on first day of life	Details All babies were started on 2.4g/kg/day AA (and 6mg/kg/minute glucose) immediately after birth. Babies were randomised within 6 hours of birth and switched to study regimen. AA plus lipids group received 2.4g/kg/day AA (and 6mg/kg/minute glucose and 2g/kg/day lipids which was advanced to 3g/kg/day on second day of life). Babies were	Results BSID-III motor score <70 - n/N AA plus lipids: 1/45 High AA plus lipids: 2/45 BSID-III psychomotor score <70 - n/N AA plus lipids: 1/45 High AA plus lipids: 1/45	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - A computer-generated block randomisation list with variable block sizes was provided by a statistician. (Taken from Vlaardingerbroek 2013) Allocation concealment: Low risk - Sealed, opaque randomisation envelopes created by a research pharmacist (Taken from Vlaardingerbroek 2013)

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
parenteral and enteral nutrition, 42, 122-131, 2018 Ref Id 1008764 Country/ies where the study was carried out Netherlands Study type RCT Aim of the study To determine the effect of early and aggressive parenteral nutrition on long term (2 year) outcomes in VLBW babies Study dates December 2008 to January 2012 Source of funding MJN, Nestle Nutrition Institute, Danone, Nutricia, Hipp, Baxter, and United Pharmaceuticals	congenital anomaly, 8 infants lost to follow-up - control group not of interest for current review) Characteristics AA plus lipids group (n=45) vs. High AA plus lipids group (n=45) Median gestational age, weeks (IQR): Soy/Mix 26+2 (25+2-28+1)/27+1 (25+6-28+6) vs. 26+5 (25+2-28+2)/27+1 (26+2-28+2) Median birthweight, grams (IQR): Soy/Mix 808 (665-920)/846 (726-1000) vs. 775 (680-988)/850 (685-1078) No. Male (%): 21 (47) vs. 20 (44) No. Small for gestational age (%): 0 (0) vs. 2 (4) Inclusion criteria Inborn babies with birthweight <1500g Exclusion criteria Congenital, metabolic, renal, hepatic or endocrine anomalies; other disorders		randomised 1:1 to either Intralipid or SMOFlipid. High AA plus lipids group received 3.6g/kg/day AA (and 6mg/kg/minute glucose and 2g/kg/day lipids which was advanced to 3g/kg/day on second day of life). Babies were randomised 1:1 to either Intralipid or SMOFlipid. After the third day of life the intervention ended and parenteral nutrition was given according to local protocol. Statistical analyses were conducted using SPSS 21.0.		Performance bias Blinding of participants and personnel: High risk - Study group randomisation was open after inclusion. (Taken from Vlaardingerbroek 2013) Detection bias Blinding of outcome assessment: Low risk - Outcome assessors were blinded to treatment allocation. Attrition bias Incomplete outcome data: Low risk - Number of infants lost to follow-up were minimal and similar between groups Reporting bias Selective reporting: Low risk - Protocol registered and pre-specified outcomes are reported (TrialRegister.nl: NTR1445) Other bias Other sources of bias: Low risk Other information Long term follow-up of Vlaardingerbroek 2013. Study underpowered and intervention may have been too short to

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	interfering with growth or neurodevelopment				produce lasting differences in neurodevelopmental outcomes.
Full citation Scattolin, S., Gaio, P., Betto, M., Palatron, S., De Terlizzi, F., Intini, F., Visintin, G., Verlato, G., Parenteral amino acid intakes: possible influences of higher intakes on growth and bone status in preterm infants, Journal of perinatology : official journal of the California Perinatal Association, 33, 33-9, 2013 Ref Id 606572 Country/ies where the study was carried out Italy Study type RCT Aim of the study To compared higher versus lower amino	Sample size N=136 enrolled (N=21 considered too unstable to continue or discharged to alternative hospital) Therefore N=115: N=55 Group S, N=60 Group H Characteristics Clinical and anthropometric parameters at birth Mean (SD) Group S (Standard) Gestational age (weeks): 27.62 (2.04) Apgar at 5min: 7.61 (1.58) CRIB score: 6.89 (3.65) Weight (g): 926.27 (216.18) Length (cm): 34.96 (2.82) Head circumference (cm): 24.94 (2.04) Lower limb length (mm): 82.62 (7.48) SGA (%): 16.3 Basal mcBTT (us): 0.43 (0.11)	Interventions Standard PN (Group S) versus PN with higher AA (Group H)	Details Standard PN (Group S): AA supplementation was started at 1.5g/kg per day and advanced from 0.5g/kg per day to a maximum of 3g/kg per day on day 4. Higher AA PN (Group H): AA supplementation started at 2g/kg per day and advanced from 1g/kg per day to a maximum of 4g/kg per day on day 4. Minimal enteral feeding was started on day 2 of life, either with preterm formula or with mother's own milk. After day 7, feedings were advanced at a rate of 10–20ml/kg per day.	Results Mean (SD) Weight growth rate, second wk (g/kg per day) Group S: 12.31 (7.81) Group H: 13.31 (7.40) p= 0.25 Weight growth rate, third wk (g/kg per day) Group S: 14.70 (8.99) Group H: 18.76 (6.83) p=<0.01 Weight at 36 wks of GA (g) Group S: 1786.64 (292.60) Group H: 1958.41 (269.25) P=<0.01 Head circumference at 36 wks of GA (cm) Group S: 30.71 (1.94)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk Allocation concealment: Unclear risk Performance bias Blinding of participants and personnel: Low risk - physicians performing QUS and collecting anthropometric measures were blinded to the group of the examined infants. Detection bias Blinding of outcome assessment: Low risk Attrition bias Incomplete outcome data: Low risk - Number of infants completing the study is described Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
acid intake in preterm infants weighing <1250g Study dates May 2009 to December 2010 Source of funding No sources of funding reported	Group H (Higher AA) Gestational age (weeks): 27.77 (1.96) Apgar at 5min: 8.07 (1.13) CRIB score: 6.50 (3.68) Weight (g): 944.67 (193.73) Length (cm): 35.64 (2.42) Head circumference (cm): 25.17 (1.95) Lower limb length (mm): 86.65 (8.11) SGA (%): 13.3 Basal mcBTT (us): 0.45 (0.09) P-values Gestational age (weeks): p=0.70 Apgar at 5min: p=0.08 CRIB score: p=0.57 Weight (g): p=0.63 Length (cm): p=0.18 Head circumference (cm): p=0.55 Lower limb length (mm): p=0.13 SGA (%): p=0.79 Basal mcBTT (us): p=0.26			Group H: 30.85 (1.34) p=0.66 Length at 36 wks of GA (cm) Group S: 42.03 (2.19) Group H: 43.06 (2.19) P=0.02 Days at 1800g Group S: 58.79 (20.02) Group H: 51.69 (16.09) P=0.052 Maximum weight decrement (%) Group S: 12.25 (5.93) Group H: 12.76 (5.96) P=0.64 Days to regain birth weight Group S: 16.15 (7.25) Group H: 14.82 (5.77) P=0.28	Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	Inclusion criteria Infants with a birth weight <1250g and the presence of a central venous line. Exclusion criteria Infants >72h of age , or with congenital infection, a major congenital anomaly or metabolic disorders.			LLL at 28 days (mm) Group S: 89.87 (7.64) Group H: 93.49 (8.86) P=0.22 LLL at 36 wks of GA (mm) Group S: 101.90 (6.48) Group H: 106.43 (7.03) P=0.16 McBTT, 3rd wk (us) Group S: 0.40 (0.08) Group H: 0.38 (0.08) p=0.27 McBTT at 36 wks of GA (us) Group S: 0.44 (0.08) Group H: 0.45 (0.07) P=0.46	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				McBTT, 3rd wk – mcBTT basal (us) Group S: -0.02 (0.09) Group H: -0.06 (0.09) p=0.04 McBTT, 36 wk – mcBTT, 3rd wk (us) Group S: 0.04 (0.06) Group H: 0.07 (0.07) p=0.03 Death (%) Group S: 1.8 Group H: 0 p=0.48 Hospitalisation period (days) Group S: 68.93 (25.78) Group H: 59.98 (22.94) p=0.06 Episodes of sepsis (%) Group S: 16.7 Group H: 15	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				p=1.00	
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 689997 Country/ies where the study was carried out UK Study type RCT Aim of the study To determine the effects of hyperalimentation (providing macronutrients at amounts above current recommendations) in	Sample size N=142 (N=91 intervention group, N=81 control group) 114 infants were included in the analysis (N=55 intervention group, N=59 control group) Characteristics No of babies Intervention group: n=68; control group: n=74 No of male infants Intervention group: n=39; control group: n=40 Mean gestation, weeks (SD) Intervention group: 26 (1.5); control group: 26.2 (1.5) Mean birth weight, g (SD) Intervention group: 911 (224); control group: 914 (219) Mean occipitofrontal circumference at birth, cm (SD) Intervention group: 24.5 (1.9); control group: 24.3 (1.9) No of SGA babies	Interventions Hyperalimented regimen versus standard regimen	Details Infants receiving the hyperalimented regimen were given PN within 24 hours after birth with 20% more energy (117 kcal/kg/day) with proportion increase in dextrose (16.3 g/kg/day), protein (4 g/kg/day) and fat (4 g/ kg/day). PN was increased stepwise from 1 g/kg/day protein and 1 g/kg/day lipid to 4 g/kg/day protein and 4 g/kg/day lipid over 7 days. Infants receiving the standard regimen were given PN within 24 hours after birth at 93 kcal/kg/day and followed ESPGHAN recommendations for dextrose (13.5 g/kg/day), protein (3 g/kg/day) and fat (3 g/kg/day). PN was increased stepwise from 1 g/kg/day protein to 3 g/kg/day protein and 1 g/kg/day lipids to 3 g/kg/day lipids over 5 days.	Results No of babies with NEC Intervention group: 6; control group: 6 Mean protein intake at 4 weeks (g/kg) Intervention group: 73 (7); control group: 64 (5) Mean occipitofrontal circumference (OFC) at 36 weeks' PMA (cm) Intervention group: 31.1 (1.5); control group: 31.4 (1.3) Mean OFC SDS at 36 weeks' PMA Intervention group: -1 (1.2); control group: -0.8 (1.1)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Unclear risk - Block randomisation was used but no further information provided Allocation concealment: Low risk - Randomisation codes were kept in sequentially numbered, opaque and sealed envelopes. Performance bias Blinding of participants and personnel: High risk - Blinding did not occur, and PN was prescribed based on daily blood biochemistry, renal function and glucose homeostasis. Detection bias Blinding of outcome assessment: High risk - Blinding of outcome assessment did not occur except for the primary outcome, OFC which was measured by trained observers blind to assignment Attrition bias Incomplete outcome data: Low risk - Number of infants lost to

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
very preterm infants on nutrition and head growth Study dates January 2004 and January 2006 Source of funding No sources of funding reported	Intervention group: 11; control group: 13 No of non-caesarean deliveries Intervention group: 45; control group: 37 No of singletons Intervention group: 48; control group: 48 Median CRIB II score Intervention group: 10; control group: 10 No who received antenatal steroids Intervention group: 58; control group: 62 Inclusion criteria Infants born before 29 weeks' gestation Exclusion criteria Triplets and infants of higher multiplicity, those admitted after 7 days of age and infants with major congenital abnormalities			Mean lower leg length (LLL) at 36 weeks' PMA (cm) Intervention group: -10.3 (0.7); control group: 10.3 (0.7) Mean length at 36 weeks PMA (cm) Intervention group: 42.9 (2.3); control group: 42.4 (2.1) Mean length standard deviation scores (SDS) at 36 weeks' PMA Intervention group: -2.3 (1.3); control group: -2.6 (1.2) Mean mid-arm circumference at 36 weeks' PMA (cm) Intervention group: 8.6 (0.8); control group: 8.5 (0.8) Mean weight at 36 weeks' PMA (g) Intervention group: 2136 (345);	follow-up and analysed were reported Reporting bias Selective reporting: Unclear risk Other bias Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				control group: 2090 (293) Mean weight SDS at 36 weeks' PMA Intervention group: -1.3 (0.9); control group: -1.4 (0.8) Babies treated with insulin (hyperglycaemia) Intervention group: 33; control group: 21 Protein intake, g/kg at 4 weeks Intervention group: 73(7); control group: 64 (5) Mortality Intervention group: n=2 (atrioventricular septal defect and congenital cytomegalovirus infection), included in the analysis; control group: n=1 (trisomy 21) Intervention group: n=13;	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				control group: n=15 control infants (died prior to 36 weeks' PMA) Intervention group: n=2; control group: n=1 control infants	
Full citation Uthaya, S., Liu, X., Babalis, D., Dore, C. J., Warwick, J., Bell, J., Thomas, L., Ashby, D., Durighel, G., Ederies, A., Yanez-Lopez, M., Modi, N., Nutritional Evaluation and Optimisation in Neonates: A randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition, American Journal of Clinical Nutrition, 103, 1443-1452, 2016 Ref Id 473291	Sample size N=168 Characteristics Number of male infants, number (%) Inc-A: 54 (64.3); Imm-RDI: 43 (51.2) Birth weight (kg), Mean (SD) Inc-AA: 1.04 (0.32); Imm-RDI 1.05 (0.29) Birth length (cm), Mean (SD) Inc-AA: 34.9 (3.9); Imm-RDI 35.2 (4.6) Head circumference (cm), Mean (SD) Inc-AA: 25.2 (2.5); Imm-RDI 25.5 (2.4) Gestational age (wks), Mean (SD) Inc-AA: 27.65 (2.15); Imm-RDI: 27.95 (2.10) Inclusion criteria	Interventions 1.7g/kg/day amino acid + 8.6g/kg/day carbohydrate+ 20% intralipid 1.7g/kg/day amino acid + 8.6g/kg/day carbohydrate + 20% SMOFlipid 3.6g/kg/day amino acid + 8.6g/kg/day carbohydrate +20% intralipid 3.6g/kg/day amino acid +8.6g/kg/day carbohydrate +20% SMOFlipid	Details Neonates were randomised within 24 hours of birth of Parenteral nutrition into one of four amino acid/lipid formulation groups. Measurements were taken from the first bag of PN changed on first day of life to 37 weeks post menstrual age or discharge from hospital	Results Weight (g) at discharge - mean (95% CI) Inc-AA/Intralipid (n=34): 3060 (2780, 3340) Inc-AA/SMOFlipid (n=28): 2924 (2686, 3162) Imm-RDI/Intralipid (n=34): 2932 (2780, 3085) Imm-RDI/SMOFlipid (n=37): 3151 (2934, 3368) Length (cm) at discharge - mean (95% CI) Inc-AA/Intralipid (n=34): 47.7 (46.4, 49.0) Inc-AA/SMOFlipid (n=28): 48.0 (46.6, 49.4)	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - minimisation with a random element and stratification by gestational age Allocation concealment: Low risk - random assignment using an interactive voice recognition telephone system Performance bias Blinding of participants and personnel: Low risk - attending clinicians were blinded to trial allocation. Detection bias Blinding of outcome assessment: Low risk Attrition bias Incomplete outcome data: Low risk - Flow chart depicting

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out UK Study type RCT Aim of the study To determine safety and effectiveness of daily amino acid intake and soya bean oil, MCTs, olive oil, fish oil lipid in parenteral nutrition on lean body mass and also lipid content Study dates July 2010 to July 2013 Source of funding Efficacy and Mechanism Evaluation (EME) Programme	Gestational age: 31 weeks (≤30 weeks plus 6 days) Parental written consent Exclusion criteria Major congenital/life threatening abnormalities Unable to be randomised to start trial within 24 hours of birth			Imm-RDI/Intralipid (n=34): 48.2 (47.4, 49.0) Imm-RDI/SMOFlipid (n=37): 49.1 (47.8, 50.3) Head circumference (cm) at discharge - mean (95% CI) Inc-AA/Intralipid (n=34): 36.0 (34.9, 37.1) Inc-AA/SMOFlipid (n=28): 35.3 (34.6, 36.0) Imm-RDI/Intralipid (n=34): 34.8 (34.3, 35.3) Imm-RDI/SMOFlipid (n=37): 35.2 (34.5, 35.9) Non-adipose (lean) body mass - mean (95% CI) Inc-AA/Intralipid (n=34): 2450 (2246, 2655) Inc-AA/SMOFlipid (n=28): 2337 (2164, 2510)	number of infants lost to follow-up and those analysed Reporting bias Selective reporting: Low risk Other bias Other sources of bias: Low risk Other information Indirect evidence for carbohydrate intake and outcome of hyperglycaemia and hypoglycaemia.

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Imm-RDI/Intralipid (n=34): 2344 (2244, 2444) Imm-RDI/SMOFlipid (n=37): 2485 (2327, 2643) Sepsis (positive blood culture while on parenteral nutrition) - n/N Inc-AA/Intralipid: 8/42 Inc-AA/SMOFlipid: 9/42 Imm-RDI/Intralipid: 8/41 Imm-RDI/SMOFlipid: 8/43 Mortality - n/N Inc-AA/Intralipid: 4/42 Inc-AA/SMOFlipid: 7/42 Imm-RDI/Intralipid: 2/41 Imm-RDI/SMOFlipid: 3/43	
Full citation van den Akker, Chris H. P., te Braake,	Sample size N=135 in the initial RCT	Interventions Standard group (Glucose only and	Details Infants in the standard group initially received	Results Mental developmental	Limitations Cochrane risk of bias tool

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Frans W. J., Weisglas-Kuperus, Nynke, van Goudoever, Johannes B., Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants, Journal of pediatric gastroenterology and nutrition, 59, 714-9, 2014 Ref Id 606618 Country/ies where the study was carried out Netherlands Study type RCT (follow-up) Aim of the study To described long term outcomes in premature infants receiving alternative nutrition regimens	N=111 at 2 year follow-up, N=57 control group, N=54 intervention group Characteristics Weight, kg at birth, Mean (SD) Control group, 1.004 (0.243) versus Intervention group, 1.047 (0.222), p=0.34 Weight, kg, Percentage <10th percentile at birth Control group, 37% versus Intervention group, 31% p=0.69 Weight kg, z scores at birth Control group, -1.16 (1.27) versus Intervention group, -0.93 (1.40) p=0.35 Head circumference, cm at birth, Mean (SD) Control group, 25.7 (2.3) versus Intervention group, 25.8 (1.6), p=0.87 Head circumference, cm, Percentage <10th percentile at birth Control group, 11% versus Intervention group, 15%, p=0.57 Head circumference, cm, z scores at birth	delayed amino acids) versus intervention (early AA) group (Glucose and amino acids from day 1)	glucose alone. Amino acids were administered 24-48 hours after birth at 1.2 g/kg/d. This was increased 24 hours later to 2.4 g/kg/d. Infants in the intervention group received glucose and amino acids at 2.4 g/kg/d within 2 hours of birth (day 1) for the first 3 days. After day 3, infants in both groups received the same nutritional protocol.	index scores at corrected age 2 years, Mean (SD) All (n=73): Control group, 96.6 (12.3) versus Intervention group, 93.1 (9.8) Males (n=30): Control group, 91.7 (12.2) versus Intervention group, 93.9 (10.2) Females (n=43): Control group, 98.7 (12.0) versus Intervention group, 92.3 (9.5) Weight, kg at 6 weeks, Mean (SD) Control group, 3.928 (0.784) versus Intervention group, 4.083 (0.799), p=0.38 Weight, kg at 2 years, Mean (SD) Control group, 11.5 (1.7) versus Intervention	(Quality assessment based on the previous RCT, te Braake 2005) Selection bias Random sequence generation: Unclear risk - Randomisation occurred but no further information provided Allocation concealment: Unclear risk Performance bias Blinding of participants and personnel: High risk - No blinding occurred and all nutrient intakes, including enteral feedings, were the decision of the attending neonatologist. Detection bias Blinding of outcome assessment: Unclear risk Attrition bias Incomplete outcome data: Low risk - No missing outcome data (analysis based on intention to treat) Reporting bias Selective reporting: Unclear risk Other bias

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Study dates Initial RCT conducted between March 2003 and September 2004 Source of funding No sources of funding reported	Control group, -0.28 (1.17) versus Intervention group, -0.41 (1.24), p=0.58 Inclusion criteria Infants born with a birth weight less than 1500g Exclusion criteria Not reported			group, 11.6 (1.9), p=0.73 Weight, kg, percentage greater than 10th percentile at 6 weeks Control group, 37% versus Intervention group, 28%, p=0.32 Weight, kg, percentage greater than 10th percentile at 2 years Control group, 28% versus Intervention group, 19%, p=0.27 Weight, kg, change in z-score 6 weeks minus birth Control group, -0.26 (1.16) versus Intervention group, -0.48 (1.39), p=0.44	Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				Weight, kg, change in z-score 2 years minus birth Control group, 0.28 (1.21) versus Intervention group, 0.11 (1.83) p=0.62 Head circumference, cm, at 6 weeks, Mean (SD) Control group, 37.7 (1.4) versus Intervention group, 37.8 (1.8), p=0.60 Head circumference, cm, at 2 years, Mean (SD) Control group, 48.2 (1.7) versus Intervention group, 48.4 (1.9), p=0.61 Head circumference, cm, percentage greater than 10th	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				percentile at 6 weeks Control group, 5% versus Intervention group, 2%, p=0.62 Head circumference, cm, percentage greater than 10th percentile at 2 years Control group, 5% versus Intervention group, 4%, p=1.00 Head circumference, cm, change in z-score 6 weeks minus birth Control group, -0.24 (1.35) versus Intervention group, 0.09 (1.37) p=0.65 Head circumference, cm, change in z-score 2 years minus birth Control group, 0.23 (1.20)	

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
				versus Intervention group, 0.26 (1.43) p=0.92	
Full citation Vlaardingerbroek, H., Vermeulen, M. J., Rook, D., Van Den Akker, C. H. P., Dorst, K., Wattimena, J. L., Vermes, A., Schierbeek, H., Van Goudoever, J. B., Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants, Journal of Pediatrics, 163, 638, 2013 Ref Id 690133 Country/ies where the study was carried out Netherlands Study type RCT	Sample size N=144 (control group, n=48; AA plus lipids group, n=49; high AA plus lipids group, n=47) Characteristics N (male:female) Control group: 48 (25:23), AA + lipids group: 49 (19:30), High AA + lipids group: 47 (21:25) Gestational age, weeks Control group: 27.8 (2.3), AA + lipids group: 27.2 (2.2), High AA + lipids group: 27.2 (2.1) Birth weight, g Control group: 843 (224), AA + lipids group: 876 (209), High AA + lipids group: 867 (223) Birth weight z -score Control group: -2.6 (2.1), AA + lipids group: -1.7 (1.6), High AA + lipids group: -1.9 (1.7)	Interventions Three groups: Control group versus AA plus lipids versus high Amino acids plus lipids	Details Infants in the control group received glucose and 2.4 g/kg/d amino acids during the first 2 days of life. Lipids were started on day 2 at 1.4 g/kg/d and increased the following day to 2.8 g/kg/d. Infants in the amino acids plus lipid group also received glucose and 2.4 g/kg/d amino acids during the first 2 days of life (similar to control). Lipids were started soon after birth at 2 g/kg/d and increased the following day to 3 g/kg/d. Infants in the high amino acids group received 3.6 g/kg/d amino acids from day 1 and lipids from day 1 at 2 g/kg/d increased the next day (day 2) to 3 g/kg/d. AA product used for all infants was Primene 10%	Results Weight gain, g/kg/d First 28 days: Control group: 13.1 (5.7); AA + lipids group: 13.4 (4.7); High AA + lipids group: 12.3 (5.8); Discharge: Control group: 25.8 (8.1); AA + lipids group: 25.0 (5.2); High AA + lipids group: 27.0 (7.3); Change in weight z-score from birth First 28 days: Control group: -1.3 (1.1); AA + lipids group: -1.3 (1.0); High AA + lipids group: -1.5 (1.1); Discharge: Control group: -0.1 (1.4); AA + lipids group: -0.3 (1.2); High AA + lipids group: -0.03 (1.3);	Limitations Cochrane risk of bias tool Selection bias Random sequence generation: Low risk - A computer-generated block randomisation list with variable block sizes was provided by a statistician. Allocation concealment: Low risk - Sealed, opaque randomisation envelopes created by a research pharmacist Performance bias Blinding of participants and personnel: High risk - Study group randomisation was open after inclusion. Detection bias Blinding of outcome assessment: Low risk - All technicians were blinded for study group randomisation throughout the study and the analyses. Attrition bias Incomplete outcome data: Low risk - Number of infants lost to

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
Aim of the study To assess the efficacy and safety of early parenteral lipid and high dose amino acid in very low birth weight infants Study dates December 2008 - January 2012 Source of funding No sources of funding reported	SGA, n (%) Control group: 25 (52%), AA + lipids group: 18 (37%), High AA + lipids group: 20 (43%) Prenatal steroids n (%) Control group: 47 (98%), AA + lipids group: 48 (98%), High AA + lipids group: 46 (98%) Apgar score at 5 minutes, Mean (SD) Control group: 7 (2), AA + lipids group: 8 (2), High AA + lipids group: 7(2) CRIB Score, Mean (SD) Control group: 5 (4), AA + lipids group: 5 (3), High AA + lipids group: 5 (3) Inclusion criteria Inborn very low birth weight infants weighing <1500g with a central venous catheter Exclusion criteria Infants with congenital anomalies, including		(Baxter, Utretcht, The Netherlands)	Head circumference gain, mm/week First 28 days: Control group: 6.6 (3.7); AA + lipids group: 5.7 (2.9)); High AA + lipids group: 5.9 (2.4); Discharge: Control group: 8.3 (1.3); AA + lipids group: 8.1 (1.5); High AA + lipids group: 8.4 (1.3); Change in head circumference z-score from birth First 28 days: Control group: -0.6 (1.2); AA + lipids group: -0.9 (0.9); High AA + lipids group: -0.9 (0.9); Discharge: Control group: 0.5 (1.0); AA + lipids group: 0.2 (1.0); High AA + lipids group: 0.6 (1.1); Lower leg length gain, mm/d	follow-up and analysed were reported Reporting bias Selective reporting: Low risk - Protocol registered and pre-specified outcomes are reported (TrialRegister.nl: NTR1445) Other bias Other sources of bias: Low risk Other information

Study Details	Participants	Interventions	Methods	Outcomes and results	Comments
	chromosome defects and known metabolic diseases or endocrine, renal or hepatic disorders.			First 28 days: Control group: 0.21 (0.14); AA + lipids group: 0.26 (0.16); High AA + lipids group: -0.27 (0.13); Late onset sepsis. n (%) First 28 days: Control group: 8 (17%); AA + lipids group: 17 (35%); High AA + lipids group: 16 (34%); Duration of hospital stay, days First 28 days: Control group: 91.0 (39.9); AA + lipids group: 86.5 (29.1); High AA + lipids group: 94.3 (31.3); Mortality (%) First 28 days: Control group: 5 (10%); AA + lipids group: 10 (21%); High AA + lipids group: 7 (15%);	

AA: amino acids; APN: aggressive parenteral nutrition; BPD: bronchopulmonary dysplasia; BSID-III: Bayley Scale of Infant and Toddler Development III; BUN: blood urea nitrogen; BW: birthweight; CPN: conventional parenteral nutrition; CRIB: clinical risk index for babies; EAA: early amino acids; EGA: estimated gestational age; ELBW: extremely low birthweight; ETPN: early total parenteral nutrition; GA: gestational age; HAA: high amino acids; Imm-RDI: immediate recommended daily intake; IQR: interquartile range; IUGR: intrauterine growth restriction; IVH: intraventricular haemorrhage; LLL: lower leg length; LTPN: late total parenteral nutrition; mcBTT: metacarpal bone transmission time; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; OFC: occipital frontal circumference; PMA: post menstrual age; PN: parenteral nutrition; PPN: partial parenteral nutrition; RCT: randomised controlled trial; ROP: retinopathy of prematurity; SAA: standard amino acids; SD: standard deviation; SDS: standard deviation score; SGA: small for gestational age; TPN: total parenteral nutrition; USA: United States of America; VLBW: very low birthweight; Wk: week.

Appendix E – Forest plots

Forest plots for review questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Figure 2: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Weight gain (g/kg/day) at 1 month

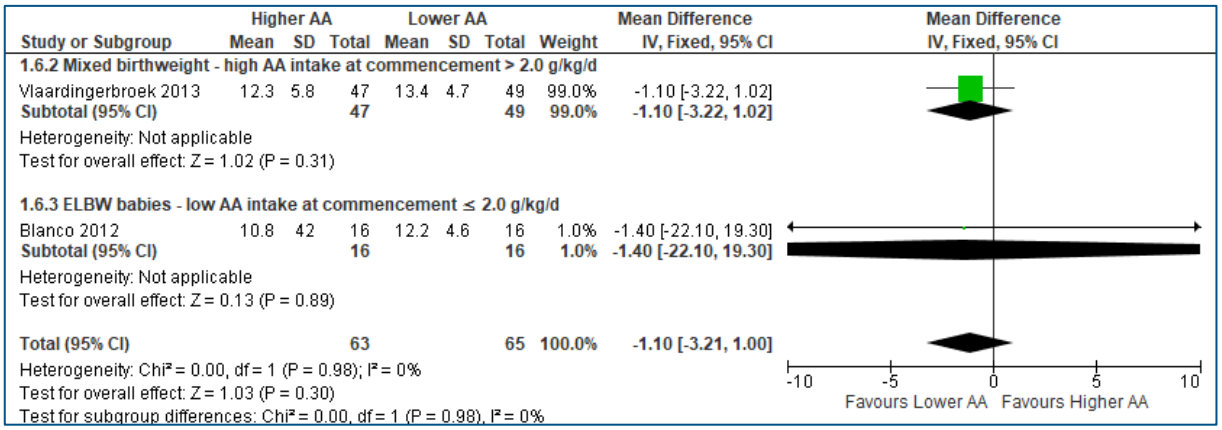


Figure 3: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Weight gain (g/kg/day) at discharge

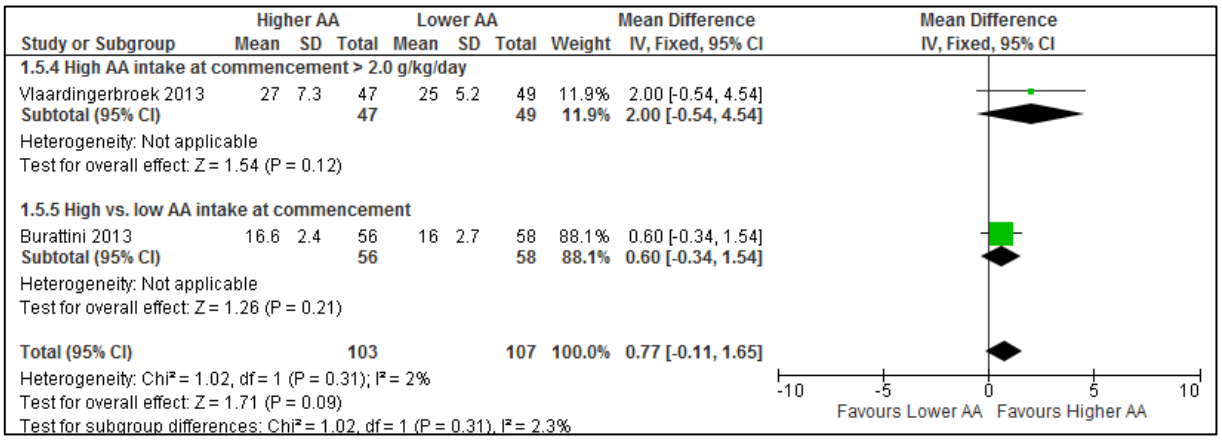


Figure 4: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Weight (g) at discharge

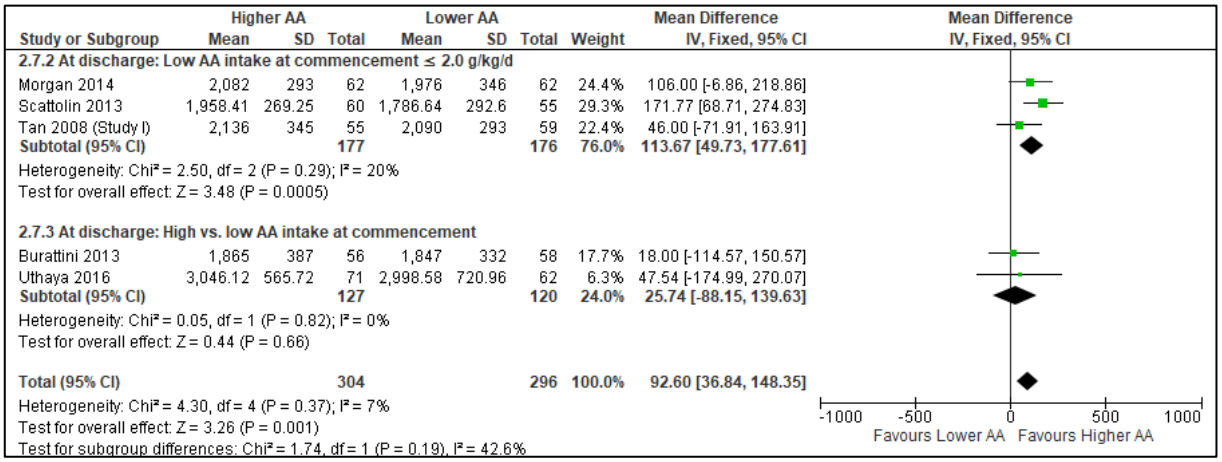


Figure 5: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Days to regain birthweight

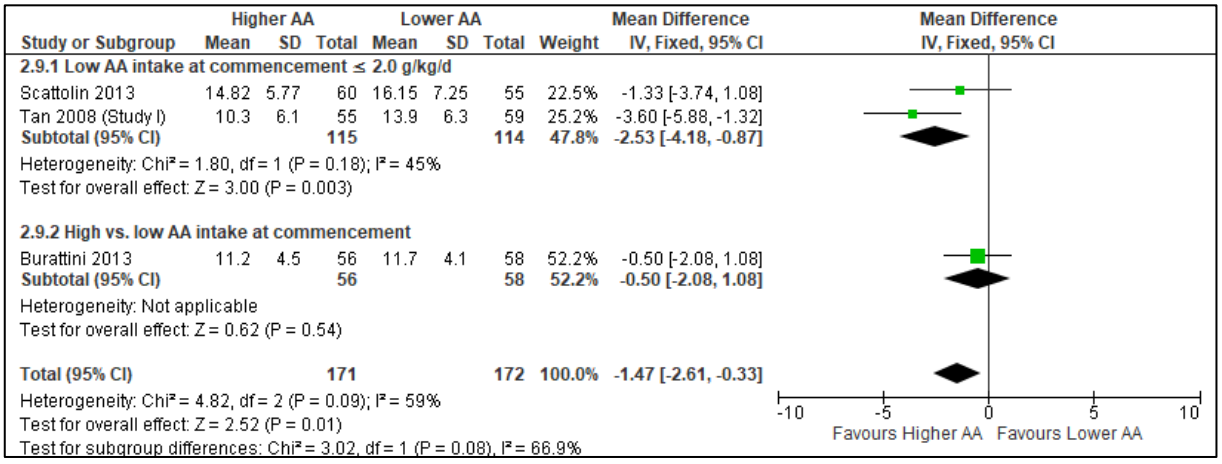


Figure 6: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Percentage weight loss

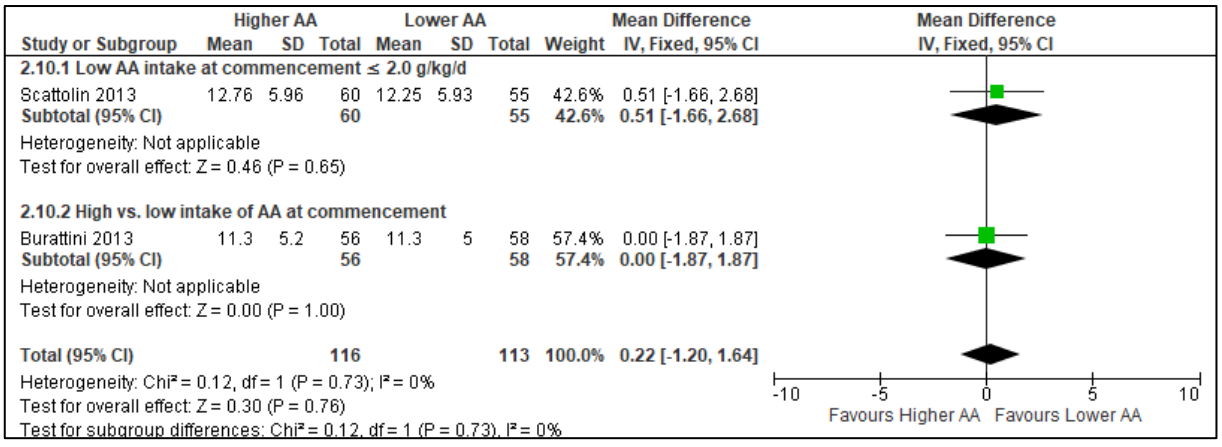


Figure 7: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Weight z-score at discharge

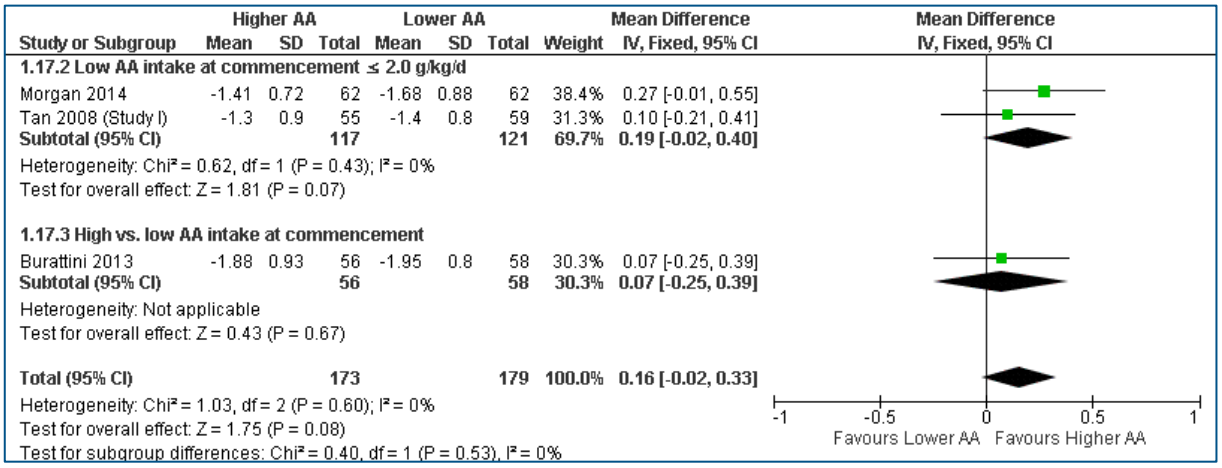


Figure 8: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Length (cm) at discharge

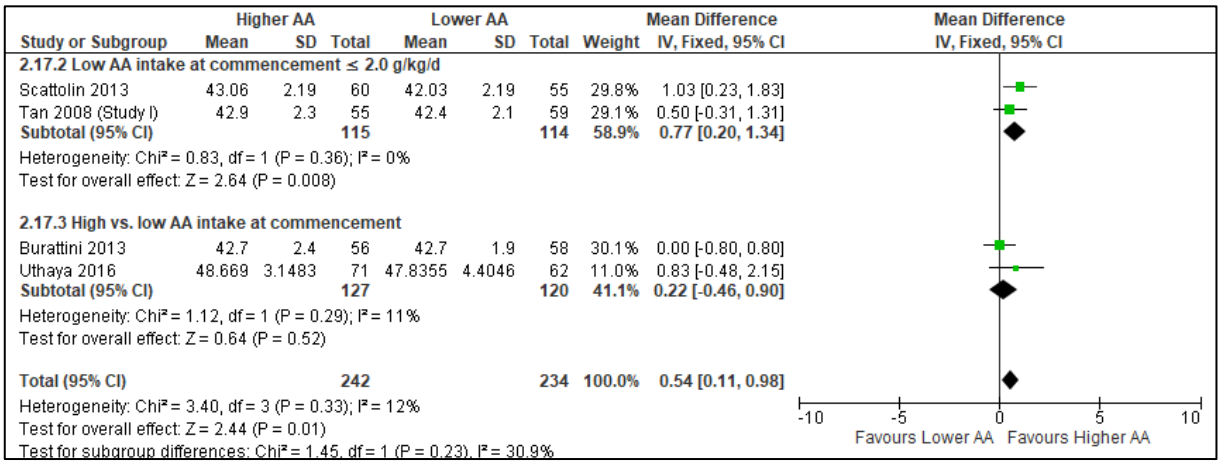


Figure 9: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Length z-score at discharge

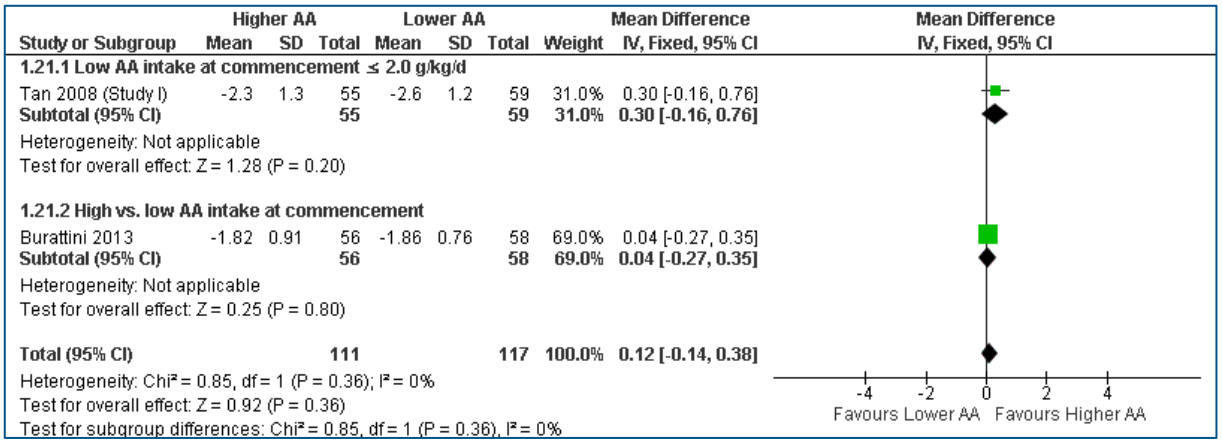


Figure 10: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Lower leg length (mm) at discharge

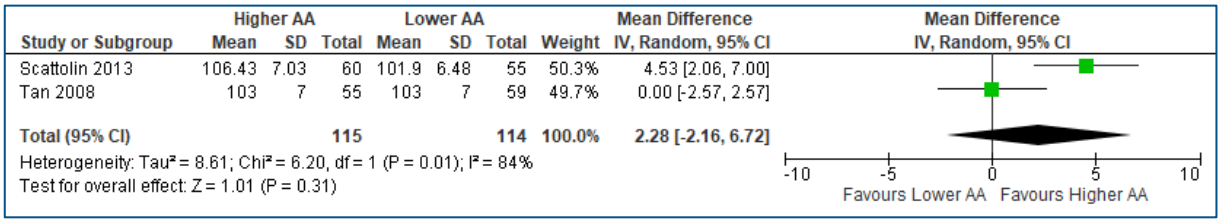


Figure 11: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Head circumference (cm) at discharge) – all studies

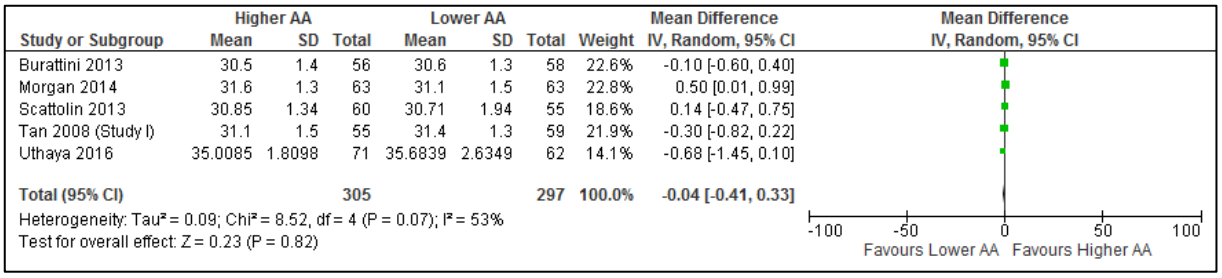


Figure 12: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Head circumference (cm) at discharge – stratified analysis for subgroups with significant heterogeneity

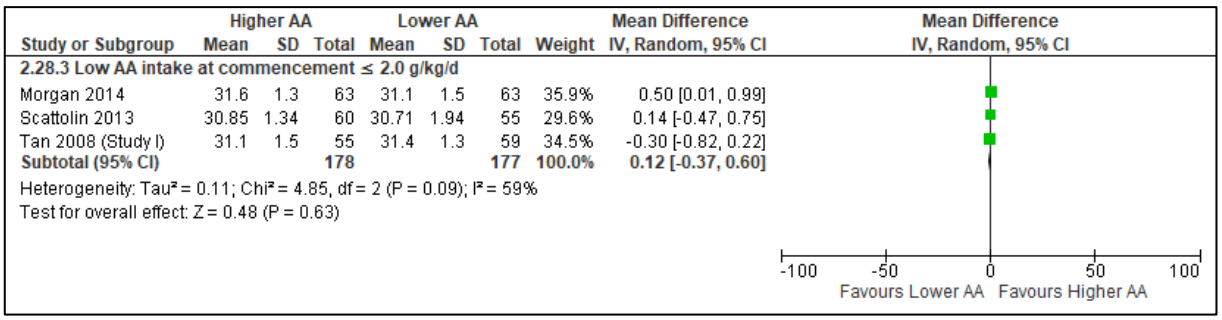


Figure 13: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Head circumference (cm) at discharge – stratified analysis for subgroups with no significant heterogeneity

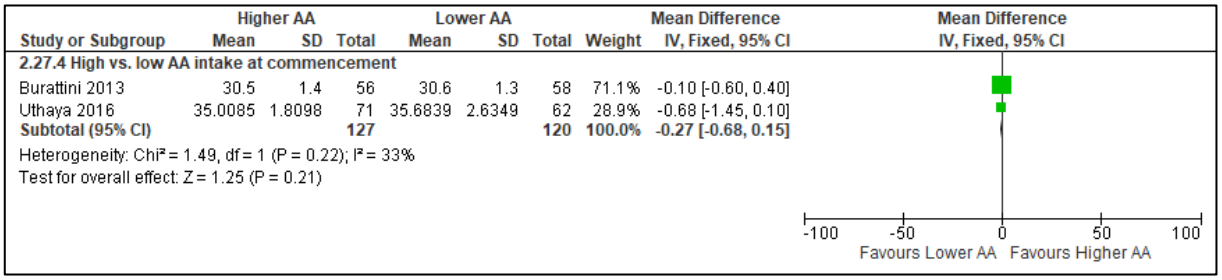


Figure 14: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Head circumference z-score at discharge

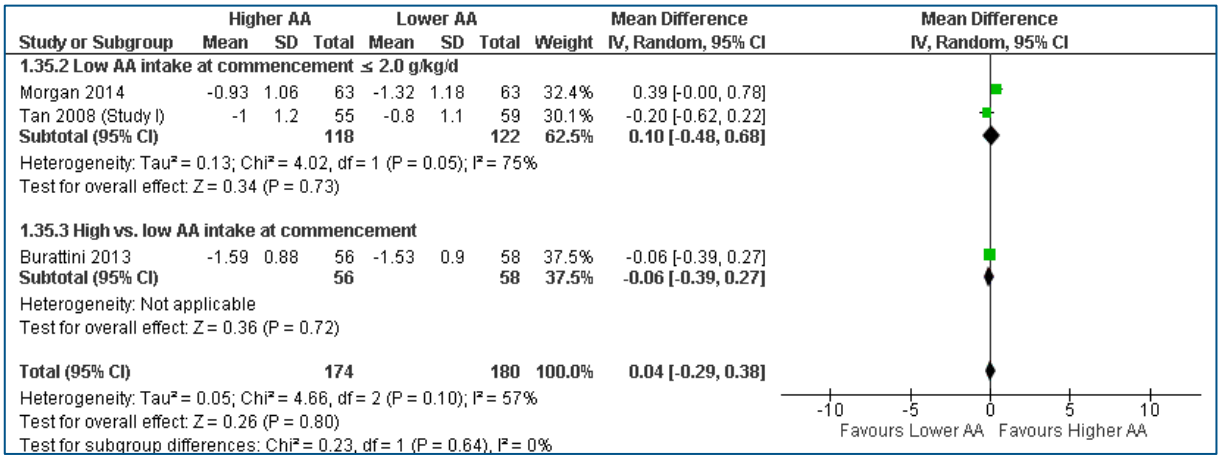


Figure 15: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Late onset sepsis

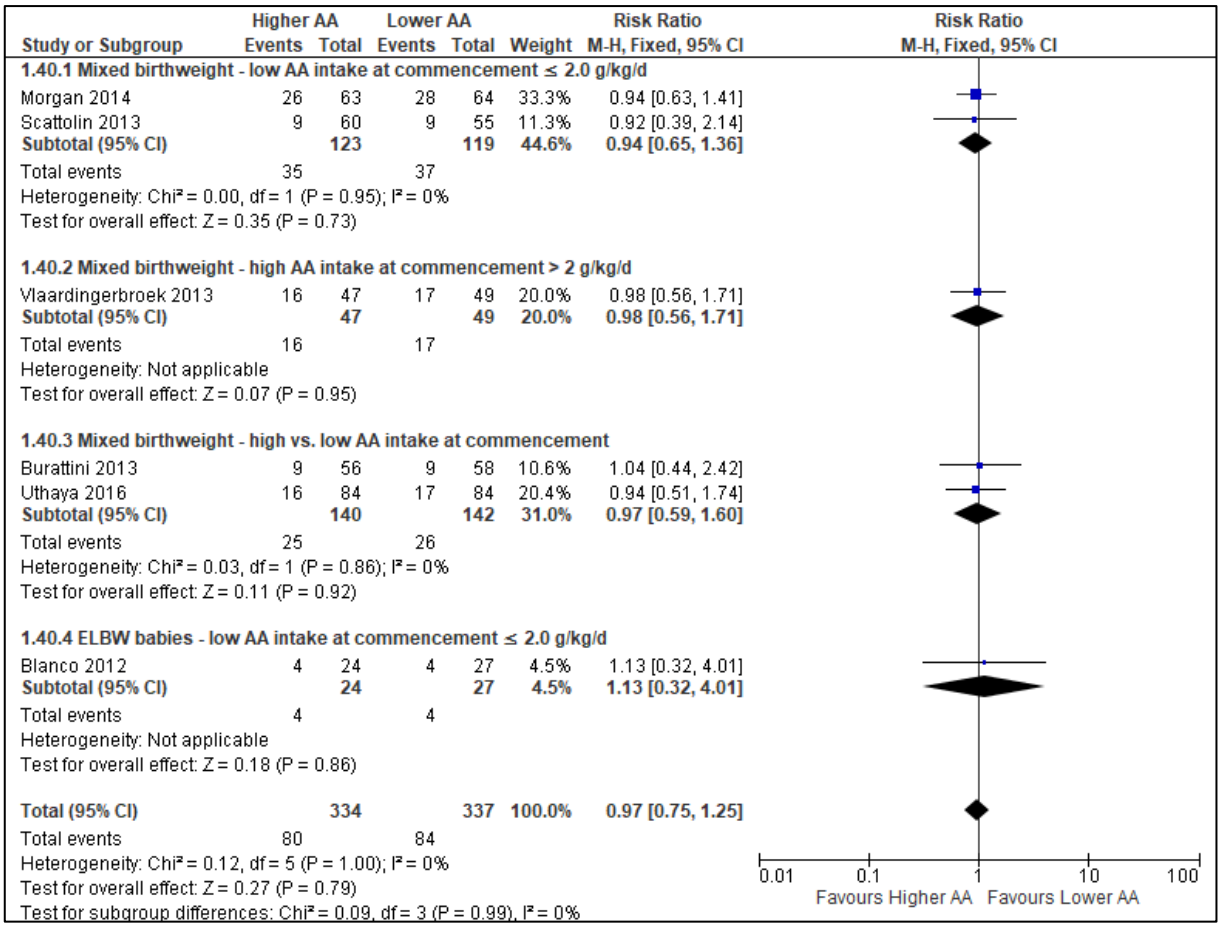


Figure 16: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Mortality to hospital discharge

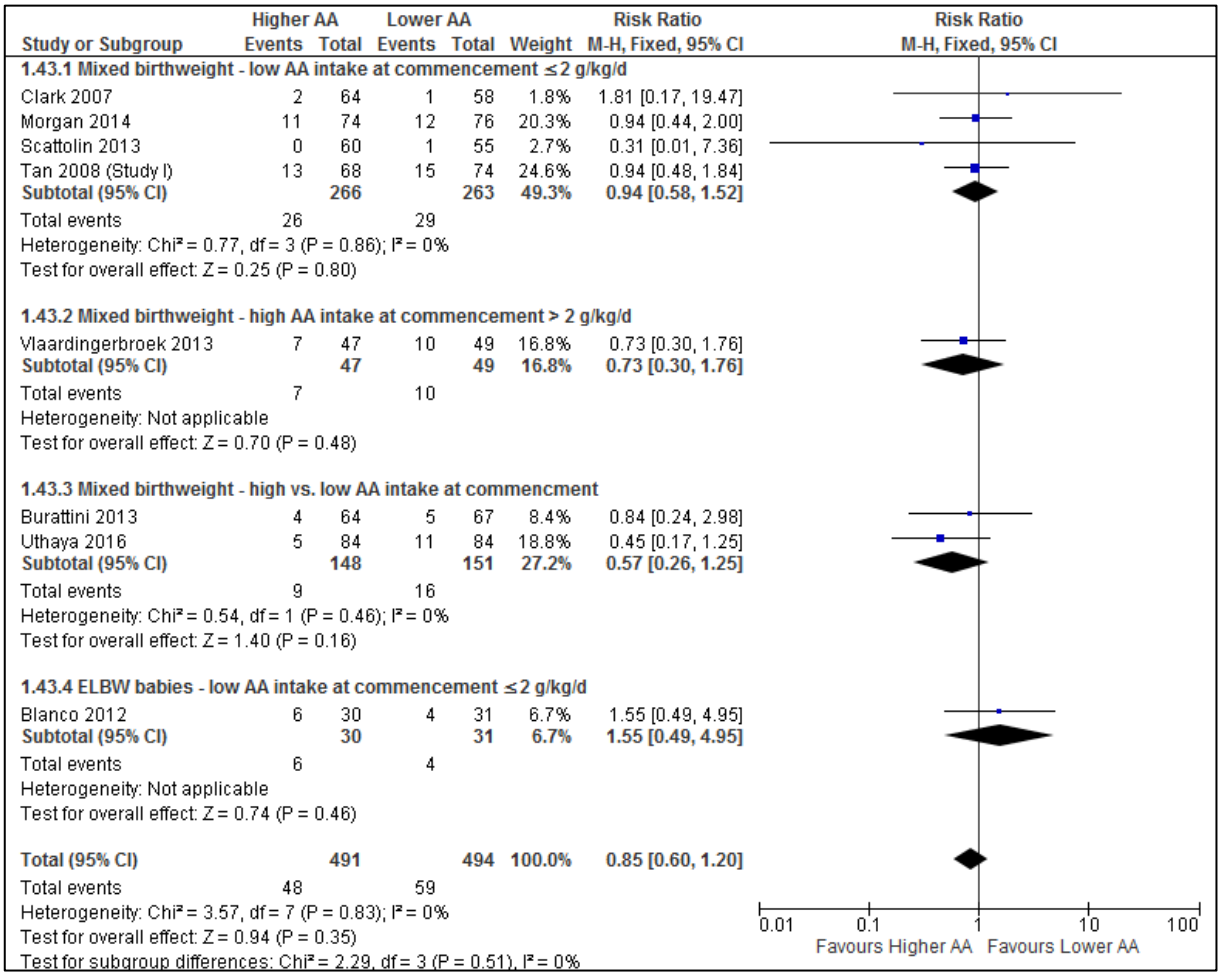


Figure 17: Forest plot for high amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake: Duration of hospital stay (days)

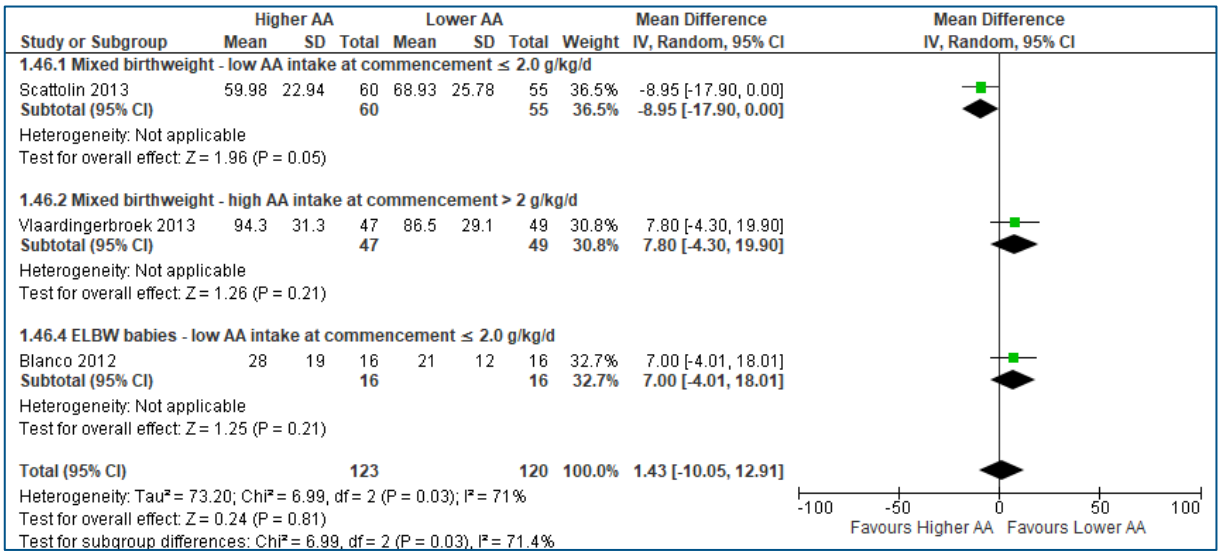


Figure 18: Forest plot for early amino acids versus delayed amino acids: Mortality

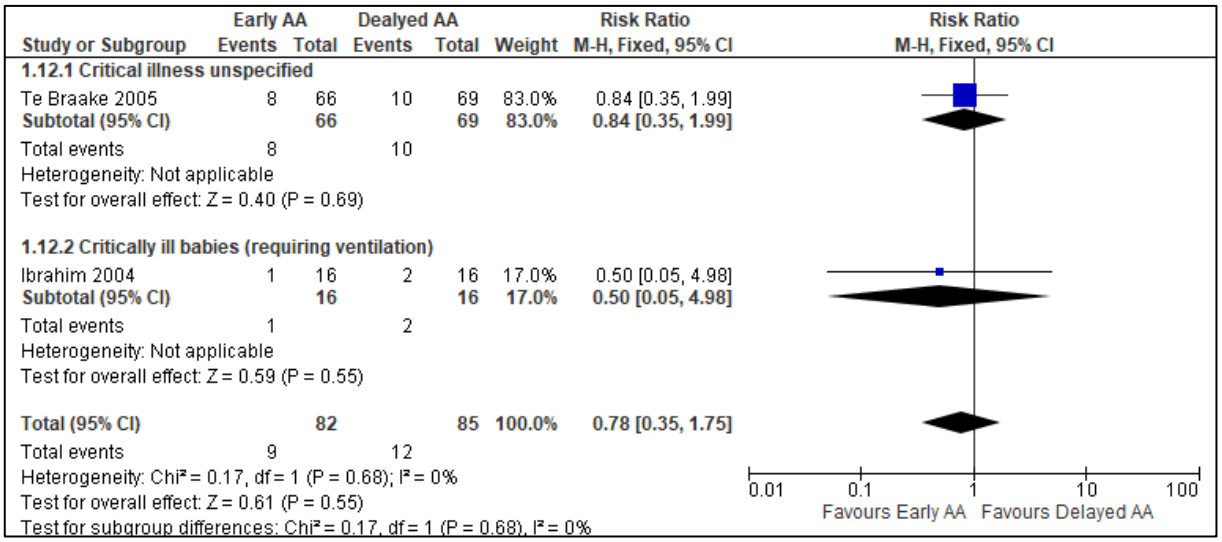


Figure 19: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Weight (g) at discharge

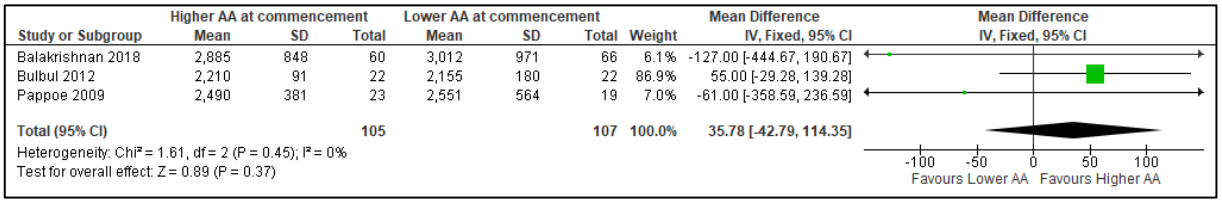


Figure 20: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Length (cm) at 1 month

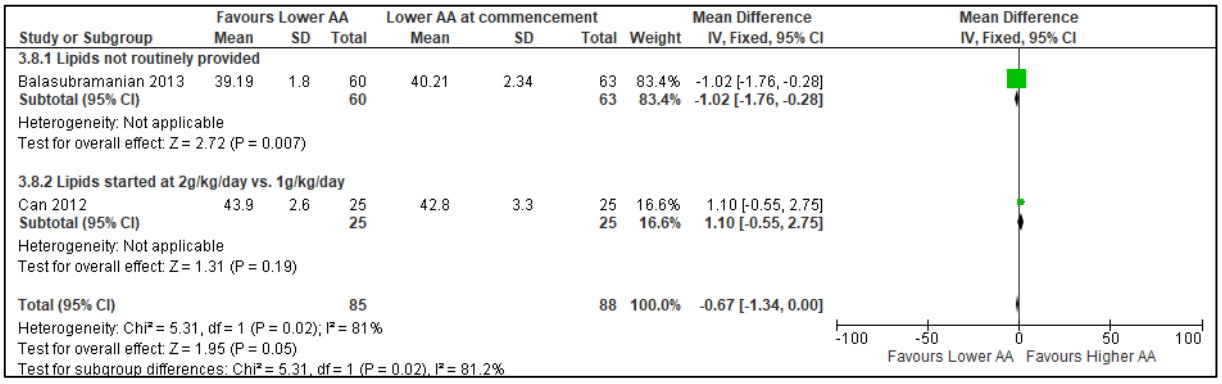


Figure 21: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Length (cm) at discharge

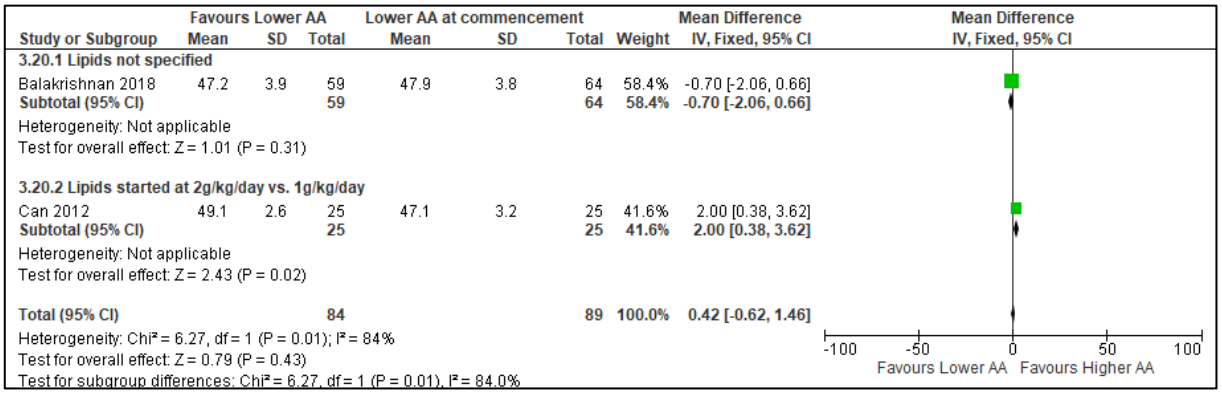


Figure 22: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Head circumference (cm) at discharge

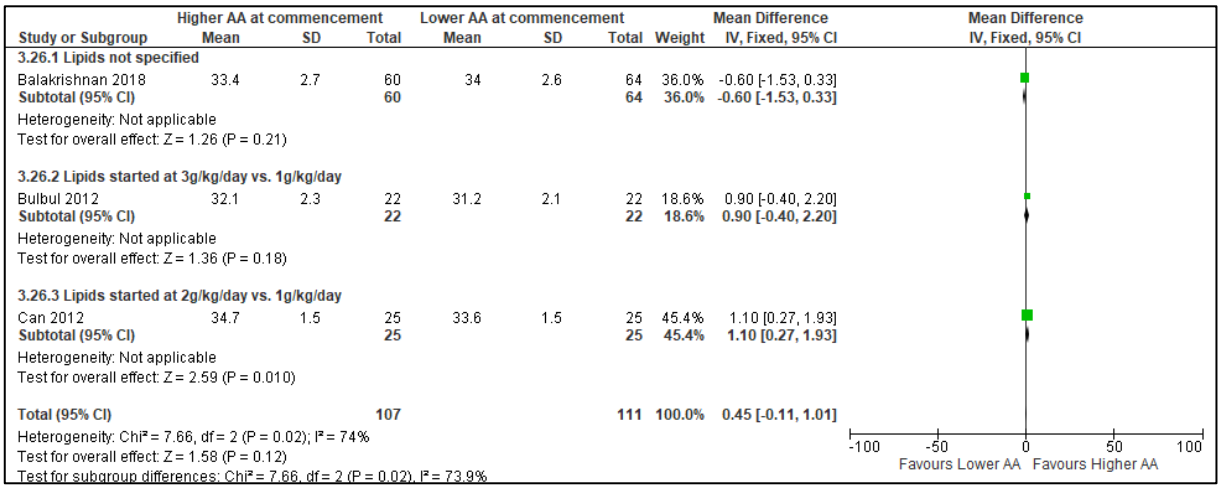


Figure 23: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Late onset sepsis

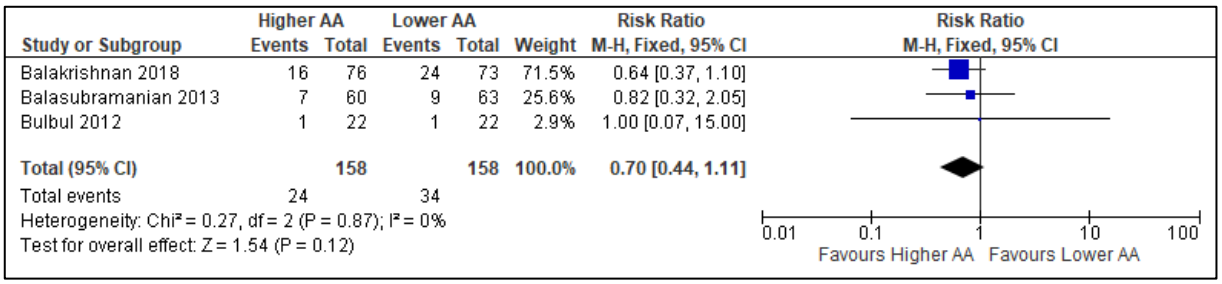


Figure 24: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Mortality

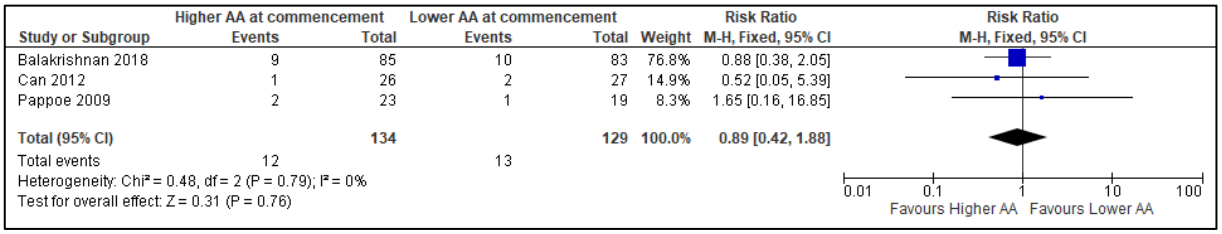


Figure 25: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Duration of hospital stay (days)

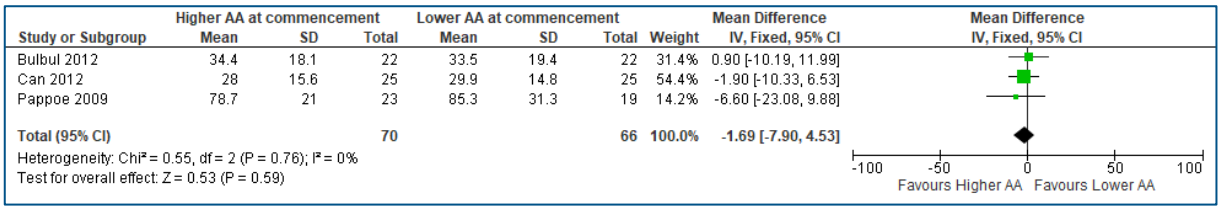
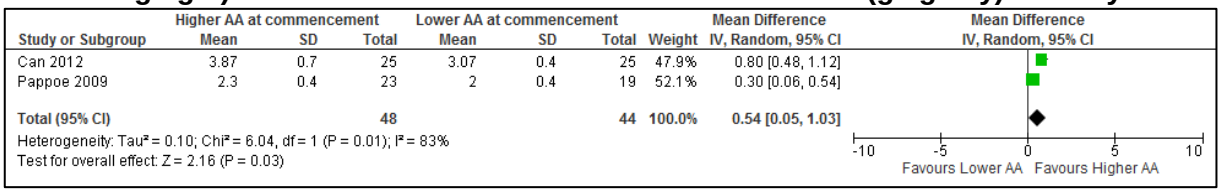


Figure 26: Forest plot for high amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement: Amino acid intake (g/kg/day) at 7 days



Appendix F – GRADE tables

GRADE tables for review questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Table 4: High amino acids (>3 g/kg/d) versus low amino acids (≤3 g/kg/d) at maximal intake

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
Bayley II Mental Development Index at 2 years (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16	16	-	MD 6 lower (14.34 lower to 2.34 higher)	⊕⊕OO LOW	CRITICAL
Bayley III Score at 2 years (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	48	52	-	MD 3 higher (2.52 lower to 8.52 higher)	⊕⊕OO LOW	CRITICAL
Bayley III Motor Score <70 at 2 years												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	2/45 (4.4%)	1/45 (2.2%)	RR 2 (0.19 to 21.28)	22 more per 1000 (from 18 fewer to 451 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
Bayley III Psychomotor Score <70 at 2 years												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	1/45 (2.2%)	1/45 (2.2%)	RR 1 (0.06 to 15.5)	0 fewer per 1000 (from 21 fewer to 322 more)	⊕OOO VERY LOW	CRITICAL
Psychomotor Developmental Index at 2 years (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	16	16	-	MD 3 higher (6.41 lower to 12.41 higher)	⊕OOO VERY LOW	CRITICAL
Weight gain (g/kg/day) - At 1 month (Better indicated by higher values)												
2	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	63	65	-	MD 1.10 lower (3.21 lower to 1 higher)	⊕⊕OO LOW	CRITICAL
Weight gain (g/kg/day) - At 1 month: Mixed birthweight - high AA intake at commencement > 2.0 g/kg/d (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[10]	none	47	49	-	MD 1.1 lower (3.22 lower to 1.02 higher)	⊕⊕OO LOW	CRITICAL
Weight gain (g/kg/day) - At 1 month: ELBW babies - low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[11]	none	16	16	-	MD 1.4 lower (22.1 lower to 19.3 higher)	⊕OOO VERY LOW	CRITICAL
Weight gain (g/kg/day) - At discharge (Better indicated by higher values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	107	-	MD 0.77 higher (0.11 lower to 1.65 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight gain (g/kg/day) - At discharge: High AA intake at commencement > 2.0 g/kg/day (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[12]	none	47	49	-	MD 2 higher (0.54 lower to 4.54 higher)	⊕⊕OO LOW	CRITICAL
Weight gain (g/kg/day) - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[13]	none	56	58	-	MD 0.6 higher (0.34 lower to 1.54 higher)	⊕⊕OO LOW	CRITICAL
Weight (g) - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[14]	none	66	69	-	MD 57.00 higher (21.29 lower to 135.29 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight (g) - At discharge (Better indicated by higher values)												
5	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	304	296	-	MD 92.6 higher (36.84 to 148.35 higher)	⊕⊕OO LOW	CRITICAL
Weight (g) - At discharge: Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
3	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	serious[16]	none	177	176	-	MD 113.67 higher (49.73 to 177.61 higher)	⊕OOO VERY LOW	CRITICAL
Weight (g) - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	120	-	MD 25.74 higher (88.15 lower to	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
										139.63 higher)		
Weight (g) - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 129 lower (821.46 lower to 563.46 higher)	⊕⊕⊕O MODERATE	CRITICAL
Days to regain birthweight (Better indicated by lower values)												
3	randomised trials	very serious[15]	serious[17]	no serious indirectness	no serious imprecision	none	171	172	-	MD 1.47 lower (2.61 to 0.33 lower)	⊕OOO VERY LOW	CRITICAL
Days to regain birthweight - Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by lower values)												
2	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	serious[18]	none	115	114	-	MD 2.53 lower (4.18 to 0.87 lower)	⊕OOO VERY LOW	CRITICAL
Days to regain birthweight - High vs. low AA intake at commencement (Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[19]	none	56	58	-	MD 0.5 lower (2.08 lower to 1.08 higher)	⊕⊕OO LOW	CRITICAL
Percentage weight loss (Better indicated by lower values)												
2	randomised trials	serious[20]	serious[17]	no serious indirectness	no serious imprecision	none	116	113	-	MD 0.22 higher (1.2 lower to 1.64 higher)	⊕⊕OO LOW	CRITICAL
Percentage weight loss - Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by lower values)												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	55	-	MD 0.51 higher (1.66	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								lower to 2.68 higher)		
Percentage weight loss - High vs. low intake of AA at commencement (Better indicated by lower values)												
1	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	58	-	MD 0 higher (1.87 lower to 1.87 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight change in z-score - At 1 month (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[21]	none	47	49	-	MD 0.2 lower (0.62 lower to 0.22 higher)	⊕⊕OO LOW	CRITICAL
Weight change in z-score - At discharge (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[22]	none	47	49	-	MD 0.27 higher (0.23 lower to 0.77 higher)	⊕⊕OO LOW	CRITICAL
Weight z-score - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[23]	none	66	69	-	MD 0.14 higher (0.11 lower to 0.39 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight z-score - At discharge (Better indicated by higher values)												
3	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	173	179	-	MD 0.16 higher (0.02 lower to 0.33 higher)	⊕⊕OO LOW	CRITICAL
Weight z-score - At discharge: Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
2	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117	121	-	MD 0.19 higher (0.02	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
										lower to 0.4 higher)		
Weight z-score - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	58	-	MD 0.07 higher (0.25 lower to 0.39 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight z-score - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.05 lower (0.53 lower to 0.43 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length (cm) - At discharge (Better indicated by higher values)												
4	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	242	234	-	MD 0.54 higher (0.11 to 0.98 higher)	⊕⊕OO LOW	CRITICAL
Length (cm) - At discharge: Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
2	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	serious[24]	none	115	114	-	MD 0.77 higher (0.2 to 1.34 higher)	⊕OOO VERY LOW	CRITICAL
Length (cm) - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	120	-	MD 0.22 higher (0.46 lower to 0.9 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length (cm) - Post discharge (2 years) (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.1 lower (1.81 lower to 1.61 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length z-score - At discharge (Better indicated by higher values)												
2	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111	117	-	MD 0.12 higher (0.14 lower to 0.38 higher)	⊕⊕OO LOW	CRITICAL
Length z-score - At discharge: Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
1	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	serious[22]	none	55	59	-	MD 0.3 higher (0.16 lower to 0.76 higher)	⊕OOO VERY LOW	CRITICAL
Length z-score - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	58	-	MD 0.04 higher (0.27 lower to 0.35 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length z-score - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.04 higher (0.43 lower to 0.51 higher)	⊕⊕⊕O MODERATE	CRITICAL
Lower leg length gain (mm/d) at 1 month (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	49	-	MD 0.01 higher (0.05 lower to 0.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
Lower leg length (mm) - At 1 month (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[25]	none	60	55	-	MD 3.62 higher (0.6 to 6.64 higher)	⊕⊕⊕O MODERATE	CRITICAL
Lower leg length (mm) - At discharge (Better indicated by higher values)												
2	randomised trials	very serious[15]	very serious[26]	no serious indirectness	serious[27]	none	115	114	-	MD 2.28 higher (-2.16 to 6.72 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference growth (cm/wk) - At 1 month (Better indicated by higher values)												
2	randomised trials	serious[5]	serious[17]	no serious indirectness	serious[28]	none	113	118	-	MD 0.08 higher (0.02 lower to 0.18 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference growth (cm/wk) - At 1 month: Low AA intake at commencement ≤ 2.0 g/kg/d (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 0.13 higher (0.05 to 0.2 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference growth (cm/wk) - At 1 month: High AA intake at commencement > 2 g/kg/d (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	49	-	MD 0.02 higher (0.09 lower to 0.13 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference growth (cm/wk) - At discharge (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[30]	none	47	49	-	MD 0.03 higher (0.03 lower to 0.09 higher)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
Head circumference (cm) - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	serious[31]	no serious indirectness	no serious imprecision	none	66	69	-	MD 0.60 higher (0.04 to 1.16 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference (cm) - At discharge (Better indicated by higher values)												
5	randomised trials	very serious[15]	serious[17]	no serious indirectness	no serious imprecision	none	305	297	-	MD 0.04 lower (0.41 lower to 0.33 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference (cm) - At discharge: Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
3	randomised trials	very serious[15]	serious[17]	no serious indirectness	no serious imprecision	none	178	177	-	MD 0.12 higher (0.37 lower to 0.6 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference (cm) - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	127	120	-	MD 0.27 lower (0.68 lower to 0.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference (cm) - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[32]	none	48	52	-	MD 0.3 lower (0.99 lower to 0.39 higher)	⊕⊕OO LOW	CRITICAL
Head circumference z-score - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[33]	none	66	69	-	MD 0.3 higher (0.01 to 0.59 higher)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
Head circumference z-score - At discharge (Better indicated by higher values)												
3	randomised trials	very serious[15]	serious[17]	no serious indirectness	no serious imprecision	none	174	180	-	MD 0.04 higher (0.29 lower to 0.38 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference z-score - At discharge: High vs. low AA intake at commencement (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	56	58	-	MD 0.06 lower (0.39 lower to 0.27 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference z-score - At discharge: Low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by higher values)												
2	randomised trials	very serious[15]	serious[17]	no serious indirectness	serious[34]	none	118	122	-	MD 0.1 higher (0.48 lower to 0.68 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference z-score - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48	52	-	MD 0.01 lower (0.5 lower to 0.48 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference change in z-score - At 1 month (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	47	49	-	MD 0 higher (0.36 lower to 0.36 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference change in z-score - At discharge (Better indicated by higher values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[35]	none	47	49	-	MD 0.4 higher (0.02 lower to 0.82 higher)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
Body composition - Non adipose (lean) body mass (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	71	62	-	MD 18.51 higher (202.96 lower to 239.98 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Late onset sepsis												
6	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[6]	none	80/334 (24%)	84/337 (24.9%)	RR 0.97 (0.75 to 1.25)	7 fewer per 1000 (from 62 fewer to 62 more)	⊕OOO VERY LOW	CRITICAL
Late onset sepsis - Mixed birthweight - low AA intake at commencement ≤ 2.0 g/kg/d												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[6]	none	35/123 (28.5%)	37/119 (31.1%)	RR 0.94 (0.65 to 1.36)	19 fewer per 1000 (from 109 fewer to 112 more)	⊕⊕OO LOW	CRITICAL
Late onset sepsis - Mixed birthweight - high AA intake at commencement > 2 g/kg/d												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	16/47 (34%)	17/49 (34.7%)	RR 0.98 (0.56 to 1.71)	7 fewer per 1000 (from 153 fewer to 246 more)	⊕OOO VERY LOW	CRITICAL
Late onset sepsis - Mixed birthweight - high vs. low AA intake at commencement												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	25/140 (17.9%)	26/142 (18.3%)	RR 0.97 (0.59 to 1.5)	5 fewer per 1000 (from 75 fewer to 92 more)	⊕OOO VERY LOW	CRITICAL
Late onset sepsis - ELBW babies - low AA intake at commencement ≤ 2.0 g/kg/d												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	4/24 (16.7%)	4/27 (14.8%)	RR 1.12 (0.32 to 4.01)	18 more per 1000 (from 101 fewer to 446 more)	⊕OOO VERY LOW	CRITICAL
Hyperkalaemia												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/30 (10%)	5/31 (16.1%)	RR 0.62 (0.16 to 2.37)	61 fewer per 1000 (from 135 fewer to 221 more)	⊕OOO VERY LOW	CRITICAL
Mortality at hospital discharge												
8	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	serious[36]	none	48/491 (9.8%)	59/494 (11.9%)	RR 0.85 (0.6 to 1.2)	18 fewer per 1000 (from 48 fewer to 24 more)	⊕OOO VERY LOW	IMPORTANT
Mortality at hospital discharge - Mixed birthweight - low AA intake at commencement ≤2 g/kg/d												
4	randomised trials	very serious[15]	no serious inconsistency	no serious indirectness	very serious[6]	none	26/266 (9.8%)	29/263 (11%)	RR 0.94 (0.58 to 1.52)	7 fewer per 1000 (from 46 fewer to 57 more)	⊕OOO VERY LOW	IMPORTANT
Mortality at hospital discharge - Mixed birthweight - high AA intake at commencement > 2 g/kg/d												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	7/47 (14.9%)	10/49 (20.4%)	RR 0.73 (0.3 to 1.76)	55 fewer per 1000 (from 143 fewer to 155 more)	⊕OOO VERY LOW	IMPORTANT
Mortality at hospital discharge - Mixed birthweight - high vs. low AA intake at commencement												
2	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	9/148 (6.1%)	16/151 (10.6%)	RR 0.57 (0.26 to 1.25)	46 fewer per 1000 (from 78 fewer to 26 more)	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at maximal intake of PN	Lower amino acid intake at maximal intake of PN	Relative (95% CI)	Absolute	Quality	Importance
Mortality to hospital discharge - ELBW babies - low AA intake at commencement ≤2 g/kg/d												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	6/30 (20%)	4/31 (12.9%)	RR 1.55 (0.49 to 4.95)	71 more per 1000 (from 66 fewer to 510 more)	⊕OOO VERY LOW	IMPORTANT
Hospital stay (days) (Better indicated by lower values)												
3	randomised trials	very serious[37]	serious[17]	no serious indirectness	serious[38]	none	123	120	-	MD 1.43 higher (10.05 lower to 12.91 higher)	⊕OOO VERY LOW	IMPORTANT
Hospital stay (days) - Mixed birthweight - high AA intake at commencement > 2 g/kg/d (Better indicated by lower values)												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[39]	none	47	49	-	MD 7.8 higher (4.3 lower to 19.9 higher)	⊕⊕OO LOW	IMPORTANT
Hospital stay (days) - Mixed birthweight - low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[40]	none	60	55	-	MD 8.95 lower (17.9 lower to 0 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Hospital stay (days) - ELBW babies - low AA intake at commencement ≤ 2.0 g/kg/d (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[41]	none	16	16	-	MD 7 higher (4.01 lower to 18.01 higher)	⊕⊕OO LOW	IMPORTANT

CI: confidence interval; ELBW: extremely low birthweight; MD: mean difference; PN: parenteral nutrition; RR: risk ratio.

[1] Evidence downgraded by 1 due to high risk of other bias and unclear risk of performance bias

[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-6.50)

[3] Evidence downgraded by 1 due to high risk of performance bias and unclear risk of reporting bias

[4] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one MID for continuous outcomes, calculated as 0.5 x SD control at baseline

(6.50)

[5] *Evidence downgraded by 1 due to high risk of performance bias*

[6] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MIDs for dichotomous outcomes (0.80, 1.25)*

[7] *Evidence was downgraded by 2 due to very serious inconsistency, 95% confidence interval crosses two MIDs for continuous outcomes, calculated as 0.5 x SD control at baseline (-6.00, 6.00)*

[8] *Evidence downgraded by 1 due to high risk of other bias and high and unclear risk of performance bias*

[9] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.34)*

[10] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.35)*

[11] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two MIDs for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.30, 2.30)*

[12] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (2.60)*

[13] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.35)*

[14] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (121)*

[15] *Evidence downgraded by 2 due to high risk of performance bias and detection bias, and unclear risk of reporting bias*

[16] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (155.81)*

[17] *Evidence downgraded by 1 due to moderate heterogeneity*

[18] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-3.38)*

[19] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.05)*

[20] *Evidence downgraded by 1 due to high risk of performance bias, and unclear selection bias*

[21] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.50)*

[22] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.60)*

[23] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.38)*

[24] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.07)*

[25] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (3.82)*

[26] *Evidence downgraded by 2 due to high heterogeneity*

[27] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (3.37)*

[28] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.13)*

[29] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.11)*

[30] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at*

baseline (0.08)
[31] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.85)
[32] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.80)
[33] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.43)
[34] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.57)
[35] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.50)
[36] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80)
[37] Evidence downgraded by 2 due to high risk of performance bias, other bias, and detection bias, and unclear selection bias
[38] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (12.69)
[39] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (14.55)
[40] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-12.89)
[41] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (6.00)

Table 5: Clinical evidence profile for early amino acid intake versus delayed amino acid intake

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early AA (day 1)	Delayed AA (day 2-3)	Relative (95% CI)	Absolute	Quality	Importance
Development index scores at 2 years (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36	37	-	MD 3.5 lower (8.59 lower to 1.59 higher)	⊕⊕OO LOW	CRITICAL
Weight (g) - At discharge (6 weeks) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	54	57	-	MD 155 higher (139.86 lower to 449.86 higher)	⊕⊕OO LOW	CRITICAL
Weight (g) - Post discharge (2 years) (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early AA (day 1)	Delayed AA (day 2-3)	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	57	-	MD 100 higher (572 lower to 772 higher)	⊕⊕⊕O MODERATE	CRITICAL
Days to regain birth weight (Better indicated by lower values)												
1	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	8	9	-	MD 1.70 lower (4.53 lower to 1.13 higher)	⊕OOO VERY LOW	CRITICAL
Percentage weight loss at 7 days (Better indicated by lower values)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[7]	none	8	9	-	MD 0.9 higher (5.36 lower to 7.16 higher)	⊕OOO VERY LOW	CRITICAL
Infants with weight <10th percentile - At 6 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	15/54 (27.8%)	21/57 (36.8%)	RR 0.75 (0.44 to 1.3)	92 fewer per 1000 (from 206 fewer to 111 more)	⊕OOO VERY LOW	CRITICAL
Infants with weight <10th percentile - At 2 years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	10/54 (18.5%)	16/57 (28.1%)	RR 0.66 (0.33 to 1.32)	95 fewer per 1000 (from 188 fewer to 90 more)	⊕OOO VERY LOW	CRITICAL
Weight change in z-score - At discharge (6 weeks) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	54	57	-	MD 0.22 lower (0.7 lower to 0.26 higher)	⊕⊕OO LOW	CRITICAL
Weight change in z-score - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[10]	none	54	57	-	MD 0.17 lower (0.75 lower to 0.41 higher)	⊕⊕OO LOW	CRITICAL
Head circumference increment (cm) at 2 weeks (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early AA (day 1)	Delayed AA (day 2-3)	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[11]	none	8	9	-	MD 0.25 higher (0.14 lower to 0.64 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference (cm) - At discharge (6 weeks) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[12]	none	54	57	-	MD 0.1 higher (0.5 lower to 0.7 higher)	⊕⊕OO LOW	CRITICAL
Head circumference (cm) - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[13]	none	54	57	-	MD 0.2 higher (0.47 lower to 0.87 higher)	⊕⊕OO LOW	CRITICAL
Infants with HC <10th percentile - At 6 weeks												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/54 (1.9%)	3/57 (5.3%)	RR 0.35 (0.04 to 3.28)	34 fewer per 1000 (from 51 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Infants with HC <10th percentile - At 2 years												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/54 (3.7%)	3/57 (5.3%)	RR 0.7 (0.12 to 4.05)	16 fewer per 1000 (from 46 fewer to 161 more)	⊕OOO VERY LOW	CRITICAL
Head circumference change in z-score - At discharge (6 weeks) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	57	-	MD 0.15 lower (0.66 lower to 0.36 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference change in z-score - Post discharge (2 years) (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	57	-	MD 0.03 higher (0.46 lower to 0.52 higher)	⊕⊕⊕O MODERATE	CRITICAL
Late onset sepsis												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early AA (day 1)	Delayed AA (day 2-3)	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	very serious[8]	none	6/14 (42.9%)	7/15 (46.7%)	RR 0.92 (0.41 to 2.07)	37 fewer per 1000 (from 275 fewer to 499 more)	⊕OOO VERY LOW	CRITICAL
Mortality												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	9/82 (11%)	12/85 (14.1%)	RR 0.78 (0.35 to 1.75)	31 fewer per 1000 (from 92 fewer to 106 more)	⊕OOO VERY LOW	IMPORTANT
Mortality - Critical illness unspecified												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	8/66 (12.1%)	10/69 (14.5%)	RR 0.84 (0.35 to 1.99)	23 fewer per 1000 (from 94 fewer to 143 more)	⊕OOO VERY LOW	IMPORTANT
Mortality - Critically ill babies (requiring ventilation)												
1	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/16 (6.3%)	2/16 (12.5%)	RR 0.5 (0.05 to 4.98)	62 fewer per 1000 (from 119 fewer to 498 more)	⊕OOO VERY LOW	IMPORTANT

AA: amino acids; CI: confidence interval; MD: mean difference; RR: risk ratio.

[1] Evidence downgraded by 1 due to high risk of performance bias, and unclear selection bias, detection bias and reporting bias

[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (6.15)

[3] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (392)

[4] Evidence downgraded by 2 due high risk of attrition bias, and an unclear risk of selection bias, performance bias, detection bias and reporting bias

[5] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.35)

[6] Evidence downgraded by 1 due to high risk of attrition bias, and an unclear risk in selection bias, performance bias, detection bias and reporting bias

[7] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-3.95, 3.95)

[8] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MIDs for dichotomous outcomes (0.80, 1.25)

[9] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at

baseline (-0.58)
[10] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.61)
[11] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MIDs for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.14, 0.14)
[12] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.70)
[13] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.85)
[14] Evidence downgraded by 1 due to high risk of performance bias, and an unclear risk of detection bias, attrition bias and reporting bias

Table 6: High amino acids (≥2 g/kg/d) versus low amino acids (<2 g/kg/d) intake at commencement to the same maximal intake

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
Bayley III cognitive composite score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	59	-	MD 0.4 higher (3.86 lower to 4.66 higher)	⊕⊕⊕O MODERATE	CRITICAL
Bayley III language composite score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	55	58	-	MD 2.3 higher (3.2 lower to 7.85 higher)	⊕⊕OO LOW	CRITICAL
Bayley III receptive communication score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	59	-	MD 0.2 lower (1.83 lower to	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
										1.43 higher)		
Bayley III expressive communication score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	54	58	-	MD 0.6 higher (0.33 lower to 1.53 higher)	⊕⊕OO LOW	CRITICAL
Bayley III motor composite score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	59	-	MD 0.1 lower (4.89 lower to 4.69 higher)	⊕⊕⊕O MODERATE	CRITICAL
Bayley III fine motor score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	58	-	MD 0.1 higher (0.66 lower to 0.86 higher)	⊕⊕⊕O MODERATE	CRITICAL
Bayley III gross motor score at 18-24 months (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	58	-	MD 0.1 lower (0.92 lower to 0.72 higher)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
Weight gain (g/kg/d) - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	63	-	MD 4.48 lower (6.17 to 2.79 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Weight gain (g/kg/d) - At discharge (Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	23	19	-	MD 0.4 higher (1.69 lower to 2.49 higher)	⊕OOO VERY LOW	CRITICAL
Weight (g) - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	60	63	-	MD 123.12 lower (198.61 to 47.63 lower)	⊕⊕⊕O MODERATE	CRITICAL
Weight (g) - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	61	-	MD 29 lower (135.93 lower to 77.93 higher)	⊕⊕⊕O MODERATE	CRITICAL
Weight (g) - At discharge (Better indicated by higher values)												
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	105	107	-	MD 35.78 higher	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
										(42.79 lower to 114.35 higher)		
Weight percentile - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	60	61	-	MD 4.7 lower (10.44 lower to 1.04 higher)	⨁⨁◯◯ LOW	CRITICAL
Weight percentile - At discharge (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	60	66	-	MD 7.2 lower (15 lower to 0.6 higher)	⨁⨁◯◯ LOW	CRITICAL
Weight z-score - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	60	61	-	MD 0.06 lower (0.31 lower to 0.19 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Weight z-score - At discharge (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[9]	none	60	66	-	MD 0.18 lower (0.46 lower to	⨁⨁◯◯ LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
										0.1 higher)		
Days to regain birthweight (Better indicated by lower values)												
3	randomised trials	serious[4]	serious[10]	no serious indirectness	serious[11]	none	70	66	-	MD 0.61 lower (2.54 lower to 1.33 higher)	⊕OOO VERY LOW	CRITICAL
Days to regain birthweight - Mixed birthweight - lipids started at 2g/kg/day vs. 1g/kg/day (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[12]	none	25	25	-	MD 1.5 lower (3.11 lower to 0.11 higher)	⊕⊕⊕O MODERATE	CRITICAL
Days to regain birthweight - Mixed birthweight - lipids started at 3g/kg/day vs. 1g/kg/day (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[13]	none	22	22	-	MD 2.3 higher (0.48 lower to 5.08 higher)	⊕⊕OO LOW	CRITICAL
Days to regain birthweight - VLBW (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[14]	none	7	3	-	MD 2.9 lower (8.31 lower to 2.51 higher)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
Days to regain birthweight - ELBW (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[15]	none	16	16	-	MD 1.17 lower (3.73 lower to 1.39 higher)	⊕⊕OO LOW	CRITICAL
Percentage weight loss (Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[16]	none	23	19	-	MD 3.8 lower (7.2 to 0.4 lower)	⊕⊕OO LOW	CRITICAL
Infants with weight < 10th percentile at discharge												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[17]	none	15/23 (65.2%)	13/19 (68.4%)	RR 0.95 (0.62 to 1.46)	34 fewer per 1000 (from 260 fewer to 315 more)	⊕OOO VERY LOW	CRITICAL
Length growth (cm/wk) at 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[18]	none	60	63	-	MD 0.27 lower (0.4 to 0.14 lower)	⊕⊕⊕O MODERATE	CRITICAL
Length (cm) - At 1 month (Better indicated by higher values)												
2	randomised trials	no serious risk of bias	very serious[19]	no serious indirectness	serious[20]	none	85	88	-	MD 0.67 lower (1.34 lower to 0 higher)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
Length (cm) - At 1 month: Lipids not routinely provided (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[21]	none	60	63	-	MD 1.02 lower (1.76 to 0.28 lower)	⊕⊕⊕O MODERATE	CRITICAL
Length (cm) - At 1 month: Lipids started at 2g/kg/day vs. 1g/kg/day (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[22]	none	25	25	-	MD 1.1 higher (0.55 lower to 2.75 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length (cm) - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[23]	none	48	55	-	MD 0.8 lower (1.81 lower to 0.21 higher)	⊕⊕OO LOW	CRITICAL
Length (cm) - At discharge (Better indicated by higher values)												
2	randomised trials	serious[1]	very serious[24]	no serious indirectness	no serious imprecision	none	84	89	-	MD 0.42 higher (0.62 lower to 1.46 higher)	⊕OOO VERY LOW	CRITICAL
Length (cm) - At discharge: Lipids not specified (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[25]	none	59	64	-	MD 0.70 lower	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
										(2.06 lower to 0.66 higher)		
Length (cm) - At discharge: Lipids started at 2g/kg/day vs. 1g/kg/day (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[26]	none	25	25	-	MD 2 higher (0.38 to 3.62 higher)	⊕⊕⊕O MODERATE	CRITICAL
Length percentile - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[27]	none	48	55	-	MD 5.2 lower (11.74 lower to 1.34 higher)	⊕⊕OO LOW	CRITICAL
Length percentile - At discharge (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[28]	none	59	64	-	MD 7.8 lower (16.5 lower to 0.9 higher)	⊕⊕OO LOW	CRITICAL
Length z-score - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[29]	none	48	55	-	MD 0.35 lower (0.74 lower to	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
										0.04 higher)		
Length z-score - At discharge (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[30]	none	59	64	-	MD 0.24 lower (0.59 lower to 0.11 higher)	⊕⊕OO LOW	CRITICAL
Head circumference (cm) - At 1 month (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[31]	none	25	25	-	MD 0.5 higher (0.03 lower to 1.03 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference (cm) - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	51	60	-	MD 0.2 lower (0.7 lower to 0.3 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference (cm) - At discharge (Better indicated by higher values)												
3	randomised trials	very serious[4,32]	serious[10]	no serious indirectness	no serious imprecision	none	107	111	-	MD 0.45 higher (0.11 lower to 1.01 higher)	⊕OOO VERY LOW	CRITICAL
Head circumference (cm) - At discharge: Lipids not specified (Better indicated by higher values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[33]	none	60	64	-	MD 0.6 lower (1.53 lower to 0.33 higher)	⊕⊕OO LOW	CRITICAL
Head circumference (cm) - At discharge: Lipids started at 3g/kg/day vs. 1g/kg/day (Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[34]	none	22	22	-	MD 0.9 higher (0.4 lower to 2.2 higher)	⊕⊕OO LOW	CRITICAL
Head circumference (cm) - At discharge: Lipids started at 2g/kg/day vs. 1g/kg/day (Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[35]	none	25	25	-	MD 1.1 higher (0.27 to 1.93 higher)	⊕⊕⊕O MODERATE	CRITICAL
Head circumference percentile - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[36]	none	51	60	-	MD 7.1 lower (15.59 lower to 1.39 higher)	⊕⊕OO LOW	CRITICAL
Head circumference percentile - At discharge (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[37]	none	60	64	-	MD 9 lower (17.24 to	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
										0.76 lower)		
Head circumference z-score - At 36 weeks PMA (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[38]	none	51	60	-	MD 0.19 lower (0.49 lower to 0.11 higher)	⊕⊕OO LOW	CRITICAL
Head circumference z-score - At discharge (Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[39]	none	60	64	-	MD 0.3 lower (0.57 to 0.03 lower)	⊕⊕OO LOW	CRITICAL
Late onset sepsis												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[17,40]	none	24/158 (15.2%)	34/158 (21.5%)	RR 0.70 (0.44 to 1.11)	65 fewer per 1000 (from 121 fewer to 24 more)	⊕⊕OO LOW	CRITICAL
Mortality												
3	randomised trials	serious[32]	no serious inconsistency	no serious indirectness	very serious[17]	none	12/134 (9%)	13/129 (10.1%)	RR 0.89 (0.42 to 1.88)	11 fewer per 1000 (from 58 fewer to 89 more)	⊕OOO VERY LOW	IMPORTANT
Hospital stay (days) (Better indicated by lower values)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher amino acid intake at commencement of PN to same maximal intake	Lower amino acid intake at commencement of PN to same maximal intake	Relative (95% CI)	Absolute	Quality	Importance
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	70	66	-	MD 1.69 lower (7.9 lower to 4.53 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Nutritional intake amino acids (g/kg/d) - At 7 days (Better indicated by higher values)												
2	randomised trials	serious[4]	very serious[24]	no serious indirectness	serious[41]	none	48	44	-	MD 0.54 higher (0.05 to 1.03 higher)	⊕OOO VERY LOW	IMPORTANT
Nutritional intake amino acids (g/kg/d) - At discharge (Better indicated by higher values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[42]	none	40	35	-	MD 0.32 higher (0.05 to 0.59 higher)	⊕⊕OO LOW	IMPORTANT

CI: confidence interval; ELBW: extremely low birthweight; MD: mean difference; PMA: post menstrual age; PN: parenteral nutrition; RR: risk ratio; VLBW: very low birthweight.

[1] Evidence downgraded by 1 due to high risk of reporting bias and unclear allocation concealment and attrition bias

[2] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (6.70)

[3] Evidence downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.20)

[4] Evidence downgraded by 1 due to unclear reporting bias

[5] Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MIDs for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.55, 1.55)

[6] Evidence was downgraded by 1 due to serious risk of imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-112.2)

[7] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (--9.65)

[8] Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-13.05)

[9] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.46)*
[10] *Evidence downgraded by 1 due to moderate heterogeneity*
[11] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.72)*
[12] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.50)*
[13] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.95)*
[14] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MIDs for continuous outcomes, calculated as 0.5 x SD control at baseline (-2.10, 2.10)*
[15] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.70)*
[16] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-3.05)*
[17] *Evidence was downgraded by 2 due to very serious imprecision, 95% confidence interval crosses two default MIDs for dichotomous outcomes (0.80, 1.25)*
[18] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.18)*
[19] *Evidence downgraded by 2 due to high heterogeneity*
[20] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.30)*
[21] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.17)*
[22] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.65)*
[23] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.75)*
[24] *Evidence downgraded by 2 due to high heterogeneity*
[25] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.90)*
[26] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.60)*
[27] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-10.50)*
[28] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-13.95)*
[29] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.49)*
[30] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.56)*
[31] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.55)*
[32] *Evidence downgraded by 1 due to high and unclear risk of reporting bias and unclear allocation concealment and attrition bias*
[33] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-1.30)*

[34] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (1.05)*
[35] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.75)*
[36] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-12.75)*
[37] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-12.85)*
[38] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.45)*
[39] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (-0.42)*
[40] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for dichotomous outcomes (0.80)*
[41] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.20)*
[42] *Evidence was downgraded by 1 due to serious imprecision, 95% confidence interval crosses one default MID for continuous outcomes, calculated as 0.5 x SD control at baseline (0.25)*

Appendix G – Economic evidence study selection

Economic evidence study selection for review questions:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care? and

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

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:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

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

Appendix I – Health Economic evidence profiles

Economic evidence profiles for review question:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

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

Appendix J – Health Economic analysis

Economic evidence analysis for review question:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded clinical and economic studies for review question:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

Clinical studies

Table 7: Excluded studies and reasons for their exclusion

Study	Reason for Exclusion
A. S. P. E. N. Intravenous Amino Acids National Shortage Task Force, Vanek, Vincent W., Mirtallo, Jay, Robinson, Larry, Kochevar, Marty, Guenter, Peggi, Parenteral nutrition amino acids product shortage considerations, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 28, 524-7, 2013	Does not match eligibility criteria - ASPEN recommendations for amino acid product shortages.
Abusabika, M., Provision of early and high amount of parental amino acids to low birth weight neonated at ICU i, Cogent Medicine, 5, 35, 2018	Abstract only.
Adamkin, D. D., Radmacher, P., Rosen, P., Comparison of a neonatal versus general-purpose amino acid formulation in preterm neonates, Journal of perinatology : official journal of the California Perinatal Association, 15, 108-13, 1995	Study does not match eligibility criteria - compares Aminosyn versus Aminosyn-PF (two amino acid formulations).
Adamkin, D. H., Issues in the nutritional support of the ventilated baby, Clinics in Perinatology, 25, 79-96, 1998	Narrative review.
Adamkin, D. H., Early aggressive nutrition: parenteral amino acids and minimal enteral nutrition for extremely low birth weight (<1 000 g) infants, Minerva Pediatrica, 59, 369-77, 2007	Narrative review.
Adamkin, D. H., Nutrition in very very low birth weight infants, Clinics in Perinatology, 13, 419-43, 1986	Narrative review.
Adamkin, D. H., McClead, R. E., Jr., Desai, N. S., McCulloch, K. M., Marchildon, M. B., Comparison of two neonatal intravenous amino acid formulations in preterm infants: a multicenter study, Journal of perinatology : official journal of the California Perinatal Association, 11, 375-82, 1991	Study does not match eligibility criteria - compares Aminosyn-PF versus TrophAmine (two amino acid formulations).
Adamkin, David H., Pragmatic approach to in-hospital nutrition in high-risk neonates, Journal of perinatology : official journal of the California Perinatal Association, 25 Suppl 2, S7-S11, 2005	Narrative review.
Agostoni, C., Francescato, G., Agosti, M., Nutrition in the critically ILL: Enteral and	Review. Abstract only.

Study	Reason for Exclusion
parenteral nutrition in the newborn, Archives of Disease in Childhood, 97, A65, 2012	
Ahola, T., Fellman, V., Laaksonen, R., Laitila, J., Lapatto, R., Neuvonen, P. J., Raivio, K. O., Pharmacokinetics of intravenous N-acetylcysteine in pre-term new-born infants, European Journal of Clinical Pharmacology, 55, 645-50, 1999	Intervention not relevant.
Ahola, T., Lapatto, R., Raivio, K. O., Selander, B., Stigson, L., Jonsson, B., Jonsbo, F., Esberg, G., Stovring, S., Kjartansson, S., Stiris, T., Lossius, K., Virkola, K., Fellman, V., N-acetylcysteine does not prevent bronchopulmonary dysplasia in immature infants: A randomized controlled trial, Journal of Pediatrics, 143, 713-719, 2003	Intervention not relevant.
Ahola,T., Fellman,V., Kjellmer,I., Raivio,K.O., Lapatto,R., Plasma 8-isoprostane is increased in preterm infants who develop bronchopulmonary dysplasia or periventricular leukomalacia, Pediatric Research, 56, 88-93, 2004	Intervention not relevant.
Albers, M. J. I. J., Steyerberg, E. W., Hazebroek, F. W. J., Mourik, M., Borsboom, G. J. J. M., Rietveld, T., Huijmans, J. G. M., Tibboel, D., Glutamine supplementation of parenteral nutrition does not improve intestinal permeability, nitrogen balance, or outcome in newborns and infants undergoing digestive-tract surgery: Results from a double-blind, randomized, controlled trial, Annals of Surgery, 241, 599-606, 2005	Study does not match eligibility criteria - comparison not relevant. Glutamine-supplemented parenteral nutrition compared to standard parenteral nutrition.
Alexander Aiken, C. G., Determinants of urea production and mineral retention in parenterally fed preterm infants, Journal of Clinical and Diagnostic Research, 7, 1655-1658, 2013	Study does not match eligibility criteria - Not a randomised controlled trial and outcomes do not match those specified in the protocol.
Algotar, A., Siler-Wurst, K., Sitaram, S., Shaikhkhalil, A., Gulati, I., Jadcherla, S., Patterns of change in body composition and anthropometric parameters in NICU infants, Gastroenterology, 150, S436, 2016	Conference abstract.
Allegaert, K., Cossey, V., Langhendries, J. P., Naulaers, G., Vanhole, C., Devlieger, H., Van Overmeire, B., Effects of co-administration of ibuprofen-lysine on the pharmacokinetics of amikacin in preterm infants during the first days of life, Biology of the Neonate, 86, 207-211, 2004	Intervention not relevant.
Alo, D., Shahidullah, M., Mannan, M. A., Noor, K., Effect of parenteral amino acid supplementation in preterm low birth weight newborn, Mymensingh medical journal : MMJ, 19, 386-90, 2010	Study does not match eligibility criteria - not a randomised controlled trial.
Al-Shahwani, Noora H., Sigalet, David L., Pathophysiology, prevention, treatment, and outcomes of intestinal failure-associated liver disease, Pediatric surgery international, 33, 405-411, 2017	Narrative review.

Study	Reason for Exclusion
Altman, R. P., Randolph, J. G., Application and hazards of total parenteral nutrition in infants, Annals of Surgery, 174, 85-90, 1971	Study design not relevant - case reports.
Amin, H. J., Zamora, S. A., McMillan, D. D., Fick, G. H., Butzner, J. D., Parsons, H. G., Scott, R. B., Arginine supplementation prevents necrotizing enterocolitis in the premature infant, Journal of Pediatrics, 140, 425-431, 2002	Study does not match eligibility criteria - Comparison not relevant. Supplemental L-arginine compared to a placebo with oral feeds/parenteral nutrition during the first 28 days of life.
Andersen, G. E., Bucher, D., Friis-Hansen, B., Nexo, E., Olesen, H., Plasma amino acid concentrations in newborn infants during parenteral nutrition, JPEN. Journal of parenteral and enteral nutrition, 7, 369-73, 1983	Outcomes not relevant and no comparison treatment.
Anderson, T. L., Muttart, C. R., Bieber, M. A., Nicholson, J. F., Heird, W. C., A controlled trial of glucose versus glucose and amino acids in premature infants, Journal of Pediatrics, 94, 947-51, 1979	Study does not match eligibility criteria - study compares glucose only with glucose in addition to amino acids (AA versus No AA).
Andronikou, S., Hanning, I., Parenteral nutrition effect on serum insulin in the preterm infant, Pediatrics, 80, 693-697, 1987	Study does not match eligibility criteria - glucose only compared to glucose in addition to amino acids which does not match the intervention/comparisons specified in the protocol.
Ardicli, B., Karnak, I., Ciftci, A. O., Ozen, H., Tanyel, F. C., Senocak, M. E., Composition of parenteral nutrition solution affects the time of occurrence but not the incidence of cholestasis in surgical infants, Turkish Journal of Pediatrics, 56, 500-506, 2014	Study does not match eligibility criteria - retrospective study.
Ayers, J., Graves, S. A., Perioperative management of total parenteral nutrition, glucose containing solutions, and intraoperative glucose monitoring in paediatric patients: a survey of clinical practice, Paediatric anaesthesia, 11, 41-4, 2001	Study does not match eligibility criteria - survey on perceived success of managing TPN.
Barclay, A. R., Beattie, L. M., Weaver, L. T., Wilson, D. C., Systematic review: Medical and nutritional interventions for the management of intestinal failure and its resultant complications in children, Alimentary Pharmacology and Therapeutics, 33, 175-184, 2011	Study does not match eligibility criteria - systematic review.
Bassiouny, M. R., Almarsafawy, H., Abdel-Hady, H., Nasef, N., Hammad, T. A., Aly, H., A randomized controlled trial on parenteral nutrition, oxidative stress, and chronic lung diseases in preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 48, 363-369, 2009	Study does not match eligibility criteria - study examines the effect of trace elements and lipids, not amino acids.
Battista, M. A., Price, P. T., Kalhan, S. C., Effect of parenteral amino acids on leucine and urea kinetics in preterm infants, Journal of Pediatrics, 128, 130-134, 1996	Study does not match eligibility criteria - study does not report any of the outcomes of interest specified in the protocol.
Beck, R., Use of a pediatric parenteral amino acid mixture in a population of extremely low birth weight neonates: frequency and spectrum of direct bilirubinemia, American Journal of Perinatology, 7, 84-6, 1990	Study does not match eligibility criteria - retrospective study.

Study	Reason for Exclusion
Beganovic, N., Kok, K., de Leeuw, R., de Vries, I. J., Schutgens, R., Amino acids in parenteral nutrition of preterm infants. Comparison of oral and parenteral supply, Acta Paediatrica Scandinavica, 72, 421-5, 1983	Study does not match eligibility criteria - not a randomised controlled trial and comparisons include parenterally fed infants versus orally fed infants.
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 does not match eligibility criteria - not a randomised controlled trial, crossover study.
Bell, E. F., Weinstein, M. R., Oh, W., Effects of intravenously administered safflower oil emulsion on respiratory gas exchange of low-birth-weight infants, Journal of pediatric gastroenterology and nutrition, 2, 517-20, 1983	No comparison group. Not an RCT.
Bellagamba, Maria Paola, Carmenati, Elisabetta, D'Ascenzo, Rita, Malatesta, Michela, Spagnoli, Cristina, Biagetti, Chiara, Burattini, Ilaria, Carnielli, Virgilio P., One Extra Gram of Protein to Preterm Infants from Birth to 1800 g: A Single-Blinded Randomized Clinical Trial, Journal of Pediatric Gastroenterology and Nutrition, 62, 879-84, 2016	Intervention outside scope - babies were randomised to different amounts of both parenteral and enteral nutrition. Babies in other trials received differing levels of enteral nutrition but this was not part of the intervention.
Ben, Xiao-Ming, Nutritional management of newborn infants: practical guidelines, World journal of gastroenterology, 14, 6133-9, 2008	Guidelines only.
Benda, G. I., Babson, S. G., Peripheral intravenous alimentation of the small premature infant, The Journal of pediatrics, 79, 494-8, 1971	Study does not match eligibility criteria - observational study examining the feasibility of high calorie feeding via the peripheral vein.
Benner, J. W., Coran, A. G., Weintraub, W. H., Wesley, J. R., The importance of different calorie sources in the intravenous nutrition of infants and children, Surgery, 86, 429-433, 1979	Study does not match eligibility criteria - not a randomised controlled trial.
Berkow, S. E., Spear, M. L., Stahl, G. E., Gutman, A., Polin, R. A., Pereira, G. R., Olivecrona, T., Hamosh, P., Hamosh, M., Total parenteral nutrition with intralipid in premature infants receiving TPN with heparin: effect on plasma lipolytic enzymes, lipids, and glucose, Journal of Pediatric Gastroenterology and Nutrition, 6, 581-8, 1987	Study does not match eligibility criteria - observational study examining the effect of intralipid.
Biagetti, C., Bellagamba, M. P., D'Ascenzo, R., Burattini, I., Cogo, P. E., Carnielli, V. P., Increasing amino acid and non-protein energy in preterms on parenteral nutrition: Higher rate of sepsis and no benefit in short-term growth, Archives of Disease in Childhood, 99, A132, 2014	Abstract only.
Biniwale, M. A., Ehrenkranz, R. A., The Role of Nutrition in the Prevention and Management of Bronchopulmonary Dysplasia, Seminars in Perinatology, 30, 200-208, 2006	Narrative review only.
Blanco, C. L., Gong, A. K., Green, B. K., Falck, A., Schoolfield, J., Liechty, E. A., Early changes in plasma amino acid concentrations during aggressive nutritional therapy in extremely low	Study is a follow-up of Blanco 2008 which is already included. Study does not report any additional outcomes of interest that are not

Study	Reason for Exclusion
birth weight infants, Journal of Pediatrics, 158, 543, 2011	already reported in the previous study or later study, Blanco 2012 (also included).
Blazer, S., Reinersman, G. T., Askanazi, J., Furst, P., Katz, D. P., Fleischman, A. R., Branched-chain amino acids and respiratory pattern and function in the neonate, Journal of perinatology : official journal of the California Perinatal Association, 14, 290-5, 1994	Study does not match eligibility criteria - crossover study that does not report any of the outcomes of interest.
Bloomfield, F. H., Crowther, C. A., Harding, J. E., Conlon, C. A., Jiang, Y., Cormack, B. E., The ProVIDe study: The impact of protein intravenous nutrition on development in extremely low birthweight babies, BMC Pediatrics, 15, 2015	Study protocol only.
Boano, E., Guardione, R., Catarinella, A., Romano, C., Manzoni, P., Farina, D., Catheter-related infections and the nurse. New strategies, Early Human Development, 88, S102-S103, 2012	Methodology paper.
Bonsante, F., Iacobelli, S., Latorre, G., Rigo, J., de Felice, C., Robillard, P. Y., Gouyon, J. B., Initial Amino Acid Intake Influences Phosphorus and Calcium Homeostasis in Preterm Infants - It Is Time to Change the Composition of the Early Parenteral Nutrition, PLoS ONE, 8, e72880, 2013	Study does not match eligibility criteria - Prospective observational study.
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	Does not match eligibility criteria - prospective observational trial.
Boon, J. M., Monnens, L. A., Knuiman, J. T., Trijbels, J. M., Serum-free amino acid concentrations in low birth weight infants during the first 4 weeks of life, Infusionstherapie und klinische Ernahrung, 7, 121-4, 1980	Study does not match eligibility criteria - population was formula fed, low birth weight children.
Borresen, H. C., Bjordal, R., Knutrud, O., Total balanced intravenous feeding by peripheral veins in paediatric surgery. A summary of 7 years' research and clinical experience, Annales chirurgiae et gynaecologiae Fenniae, 62, 319-27, 1973	No relevant comparisons.
Borresen, H. C., Coran, A. G., Knutrud, O., Metabolic results of parenteral feeding in neonatal surgery: A balanced parenteral feeding program based on a synthetic 1 amino acid solution and a commercial fat emulsion, Annals of Surgery, 172, 291-301, 1970	Case reports.
Botet, F., Figueras-Aloy, J., Miracle-Echegoyen, X., Rodriguez-Miguelez, J. M., Salvia-Roiges, M., Carbonell-Estrany, X., Trends in survival among extremely-low-birth-weight infants (less than 1000 g) without significant bronchopulmonary dysplasia, BMC Pediatrics, 12, 63, 2012	Non-RCT.
Boubred, F., Herlenius, E., Bartocci, M., Jonsson, B., Vanpee, M., Extremely preterm	Study does not match eligibility criteria - prospective, observational cohort study.

Study	Reason for Exclusion
infants who are small for gestational age have a high risk of early hypophosphatemia and hypokalemia, Acta Paediatrica, International Journal of Paediatrics, 104, 1077-1083, 2015	
Bouchoud, L., Sadeghipour, F., Klingmuller, M., Fonzo-Christe, C., Bonnabry, P., Long-term physico-chemical stability of standard parenteral nutritions for neonates, Clinical Nutrition, 29, 808-812, 2010	Storage study.
Bourgoin-Heck, M., Bulteau-Cowan, A., Mulliez-Petitpas, J., Husseini, K., Bott-Lebreton, L., Drouot, X., Diaz, V., Impact of early parenteral protein intake on lung function of children suffering from bronchopulmonary dysplasia, Pediatric Pulmonology, 50, S67-S68, 2015	Abstract only.
Bresson, J. L., Bader, B., Rocchiccioli, F., Mariotti, A., Ricour, C., Sachs, C., Rey, J., Protein-metabolism kinetics and energy-substrate utilization in infants fed parenteral solutions with different glucose-fat ratios, The American journal of clinical nutrition, 54, 370-6, 1991	Glucose and fat.
Brown, Jennifer Ve, Moe-Byrne, Thirimon, McGuire, William, Glutamine supplementation for young infants with severe gastrointestinal disease, Cochrane Database of Systematic Reviews, 2014	Comparison not relevant.
Brown, M. R., Thunberg, B. J., Golub, L., Maniscalco, W., Cox, C., Shapiro, D. L., Decreased cholestasis with enteral instead of intravenous protein in the very low-birth-weight infant, Journal of Pediatric Gastroenterology and Nutrition, 9, 21-27, 1989	Study does not match eligibility criteria - interventions and comparisons not relevant to those specified in the protocol. Whey fed babies without IV amino acids (whey protein started enterally) vs amino acid PN.
Brunton, J. A., Ball, R. O., Pencharz, P. B., Current total parenteral nutrition solutions for the neonate are inadequate, Current Opinion in Clinical Nutrition and Metabolic Care, 3, 299-304, 2000	Narrative review.
Burattini, Ilaria, Bellagamba, Maria Paola, D''Ascenzo, Rita, Biagetti, Chiara, Carnielli, Virgilio Paolo, Amino Acid Intake in Preterm Infants, Nestle Nutrition Institute workshop series, 86, 151-60, 2016	Narrative review.
Burger, U., Fritsch, U., Bauer, M., Peltner, H. U., Comparison of two amino acid mixtures for total parenteral nutrition of premature infants receiving assisted ventilation, JPEN. Journal of parenteral and enteral nutrition, 4, 290-3, 1980	Study does not match eligibility criteria - Clinical tolerance, nitrogen balance, and AA blood levels were investigated but study does not report useable data on any of the outcomes of interest specified in the protocol.
Burger, U., Wolf, H., Fritsch, U., Bauer, M., Parenteral nutrition in preterm infants: influence of respiratory treatment and effect of different amino acid compositions, Journal of Pediatric Gastroenterology and Nutrition, 2, 644-52, 1983	Comparisons not relevant.
Burgess, L., Flanagan, B., Turner, M., Morgan, C., Elevated essential amino acid levels in very preterm infants receiving total parenteral	Abstract only.

Study	Reason for Exclusion
nutrition, Journal of Pediatric Gastroenterology and Nutrition, 64, 797, 2017	
Burgess, L., McGowan, P., Morgan, C., Hyperalimentation and plasma levels of amino acids in very preterm infants dependent on parenteral nutrition, Archives of Disease in Childhood, 99, A443, 2014	Conference abstract. Outcome not relevant.
Burgess, L., McGowan, P., Morgan, C., Hyperalimentation and plasma levels of conditionally essential amino acids in very preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A41-A42, 2014	Conference abstract. Outcome not relevant.
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 does not match eligibility criteria. Follow-up study of Tan 2008. Data was stratified within the high-protein/calorie and control groups according to arginine level to determine the association between arginine levels and hyperglycaemia, and the defining of arginine deficiency.
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	No relevant comparisons - regimens including, PN, mother's or donor milk and EN.
Calkins, K. L., Sanchez, L. A., Tseng, C. H., Faull, K. F., Yoon, A. J., Ryan, C. M., Le, T. H. U. C., Shew, S. B., Effect of High-Dose Cysteine Supplementation on Erythrocyte Glutathione, Journal of Parenteral and Enteral Nutrition, 40, 226-234, 2016	Outcomes not relevant.
Calkins, K. L., Venick, R. S., Devaskar, S. U., Complications Associated with Parenteral Nutrition in the Neonate, Clinics in Perinatology, 41, 331-345, 2014	Narrative review.
Calkins, Kara L., Sanchez, Lauren A., Tseng, Chi-Hong, Faull, Kym F., Yoon, Alexander J., Ryan, Christopher M., Le, Thuc, Shew, Stephen B., Effect of High-Dose Cysteine Supplementation on Erythrocyte Glutathione: A Double-Blinded, Randomized Placebo-Controlled Pilot Study in Critically Ill Neonates, JPEN. Journal of parenteral and enteral nutrition, 40, 226-34, 2016	Study does not match eligibility criteria - compared 121mg/k/d of supplement with either cysteine-HCl and sodium acetate versus Premasol amino acids.
Callaghan, F., Morgan, C., Target parenteral protein attainment in parenterally fed preterm infants following the implementation of the concentrated macronutrients in parenteral standardised solutions (CoMPaSS) programme, Journal of Pediatric Gastroenterology and Nutrition, 64, 805, 2017	Audit.
Campfield, T., Braden, G., Urinary oxalate excretion by very low birth weight infants receiving parenteral nutrition, Pediatrics, 84, 860-863, 1989	No relevant outcomes.

Study	Reason for Exclusion
Campfield, T., Braden, G., Flynn-Valone, P., Clark, N., Urinary oxalate excretion in premature infants: Effect of human milk versus formula feeding, Pediatrics, 94, 674-678, 1994	No relevant outcomes.
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. Combination treatment amino acids/lipids.
Candy, D. C., Parenteral nutrition in paediatric practice: a review, Journal of human nutrition, 34, 287-96, 1980	Narrative review.
Carlson,S.J., Current nutrition management of infants with chronic lung disease, Nutrition in Clinical Practice, 19, 581-586, 2004	Narrative review.
Cashore, W. J., Sedaghatian, M. R., Usher, R. H., Nutritional supplements with intravenously administered lipid, protein hydrolysate, and glucose in small premature infants, Pediatrics, 56, 8-16, 1975	AA dosages have not been targeted.
Castillo, L., DeRojas-Walker, T., Yu, Y. M., Sanchez, M., Chapman, T. E., Shannon, D., Tannenbaum, S., Burke, J. F., Young, V. R., Whole body arginine metabolism and nitric oxide synthesis in newborns with persistent pulmonary hypertension, Pediatric Research, 38, 17-24, 1995	Topic not relevant.
Castrodale, V., Rinehart, S., The golden hour improving the stabilization of the very low birth-weight infant, Advances in Neonatal Care, 14, 9-14, 2014	Outcomes not relevant to protocol.
Chan, J. C., The influence of synthetic amino acid and casein hydrolysate on the endogenous production and urinary excretion of acid in total intravenous alimentation, Pediatric Research, 6, 789-96, 1972	Case reports.
Chapman, K. P., Courtney-Martin, G., Moore, A. M., Ball, R. O., Pencharz, P. B., Threonine requirement of parenterally fed postsurgical human neonates, American Journal of Clinical Nutrition, 89, 134-141, 2009	Non-RCT.
Chapman, K. P., Courtney-Martin, G., Moore, A. M., Langer, J. C., Tomlinson, C., Ball, R. O., Pencharz, P. B., Lysine requirement in parenterally fed postsurgical human neonates, American Journal of Clinical Nutrition, 91, 958-965, 2010	Outcome not relevant.
Chaudhari, S., Kadam, S., Total parenteral nutrition in neonates, Indian Pediatrics, 43, 953-964, 2006	Narrative review.
Chessex, P., Belanger, S., Piedboeuf, B., Pineault, M., Influence of energy substrates on respiratory gas exchange during conventional mechanical ventilation of preterm infants, Journal of Pediatrics, 126, 619-624, 1995	Exclude combination treatment carbs and lipids. No relevant outcomes.

Study	Reason for Exclusion
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	Doesn't address the objectives of the review.
Chilimindris, C. P., The current status of parenteral nutritional therapy, Maryland state medical journal, 27, 61-5, 1978	General review.
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	Combination treatment. Amino acids/lipids. Combination
Christensen, M. L., Helms, R. A., Veal, D. F., Boehm, K. A., Storm, M. C., Clearance of N-acetyl-L-tyrosine in infants receiving a pediatric amino acid solution, Clinical pharmacy, 12, 606-9, 1993	Study does not match eligibility criteria - study evaluates N-acetyl-L-tyrosine clearance in infants receiving PN. Not a randomised controlled trial.
Christmann, V., Visser, R., Engelkes, M., De Grauw, A. M., Van Goudoever, J. B., Van Heijst, A. F. J., The enigma to achieve normal postnatal growth in preterm infants - Using parenteral or enteral nutrition?, Acta Paediatrica, International Journal of Paediatrics, 102, 471-479, 2013	Study does not match eligibility criteria - Observational study.
Clark, R. H., Spitzer, A., Effects of two different doses of amino Acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: A randomized. controlled trial: in reply, Pediatrics, 121, 656, 2008	Study not relevant-Letter.
Clark, S. E., Karn, C. A., Ahlrichs, J. A., Wang, J., Leitch, C. A., Liechty, E. A., Denne, S. C., Acute changes in leucine and phenylalanine kinetics produced by parenteral nutrition in premature infants, Pediatric Research, 41, 568-574, 1997	Cohort study.
Cochran, E. B., Phelps, S. J., Helms, R. A., Parenteral nutrition in pediatric patients, Clinical pharmacy, 7, 351-366, 1988	Narrative review.
Cohen, C., Olsen, M. M., Pediatric total parenteral nutrition. Liver histopathology, Archives of pathology & laboratory medicine, 105, 152-6, 1981	Out of protocol's scope.
Cole, D. E. C., Zlotkin, S. H., Increased sulfate as an etiological factor in the hypercalciuria associated with total parenteral nutrition, American Journal of Clinical Nutrition, 37, 108-113, 1983	Outcome not relevant.
Conway, A., Williams, T., Care of the critically ill newborn: parenteral alimentation, The American journal of nursing, 76, 574-7, 1976	Narrative review.
Coran, A. G., Drongowski, R. A., Studies on the toxicity and efficacy of a new amino acid solution in pediatric parenteral nutrition, Journal of	Comparison of two different amino acid solutions, but both provided same amount of amino acids (1 g Aminosyn vs 1 g Neopham).

Study	Reason for Exclusion
Parenteral and Enteral Nutrition, 11, 368-377, 1987	
Coran,A.G., Drongowski,R.A., Sarahan,T.M., Studies on the toxicity and efficacy of a new amino acid solution in pediatric parenteral nutrition, Acta Chirurgica Scandinavica - Supplementum, 517, 57-67, 1983	Not an RCT.
Costa, S., Maggio, L., Sindico, P., Cota, F., De Carolis, M. P., Romagnoli, C., Preterm Small for Gestational Age Infants Are Not at Higher Risk for Parenteral Nutrition-Associated Cholestasis, Journal of Pediatrics, 156, 575-579, 2010	Not relevant to protocol. Infants receive similar PN plus EN, comparison parenteral nutrition-associated cholestasis vs no cholestasis.
Costello, I., Powell, C., Williams, A. F., Sodium glycerophosphate in the treatment of neonatal hypophosphataemia, Archives of Disease in Childhood, 73, F44-F45, 1995	Comparison not relevant.
Courtney-Martin, G., Chapman, K. P., Moore, A. M., Kim, J. H., Ball, R. O., Pencharz, P. B., Total sulfur amino acid requirement and metabolism in parenterally fed postsurgical human neonates, American Journal of Clinical Nutrition, 88, 115-124, 2008	Outcome not relevant.
Courtney-Martin, G., Moore, A. M., Ball, R. O., Pencharz, P. B., The addition of cysteine to the total sulphur amino acid requirement as methionine does not increase erythrocytes glutathione synthesis in the parenterally fed human neonate, Pediatric Research, 67, 320-324, 2010	Outcome not relevant. Non-RCT.
Courtney-Martin, G., Moore, A. M., Ball, R. O., Pencharz, P. B., The addition of cysteine to the total sulphur amino acid requirement as methionine does not increase erythrocytes glutathione synthesis in the TPN fed human neonate, The FASEB Journal, 23, 2009	Outcome not relevant. Non-RCT.
Cowles, Robert A., Ventura, Kara A., Martinez, Mercedes, Lobritto, Steven J., Harren, Patricia A., Brodlie, Susan, Carroll, Joanne, Jan, Dominique M., Reversal of intestinal failure-associated liver disease in infants and children on parenteral nutrition: experience with 93 patients at a referral center for intestinal rehabilitation, Journal of Pediatric Surgery, 45, 84-8, 2010	Not relevant population - median age at referral 5 months.
Dani, C., Poggi, C., Nutrition and bronchopulmonary dysplasia, Journal of Maternal-Fetal and Neonatal Medicine, 25, 37-40, 2012	Study design not relevant; narrative review.
Darmaun, D., Roig, J. C., Auestad, N., Sager, B. K., Neu, J., Glutamine metabolism in very low birth weight infants, Pediatric research, 41, 391-6, 1997	Comparisons not relevant to protocol - enteral formula vs supplemented formula.
Das, J. B., Filler, R. M., Amino acid utilization during total parenteral nutrition in the surgical neonate, Journal of Pediatric Surgery, 8, 793-799, 1973	Not an RCT.

Study	Reason for Exclusion
De Pipaon, M. S., Quero, J., Wattimena, D. J. L., Sauer, P. J. J., Effect of two amino acid solutions on leucine turnover in preterm infants, Biology of the Neonate, 87, 236-241, 2005	Non-RCT.
Denne, S. C., Karn, C. A., Ahlrichs, J. A., Dorotheo, A. R., Wang, J., Liechty, E. A., Proteolysis and phenylalanine hydroxylation in response to parenteral nutrition in extremely premature and normal newborns, Journal of Clinical Investigation, 97, 746-754, 1996	Comparison between extremely premature vs term newborns; after 150 minutes, IV nutrition begun in extremely premature infants, delivering glucose, protein and lipid ate rates identical to term infants.
Denne, S. C., Karn, C. A., Wang, J., Liechty, E. A., Effect of intravenous glucose and lipid on proteolysis and glucose production in normal newborns, American Journal of Physiology - Endocrinology and Metabolism, 269, E361-E367, 1995	No relevant outcomes.
Denne, S. C., Poindexter, B. B., Evidence supporting early nutritional support with parenteral amino acid infusion, Seminars in Perinatology, 31, 56-60, 2007	Non-RCT.
Denne, Scott C., Regulation of proteolysis and optimal protein accretion in extremely premature newborns, The American journal of clinical nutrition, 85, 621S-624S, 2007	Narrative review.
Des Robert, C., Bacquer, O. L., Piloquet, H., Roze, J. C., Darmaun, D., Acute effects of intravenous glutamine supplementation on protein metabolism in very low birth weight infants: A stable isotope study, Pediatric Research, 51, 87-93, 2002	No relevant outcomes.
DeSilva, S., Hana, M., Sutija, V. G., Raziuddin, K., Effect of amino acids on glucose tolerance and hyperkalemia in very low birth weight infants, Journal of Perinatal Medicine, 30, 128-131, 2002	No comparison group.
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	Combination treatment.
Dolanski, E. A., Stahlman, M. T., Meng, H. C., Parenteral alimentation of premature infants under 1,200 grams, Southern medical journal, 66, 41-6, 1973	Doesn't address the objectives of the review.
Driscoll, J. M., Jr., Heird, W. C., Schullinger, J. N., Gongaware, R. D., Winters, R. W., Total intravenous alimentation in low-birth-weight infants: a preliminary report, The Journal of pediatrics, 81, 145-53, 1972	Study design not relevant - no comparison group.
Drysdale, Simon B., Coulson, Timothy, Cronin, Natalie, Manjaly, Zita-Rose, Piyasena, Chinthika, North, Adam, Ford-Adams, Martha E., Broughton, Simon, The impact of the National Patient Safety Agency intravenous fluid alert on iatrogenic hyponatraemia in children, European Journal of Pediatrics, 169, 813-7, 2010	Population not relevant to protocol - children median age 6.0 and 6.9 years.

Study	Reason for Exclusion
Dudrick, S. J., Ruberg, R. L., Principles and practice of parenteral nutrition, Gastroenterology, 61, 901-10, 1971	Old guidelines.
Duffy, B., Pencharz, P., The effects of surgery on the nitrogen metabolism of parenterally fed human neonates, Pediatric Research, 20, 32-5, 1986	Study does not match eligibility criteria -relevant outcomes are not reported.
Duggan, C, Stark, Ar, Auestad, N, Collier, S, Fulhan, J, Gura, K, Utter, S, Teixeira-Pinto, A, Donovan, K, Lund, D, Glutamine supplementation in infants with gastrointestinal disease: a randomized, placebo-controlled pilot trial, Nutrition (Burbank, Los Angeles County, Calif.), 20, 752-756, 2004	Infants received similar amounts of amino acids via both PN and EN feeds.
Ehrenkranz, R. A., Early, aggressive nutritional management for very low birth weight infants: what is the evidence?, Seminars in Perinatology, 31, 48-55, 2007	Narrative review.
Ehrenkranz, Richard A., Das, Abhik, Wrage, Lisa A., Poindexter, Brenda B., Higgins, Rosemary D., Stoll, Barbara J., Oh, William, Eunice Kennedy Shriver National Institute of Child, Health, Human Development Neonatal Research, Network, Jobe Ah, Caplan M. S. Vohr B. R. Walden R. V. Alksininis B. Hensman A. M. Leonard M. R. Noel L. Leach T. M. Watson V. E. Fanaroff A. A. Walsh M. C. Wilson-Costello D. E. Newman N. S. Siner B. S. Friedman H. G. Donovan E. F. Schibler K. Steichen J. Alexander B. Grisby C. Mersmann M. Mincey H. L. Hessling J. Gratton T. L. Adams-Chapman I. Hale E. C. LaRossa M. M. Carter S. Wright L. L. McClure E. M. Lemons J. A. Dusick A. M. Kardatzke D. Lytle C. Appel D. D. Bohnke L. G. Eaken G. Herron D. E. Miller L. C. Richard L. Wilson L. D. Poole W. K. Hastings B. McClure E. M. O'Donnell Auman J. Schaefer S. E. Taylor S. Stevenson D. K. Hintz S. R. Ball M. B. Kohn J. G. Baran J. M. Lee-Ancajas J. C. St John N. H. Carlo W. A. Ambalavanan N. Nelson K. G. Peralta-Carcelen M. Bailey K. J. Biasini F. J. Chopko S. A. Collins M. V. Cosby S. S. Phillips V. A. Rector R. V. Finer N. N. Vaucher Y. E. Anderson J. M. Rasmussen M. R. Arnell K. Demetrio C. Fuller M. G. Henderson C. Posin D. Bauer C. R. Duara S. Worth A. M. Everett-Thomas R. Diaz A. N. Mathews E. O. Hamlin-Smith K. Jean-Gilles L. Calejo M. Frade S. M. Hiriart-Fajardo S. Gideon Y. Korones S. B. Bada H. S. Hudson T. Yolton K. Williams M. Laptook A. R. Salhab W. A. Broyles S. Madison S. Hickman J. F. Guzman A. Adams S. S. Madden L. A. Heyne E. Dooley C. Shankaran S. Shankaran S. Johnson Y. R. Bara R. Muran G. Kennedy D. Goldston L. Gettner P. Konstantino M. Romano E. Close N. Gilliam W. Poulsen J., Early nutrition mediates the influence of severity of illness on extremely LBW infants, Pediatric Research, 69, 522-9, 2011	Secondary analysis - PN components and differences between infant groups not stated.

Study	Reason for Exclusion
Embleton, N. D., Morgan, C., King, C., Balancing the risks and bene fits of parenteral nutrition for preterm infants: Can we define the optimal composition?, Archives of Disease in Childhood: Fetal and Neonatal Edition, 100, F72-F75, 2015	Narrative review.
Embleton, N. D., Simmer, K., Practice of parenteral nutrition in VLBW and ELBW infants, World Review of Nutrition & Dietetics, 110, 177-89, 2014	Narrative review.
Embleton, Nicholas D., Van Den Akker, Chris Hp, Early parenteral amino acid intakes in preterm babies: does NEON light the way?, Archives of disease in childhood. Fetal and neonatal edition, 103, F92-F94, 2018	Editorial.
Ergin, H., Ozdemir, O. M., Cirali, C., Korkut, M., Growth failure of very low birth weight neonates at discharge, European Journal of Pediatrics, 175 (11), 1719, 2016	Abstract only.
Filler, R. M., Eraklis, A. J., Care of the critically ill child: intravenous alimentation, Pediatrics, 46, 456-61, 1970	Case series.
Forsyth,J.S., Crighton,A., Low birthweight infants and total parenteral nutrition immediately after birth. I. Energy expenditure and respiratory quotient of ventilated and non-ventilated infants, Archives of Disease in Childhood Fetal and Neonatal Edition, 73, F4-F7, 1995	Infants received same PN regimen.
Fox, H. A., Krasna, I. H., Total intravenous nutrition by peripheral vein in neonatal surgical patients, Pediatrics, 52, 14-20, 1973	Not available.
Francescato, G., Mosca, F., Agosti, M., Update on lipid and protein intakes in the critical newborn, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 25 Suppl 4, 60-62, 2012	Narrative review.
Frey, G., Hyperalimentation: a review, Arizona Medicine, 30, 613-619, 1973	Narrative review.
Friel, J. K., Bessie, J. C., Belkhode, S. L., Edgecombe, C., Steele-Rodway, M., Downton, G., Kwa, P. G., Aziz, K., Thiamine, riboflavin, pyridoxine, and vitamin C status in premature infants receiving parenteral and enteral nutrition, Journal of Pediatric Gastroenterology and Nutrition, 33, 64-69, 2001	Comparison/outcomes not relevant – IV glucose and electrolytes vs PN vs full oral feedings.
Furst, P., Stehle, P., Are intravenous amino acid solutions unbalanced?, New horizons (Baltimore, Md.), 2, 215-223, 1994	Narrative review.
Gaio, P., Fantinato, M., Daverio, M., Nardo, D., Favero, V., Meneghelli, M., De Terlizzi, F., Verlato, G., Bone status in preterm infants: Influences of maternal factors and nutritional	Abstract only.

Study	Reason for Exclusion
regimens, Journal of Pediatric Gastroenterology and Nutrition, 62, 707, 2016	
Ganzevoort, W., Rep, A., Bonsel, G. J., Fetter, W. P. F., Van Sonderen, L., De Vries, J. I. P., Wolf, H., A randomised controlled trial comparing two temporising management strategies, one with and one without plasma volume expansion, for severe and early onset pre-eclampsia, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1358-1368, 2005	Not a relevant intervention - plasma volume expansion vs no plasma volume expansion.
Garlick, P. J., Assessment of the safety of glutamine and other amino acids, Journal of Nutrition, 131, 2556S-2561S, 2001	Narrative review.
Geary, C. A., Fonseca, R. A., Caskey, M. A., Malloy, M. H., Improved growth and decreased morbidities in <1000 g neonates after early management changes, Journal of perinatology : official journal of the California Perinatal Association, 28, 347-53, 2008	Cohort study.
Ghadimi, H., A review: current status of parenteral amino acid therapy, Pediatric Research, 7, 169-173, 1973	Narrative review.
Gielen, Marijke, Vanhorebeek, Ilse, Wouters, Pieter J., Mesotten, Dieter, Wernerman, Jan, Van den Berghe, Greet, Rooyackers, Olav, Amino acid concentrations in critically ill children following cardiac surgery*, Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies, 15, 314-28, 2014	Population not relevant - aged <1 years.
Glynn, A., Barr, S., Lewis, A., Tuthill, D. P., A national audit of parenteral nutrition practise in uk neonatal intensive care units: Is practise consistent with guidelines?, Archives of Disease in Childhood: Education and Practice Edition, 98, A30-A31, 2013	Not a relevant review.
Grande, E., Infante, L., Pomero, G., Dogliani, E., Isoardo, A., Mondini, M., Perlo, G., Gancia, P., Abrate, M., Ferrero, M. M., The use of a different amino acid solution in total parenteral nutrition mixtures for critical newborns, European Journal of Hospital Pharmacy, 21, A157-A158, 2014	Conference abstract.
Gravari, E., Radmacher, P. G., Adamkin, D. H., Myers, S. R., Amino acid profiles and serial blood urea nitrogen levels in infants less than 1250 g receiving early parenteral nutrition, Journal of Neonatal-Perinatal Medicine, 5, 149-153, 2012	Non-RCT.
Green, J., McGowan, P., Hyperalimentation and electrolyte requirements in very preterm infants: A randomised controlled parenteral nutrition study, Archives of Disease in Childhood: Fetal and Neonatal Edition, 99, A6, 2014	Conference abstract.
Green, J., McGowan, P., Morgan, C., Hyperalimentation and electrolyte requirements	Conference abstract. Outcomes not relevant.

Study	Reason for Exclusion
in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood, 99, A58, 2014	
Guellec, I., Gascoin, G., Beuchee, A., Boubred, F., Tourneux, P., Ramful, D., Zana-Taieb, E., Baud, O., Biological Impact of Recent Guidelines on Parenteral Nutrition in Preterm Infants, Journal of Pediatric Gastroenterology & Nutrition, 61, 605-9, 2015	No relevant studies.
Hata, S., Kubota, A., Okada, A., A pediatric amino acid solution for total parenteral nutrition does not affect liver function test results in neonates, Surgery Today, 32, 800-803, 2002	Study does not match eligibility criteria - no relevant outcomes reported.
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.
Hay, W. W., Thureen, P., Protein for preterm infants: how much is needed? How much is enough? How much is too much?, Pediatrics and Neonatology, 51, 198-207, 2010	Narrative review.
Hay, William W., Jr., Strategies for feeding the preterm infant, Neonatology, 94, 245-54, 2008	Narrative review.
Hay, William W., Jr., Intravenous nutrition of the very preterm neonate, Acta paediatrica (Oslo, Norway : 1992). Supplement, 94, 47-56, 2005	Narrative review.
Hays, D. M., Kaplan, M. S., Mahour, G. H., Strauss, J., Huxtable, R. F., High-calorie infusion therapy following surgery in low-birth-weight infants: metabolic problems encountered, Surgery, 71, 834-41, 1972	Full text is not available.
Heird, W. C., Amino acids in pediatric and neonatal nutrition, Current Opinion in Clinical Nutrition and Metabolic Care, 1, 73-78, 1998	Narrative review.
Heird, W. C., Anderson, T. L., Nutritional requirements and methods of feeding low birth weight infants, Current problems in pediatrics, 7, 1-40, 1977	Narrative review.
Heird, W. C., Driscoll, J. M., Jr., Schullinger, J. N., Grebin, B., Winters, R. W., Intravenous alimentation in pediatric patients, The Journal of pediatrics, 80, 351-72, 1972	Narrative review.
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	Non-RCT.
Heird, W. C., Winters, R. W., Total intravenous alimentation, American journal of diseases of children (1960), 126, 287-9, 1973	Narrative review.
Helms, R. A., Chesney, R. W., Storm, M. C., Sulfur amino acid metabolism in infants on parenteral nutrition, Clinical Nutrition, 14, 381-387, 1995	Non-RCT.
Helms, R. A., Christensen, M. L., Mauer, E. C., Storm, M. C., Comparison of a pediatric versus standard amino acid formulation in preterm	Non-RCT.

Study	Reason for Exclusion
neonates requiring parenteral nutrition, Journal of Pediatrics, 110, 466-470, 1987	
Helmuth, W. V., Adam, P. A., Sweet, A. Y., The effects of protein hydrolysate-monosaccharide infusion on low-birth-weight infants, The Journal of pediatrics, 81, 129-36, 1972	Case series; no comparison group.
Hermanussen, M., Tresguerres, J. A. F., How much glutamate is toxic in paediatric parenteral nutrition?, Acta paediatrica (Oslo, Norway : 1992), 94, 16-9, 2005	Narrative review.
Heyman, M. B., General and specialized parenteral amino acid formulations for nutrition support, Journal of the American Dietetic Association, 90, 401-411, 1990	Narrative review.
Hirai, Y., Kubo, M., Nakamura, K., Imai, T., Hasegawa, S., Parenteral nutrition in pediatrics: evaluation in amino acid metabolism for the composition of infusates, Acta chirurgica Scandinavica. Supplementum, 466, 8-9, 1976	Unavailable.
Ho, Man-Yau, Yen, Y. u-Hsuan, Hsieh, Mao-Chih, Chen, Hsiang-Yin, Chien, Shu-Chen, Hus-Lee, Shing-Mei, Early versus late nutrition support in premature neonates with respiratory distress syndrome, Nutrition (Burbank, Los Angeles County, Calif.), 19, 257-60, 2003	Retrospective study.
Hong, L., Gu, Y., Feng, Y., Stability assessment of neonatal total nutrition admixture with various amino acid concentration, Journal of Pediatric Gastroenterology and Nutrition, 64, 873, 2017	Non-RCT.
Hopewell, J., Miletin, J., Parenteral nutrition in very low birth weight infants in the United Kingdom and Ireland, Irish Medical Journal, 105, 2012	No relevant outcomes.
Hornchen, H., Neubrand, W., Amino acids for parenteral nutrition in premature and newborn infants. Use of a mother's milk-adapted solution, JPEN. Journal of parenteral and enteral nutrition, 4, 294-299, 1980	Narrative review.
House, J. D., Pencharz, P. B., Ball, R. O., Glutamine supplementation to total parenteral nutrition promotes extracellular fluid expansion in piglets, The Journal of nutrition, 124, 396-405, 1994	Population not relevant; animals.
House, J. D., Thorpe, J. M., Wykes, L. J., Pencharz, P. B., Ball, R. O., Evidence that phenylalanine hydroxylation rates are overestimated in neonatal subjects receiving total parenteral nutrition with a high phenylalanine content, Pediatric Research, 43, 461-466, 1998	Population not relevant; animals.
Hsiao, Chien-Chou, Tsai, Ming-Luen, Chen, Chih-Chen, Lin, Hung-Chih, Early optimal nutrition improves neurodevelopmental outcomes for very preterm infants, Nutrition reviews, 72, 532-40, 2014	Narrative review.

Study	Reason for Exclusion
Huston, R. K., Christensen, J. M., Alshahrani, S. M., Mohamed, S. M., Clark, S. M., Nason, J. A., Wu, Y. X., Calcium chloride in neonatal parenteral nutrition solutions with and without added cysteine: Compatibility studies using laser and micro-flow imaging methodology, PLoS ONE, 10, e0136894, 2015	Intervention not relevant.
Iacobelli, S., Viaud, M., Lapillonne, A., Robillard, P. Y., Gouyon, J. B., Bonsante, F., Kollen, L., Akbaraly, T., Menguy, A. C., Astruc, D., Dillenseger, C., Auburtin, B., Bauvin, I., Bedu, A., Benababdelmalek, F., Blasquez, A., Nelson, J. R., Boubred, F., Bruel, H., Moursie, J., Cambonie, G., Masson, F., Carbonnier, M., De Luca, D., Mokraoui, F., Romain, O., Dumont, B., Francoise, M., Labaste, A., Guerreiro, J., Hodonou, J., Husseini, K., Jarraud, P. H., Madelenau, D., Jouvencel, P., Klosowski, S., Komlan, D., Mirc, M., Pognon, L., Storme, L., Ramful, D., Rousseau, S., Semama, D., Vintejoux, A., Varela, C., Nutrition practice, compliance to guidelines and postnatal growth in moderately premature babies: The NUTRIQUAL French survey, BMC Pediatrics, 15 (1) (no pagination), 2015	Survey of feeding practices (PN and EN). Composition of PN unclear.
Imura, K., Okada, A., Fukui, Y., Kawahara, H., Yagi, M., Kubota, A., Kanaya, S., Kamata, S., Nagata, Y., Clinical studies on a newly devised amino acid solution for neonates, JPEN. Journal of parenteral and enteral nutrition, 12, 496-504, 1988	Non-RCT.
Jadhav, P., Parimi, P. S., Kalhan, S. C., Parenteral amino acid and metabolic acidosis in premature infants, Jpen, Journal of parenteral and enteral nutrition. 31, 278-83, 2007	Cohort study.
Jakobsen, Marianne Skytte, Jorgensen, Marianne Horby, Husby, Steffen, Andersen, Leis, Jeppesen, Palle Bekker, Low-fat, high-carbohydrate parenteral nutrition (PN) may potentially reverse liver disease in long-term PN-dependent infants, Digestive diseases and sciences, 60, 252-9, 2015	Cohort study with no comparison arm. Included infants not relevant to protocol (>28 weeks of age).
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	Combination treatment for amino acids and lipids - similar lipid regimen for both treatment groups; non-RCT.
Johnson, J. D., Albritton, W. L., Sunshine, P., Hyperammonemia accompanying parenteral nutrition in newborn infants, The Journal of pediatrics, 81, 154-61, 1972	No comparison treatment group.
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	AA dosages were the same for both groups. - none of the outcomes of interest were assessed.

Study	Reason for Exclusion
Joosten, K. F., Verhoeven, J. J., Hazelzet, J. A., Energy expenditure and substrate utilization in mechanically ventilated children, Nutrition (Burbank, Los Angeles County, Calif.), 15, 444-8, 1999	Topic not relevant.
Jordan, I, Balaguer, M, Esteban, Me, Cambra, Fj, Felipe, A, Hernández, L, Alsina, L, Molero, M, Villaronga, M, Esteban, E, Glutamine effects on heat shock protein 70 and interleukines 6 and 10: randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children, Clinical nutrition (Edinburgh, Scotland), 35, 34-40, 2016	Population not relevant; median age 4.21 years and 5.27 years.
Kadrofske, M. M., Parimi, P. S., Gruca, L. L., Kalhan, S. C., Effect of intravenous amino acids on glutamine and protein kinetics in low-birth-weight preterm infants during the immediate neonatal period, American Journal of Physiology - Endocrinology and Metabolism, 290, E622-E630, 2006	Study does not match eligibility criteria - relevant outcomes are not reported.
Kaemmer, A., Miller, J. D., Hyperalimentation in infancy. Experiences at the Maine Medical Center, The Journal of the Maine Medical Association, 63, 200-passim, 1972	General review.
Kalhan, S. C., Edmison, J. M., Effect of intravenous amino acids on protein kinetics in preterm infants, Current Opinion in Clinical Nutrition and Metabolic Care, 10, 69-74, 2007	Narrative review.
Kalhan, S. C., Parimi, P. S., Transamination of leucine and nitrogen accretion in human pregnancy and the newborn infant, Journal of Nutrition, 136, 281S-287S, 2006	Narrative review.
Kalhan, S. C., Parimi, P. S., Gruca, L. L., Hanson, R. W., Glutamine supplement with parenteral nutrition decreases whole body proteolysis in low birth weight infants, Journal of Pediatrics, 146, 642-7, 2005	No relevant outcomes.
Kalikstad, Betty, Skjerdal, Ase, Hansen, Thor Willy Ruud, Compatibility of drug infusions in the NICU, Archives of Disease in Childhood, 95, 745-8, 2010	Topic not relevant.
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	Retrospective study.
Kanaya, S., Nose, O., Harada, T., Kai, H., Ogawa, M., Maki, I., Tajiri, H., Kimura, S., Yabuuchi, H., Imura, K., Total parenteral nutrition with a new amino acid solution for infants, Journal of Pediatric Gastroenterology and Nutrition, 3, 440-5, 1984	Infants receive same dose of amino acid solutions.
Kashyap, S., Is the early and aggressive administration of protein to very low birth weight	Narrative review.

Study	Reason for Exclusion
infants safe and efficacious?, Current Opinion in Pediatrics, 20, 132-136, 2008	
Kelleher, A. S., Clark, R. H., Steinbach, M., Chace, D. H., Spitzer, A. R., The influence of amino-acid supplementation, gestational age and time on thyroxine levels in premature neonates, Journal of Perinatology, 28, 270-274, 2008	No relevant outcomes provided in the article - study examines thyroxine levels.
Keshen, T. H., Miller, R. G., Jahoor, F., Jaksic, T., Stable isotopic quantitation of protein metabolism and energy expenditure in neonates on- and post-extracorporeal life support, Journal of pediatric surgery, 32, 958-3, 1997	Infants received similar PN regimens.
Kilani, R. A., Cole, F. S., Bier, D. M., Phenylalanine hydroxylase activity in preterm infants: Is tyrosine a conditionally essential amino acid?, American Journal of Clinical Nutrition, 61, 1218-1223, 1995	Non-RCT.
Kirk, E. L., Audit to determine whether current parenteral nutrition regimens for pre-term infants on the neonatal unit are in accordance with international guidelines, Archives of Disease in Childhood, 94, e2, 2009	Study design not relevant; audit.
Koksal, N., Batci, O., Ozkan, H., Dotan, P., Varal, I., Role of c-reactive protein, procalcitonin and serum amiloid a as early detecting markers of total parenteral nutrition induced cholestasis in premature infants, Journal of Maternal-Fetal and Neonatal Medicine, 27, 338, 2014	Conference abstract. Combined treatment lipids and protein.
Kotsopoulos, K., Benadiba-Torch, A., Cuddy, A., Shah, P. S., Safety and efficacy of early amino acids in preterm <28 weeks gestation: Prospective observational comparison, Journal of Perinatology, 26, 749-754, 2006	Cohort study.
Kraus, H., Stubbe, P., Von Berg, W., Effects of arginine infusion in infants: increased urea synthesis associated with unchanged ammonia blood levels, Metabolism: Clinical and Experimental, 25, 1241-1247, 1976	Narrative review.
Kubota, A., Okada, A., Nezu, R., Kamata, S., Imura, K., Takagi, Y., Hyperbilirubinemia in neonates associated with total parenteral nutrition, Journal of Parenteral and Enteral Nutrition, 12, 602-606, 1988	No relevant outcomes not reported by PN regimen.
Kulkarni, Sakil, Mercado, Velma, Rios, Mirta, Arboleda, Richard, Gomara, Roberto, Muinos, William, Reeves-Garcia, Jesse, Hernandez, Erick, Breast milk is better than formula milk in preventing parenteral nutrition-associated liver disease in infants receiving prolonged parenteral nutrition, Journal of Pediatric Gastroenterology and Nutrition, 57, 383-8, 2013	Comparisons not relevant to protocol - breast milk vs formula-feeding.
Kumpf, V. J., Parenteral nutrition-associated liver disease in adult and pediatric patients, Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition, 21, 279-290, 2006	Narrative review.

Study	Reason for Exclusion
Lacey, J. M., Crouch, J. B., Benfell, K., Ringer, S. A., Wilmore, C. K., Maguire, D., Wilmore, D. W., The effects of glutamine-supplemented parenteral nutrition in premature infants, Jpen: Journal of Parenteral & Enteral Nutrition, 20, 74-80, 1996	Doesn't address AA.
Lai, Nai Ming, Ahmad, Kamar Azanna, Choo, Yao Mun, Kong, Juin Yee, Ngim, Chin Fang, Fluid supplementation for neonatal unconjugated hyperbilirubinaemia, Cochrane Database of Systematic Reviews, 2017	Fluid supplementation.
Lai, Nai Ming, Rajadurai, Samuel V, Tan, Kenneth, Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/chronic lung disease, Cochrane Database of Systematic Reviews, 2006	Cochrane review - no relevant studies identified; 2 excluded studies provided insight into formula feeds.
Laine, L., Shulman, R. J., Pitre, D., Lifschitz, C. H., Adams, J., Cysteine usage increases the need for acetate in neonates who receive total parenteral nutrition, American Journal of Clinical Nutrition, 54, 565-567, 1991	Non-RCT.
Lee, H. J., Choi, C. W., Blood urea nitrogen concentration during early and aggressive parental amino acid administration in extremely low birth weight infants, Archives of Disease in Childhood, 97, A396, 2012	Cohort study.
Leenders, Erika K. S. M., de Waard, Marita, van Goudoever, Johannes B., Low- versus High-Dose and Early versus Late Parenteral Amino-Acid Administration in Very-Low-Birth-Weight Infants: A Systematic Review and Meta-Analysis, Neonatology, 113, 187-205, 2018	Review. No new studies identified.
Li, Zheng-hong, Wang, Dan-hua, Dong, Mei, Effect of parenteral glutamine supplementation in premature infants, Chinese medical journal, 120, 140-4, 2007	Cohort study.
Lindblad, B. S., Gardiner, R. M., Holmgren, A., Amino acid supply to the infant in different regimens of parenteral nutrition, Acta chirurgica Scandinavica. Supplementum, 498, 61-6, 1980	Review (speech) only.
Liu, Zj, Liu, Gs, Chen, Yg, Zhang, Hl, Wu, Xf, [Value of early application of different doses of amino acids in parenteral nutrition among preterm infants], Zhongguo dang dai er ke za zhi = Chinese journal of contemporary pediatrics, 17, 53-7, 2015	Non-English publication.
Loui, Andrea, Buhrer, Christoph, Growth of very low birth weight infants after increased amino acid and protein administration, Journal of Perinatal Medicine, 41, 735-41, 2013	Non-RCT.
Mahaveer, A., Grime, C., Morgan, C., Increasing early protein intake is associated with a reduction in insulin-treated hyperglycaemia in very preterm infants, Archives of Disease in Childhood: Fetal and Neonatal Edition, 96, 2011	Audit.

Study	Reason for Exclusion
Mahaveer, A., Grime, C., Morgan, C., Increasing early protein intake is associated with a reduction in insulin-treated hyperglycemia in very preterm infants, Nutrition in Clinical Practice, 27, 399-405, 2012	Not an RCT.
Maldonado, J., Faus, M. J., Bayes, R., Molina, J. A., Gil, A., Apparent nitrogen balance and 3-methylhistidine urinary excretion in intravenously fed children with trauma and infection, European journal of clinical nutrition, 42, 93-100, 1988	Non-RCT.
Mayes, K., Tan, M., Morgan, C., Effect of hyperalimentation and insulin-treated hyperglycemia on tyrosine levels in very preterm infants receiving parenteral nutrition, Jpen: Journal of Parenteral & Enteral Nutrition, 38, 92-8, 2014	Outcomes not relevant.
McIntosh, N., Crockford, H., Portnoy, S., Berger, M., Outcome at three years of sick neonates involved in a double-blind trial of two parenteral amino acid preparations, Developmental Medicine and Child Neurology, 37, 221-5, 1995	AA dosages unclear; <50 infants (n=50 specified in protocol for neurodevelopment studies). Didn't address outcomes of interest.
McIntosh, N., Mitchell, V., A clinical trial of two parenteral nutrition solutions in neonates, Archives of Disease in Childhood, 65, 692-9, 1990	Study does not match eligibility criteria - comparisons do not match those specified in the protocol. Vamin 9 glucose was compared to MB233G. Outcomes examined were the tolerance of the preparation, in addition to intravenous and oral nitrogen, amino acid, energy, and volume intakes.
Minoli, I., Raiha, N. C., Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: A randomized, controlled trial, Pediatrics, 121, 655-656, 2008	Commentary.
Moe, K., Beck-Nielsen, S. S., Lando, A., Greisen, G., Zachariassen, G., Administering different levels of parenteral phosphate and amino acids did not influence growth in extremely preterm infants, Acta Paediatrica, International Journal of Paediatrics, 104, 894-899, 2015	Cohort study.
Moe-Byrne, Thirimon, Brown, Jennifer V. E., McGuire, William, Glutamine supplementation to prevent morbidity and mortality in preterm infants, The Cochrane database of systematic reviews, 4, CD001457, 2016	Glutamine supplementation vs no glutamine supplementation.
Mohamad Ikram, I., Quah, B. S., Noraida, R., Djokomuljanto, S., Faris Irfan, C. Y., Van Rostenberghe, H., A randomised controlled trial of glutamine-enriched neonatal parenteral nutrition in Malaysia, Singapore medical journal, 52, 356-60, 2011	Comparison not relevant glutamine supplementation vs no glutamine supplementation.
Morgan, C., Burgess, L., High protein intake does not prevent low plasma levels of conditionally essential amino acids in very preterm infants receiving parenteral nutrition,	Study does not match eligibility criteria. Follow-up study of Morgan 2014 and no relevant outcomes are reported. Plasma AA profiles are compared.

Study	Reason for Exclusion
Journal of Parenteral and Enteral Nutrition, 41, 455-462, 2017	
Morgan, C., Mahaveer, A., Grime, C., Increasing early protein intake is associated with a reduction in the incidence of insulin-treated hyperglycaemia in very preterm infants, Journal of Pediatric Gastroenterology and Nutrition, 52, E12-E13, 2011	Non-RCT.
Morgan, C., McGowan, P., Burgess, L., Tan, M., Mayes, K., Hyperalimentation using current UK parenteral amino acid formulations does not prevent low plasma arginine levels in very preterm infants, Archives of Disease in Childhood, 99, A30, 2014	Conference abstract.
Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Preventing early postnatal head growth failure in very preterm infants: The randomised controlled scamp nutrition study, Archives of Disease in Childhood: Education and Practice Edition, 98, 2013	Conference abstract.
Morgan, C., McGowan, P., Herwitker, S., Hart, A. E., Turner, M. A., Early postnatal head growth in very preterm infants: The randomised controlled scamp nutrition study, Journal of Neonatal-Perinatal Medicine, 6, 197, 2013	Conference abstract.
Morgan, C., Parry, S., Tan, M., Neurodevelopmental outcome in very preterm infants randomised to receive two different parenteral nutrition regimens: The scamp nutrition study, European Journal of Pediatrics, 175, 1516-1517, 2016	Conference abstract.
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, Colin, Burgess, Laura, High Protein Intake Does Not Prevent Low Plasma Levels of Conditionally Essential Amino Acids in Very Preterm Infants Receiving Parenteral Nutrition, JPEN. Journal of parenteral and enteral nutrition, 41, 455-462, 2017	No relevant outcomes - plasma amino acid levels.
Murdock, N., Crighton, A., Nelson, L. M., Forsyth, J. S., Low birthweight infants and total parenteral nutrition immediately after birth. II. Randomised study of biochemical tolerance of intravenous glucose, amino acids, and lipid, Archives of disease in childhood. Fetal and neonatal edition, 73, F8-12, 1995	Comparisons not relevant to protocol.

Study	Reason for Exclusion
Ogata, E. S., Boehm, J. J., Deddish, R. B., Wiringa, K. S., Yanagi, R. B., Bussey, M. E., Clinical trial of a 6.5% amino acid infusion in appropriate-for-gestational-age premature neonates, Acta chirurgica Scandinavica. Supplementum, 517, 39-48, 1983	Study does not match eligibility criteria - compares two amino acid solutions; Neopham VS Aminosyn.
Ohnishi, S., Ichiba, H., Tanaka, Y., Harada, S., Matsumura, H., Kan, A., Asada, Y., Shintaku, H., Early and intensive nutritional strategy combining parenteral and enteral feeding promotes neurodevelopment and growth at 18 months of corrected age and 3 years of age in extremely low birth weight infants, Early Human Development, 100, 35-41, 2016	Cohort study.
Ohnishi, Satoshi, Ichiba, Hiroyuki, Tanaka, Yuko, Harada, Sayaka, Matsumura, Hisako, Kan, Ayako, Asada, Yuki, Shintaku, Haruo, Early and intensive nutritional strategy combining parenteral and enteral feeding promotes neurodevelopment and growth at 18months of corrected age and 3years of age in extremely low birth weight infants, Early Human Development, 100, 35-41, 2016	Not an RCT.
O'Neill, J. A., Caldwell, M. D., Meng, H. C., Otten, A., Stahlman, M. T., Use of a 10% l-amino acid solution with glucose in pediatric parenteral nutrition, Acta chirurgica Scandinavica. Supplementum, 466, 106-7, 1976	Not available.
Ong, E. G. P., Eaton, S., Wade, A. M., Horn, V., Losty, P. D., Curry, J. I., Sugarman, I. D., Klein, N. J., Pierro, A., Randomized clinical trial of glutamine-supplemented versus standard parenteral nutrition in infants with surgical gastrointestinal disease, British Journal of Surgery, 99, 929-938, 2012	Infants >28 weeks; glutamine supplementation vs no glutamine supplementation.
Osborn, D. A., Bolisetty, S., Jones, L. J., Sinn, J. K. H., Systematic review of higher versus lower amino acid intake in parenteral nutrition for newborn infants, Journal of Paediatrics and Child Health, 52, 58, 2016	Conference abstract.
Osborn, D. A., Schindler, T., Jones, L. J., Sinn, J. K. H., Bolisetty, S., Higher versus lower amino acid intake in parenteral nutrition for newborn infants, Cochrane Database of Systematic Reviews, 2018, CD005949, 2018	Includes some comparisons that are not relevant - amino acid versus no amino acid.
Ozlu, F., Yapicioglu, P. H., Mer, K., Satar, M., Narli, N., Sertdemir, Y., The effect of two different parenteral nutrition regimens on parenteral nutrition-associated cholestasis, Journal of Maternal-Fetal and Neonatal Medicine, 26, 724-727, 2013	Study does not match eligibility criteria - retrospective study.
Parimi, P. S., Kadrofske, M. M., Gruca, L. L., Hanson, R. W., Kalhan, S. C., Amino acids, glutamine, and protein metabolism in very low birth weight infants, Pediatric Research, 58, 1259-1264, 2005	Intervention not relevant; short-term infusion with crossover design.

Study	Reason for Exclusion
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	Cohort study.
Piedboeuf, B., Chessex, P., Hazan, J., Pineault, M., Lavoie, J. C., Total parenteral nutrition in the newborn infant: Energy substrates and respiratory gas exchange, Journal of Pediatrics, 118, 97-102, 1991	Dose not address AA.
Pildes, R. S., Wong, P. W., Plasma insulin in intravenous glucose and amino acid infusion, The New England journal of medicine, 288, 914-5, 1973	Not available.
Pillai, Anish, Albersheim, Susan, Elango, Rajavel, High-dose parenteral amino acid intake in very low birthweight infants: what is the current evidence?, Current opinion in clinical nutrition and metabolic care, 22, 236-241, 2019	Narrative review.
Pineault, M., Chessex, P., Lepage, D., Dallaire, L., Brisson, G., Qureshi, I., Total parenteral nutrition in very low birth weight infants with Travasol 10% blend C, JPEN. Journal of parenteral and enteral nutrition, 10, 296-9, 1986	Infants receive similar doses; different solution/composition. Non-RCT.
Poindexter, B. B., Ehrenkranz, R. A., Stoll, B. J., Koch, M. A., Wright, L. L., Oh, W., Papile, L. A., Bauer, C. R., Carlo, W. A., Donovan, E. F., Fanaroff, A. A., Korones, S. B., Laptook, A. R., Shankaran, S., Stevenson, D. K., Tyson, J. E., Lemons, J. A., Effect of parenteral glutamine supplementation on plasma amino acid concentrations in extremely low-birth-weight infants, American Journal of Clinical Nutrition, 77, 737-743, 2003	TrophAmine vs glutamine doses unclear at start; same amounts of cysteine hydrochloride administered to both treatment groups.
Poindexter, B. B., Ehrenkranz, R. A., Stoll, B. J., Wright, L. L., Poole, W. K., Oh, W., Bauer, C. R., Papile, L. A., Tyson, J. E., Carlo, W. A., Laptook, A. R., Narendran, V., Stevenson, D. K., Fanaroff, A. A., Korones, S. B., Shankaran, S., Finer, N. N., Lemons, J. A., Parenteral Glutamine Supplementation Does Not Reduce the Risk of Mortality or Late-Onset Sepsis in Extremely Low Birth Weight Infants, Pediatrics, 113, 1209-1215, 2004	TrophAmine vs glutamine doses unclear at start; same amounts of cysteine hydrochloride administered to both treatment groups.
Poindexter, B. B., Karn, C. A., Ahlrichs, J. A., Wang, J., Leitch, C. A., Liechty, E. A., Denne, S. C., Amino acids suppress proteolysis independent of insulin throughout the neonatal period, American Journal of Physiology - Endocrinology and Metabolism, 272, E592-E599, 1997	Non-RCT.
Polycarpou,E., Zachaki,S., Tsolia,M., Papaevangelou,V., Polycarpou,N., Briana,D.D., Gavrili,S., Kostalos,C., Kafetzis,D., Enteral L-arginine supplementation for prevention of necrotizing enterocolitis in very low birth weight	Infants receive enteral feeds; not PN.

Study	Reason for Exclusion
neonates: A double-blind randomized pilot study of efficacy and safety, Journal of Parenteral and Enteral Nutrition, 37, 617-622, 2013	
Popinska, K., Kierkus, J., Lyszkowska, M., Socha, J., Pietraszek, E., Kmiotek, W., Ksiazyk, J., Aluminum contamination of parenteral nutrition additives, amino acid solutions, and lipid emulsions, Nutrition, 15, 683-6, 1999	No relevant outcomes.
Porcelli Jr, P. J., Sisk, P. M., Increased parenteral amino acid administration to extremely low-birth-weight infants during early postnatal life, Journal of Pediatric Gastroenterology and Nutrition, 34, 174-179, 2002	Non RCT.
Radmacher, P. G., Lewis, S. L., Adamkin, D. H., Early amino acids and the metabolic response of ELBW infants (< or = 1000 g) in three time periods, Journal of perinatology : official journal of the California Perinatal Association, 29, 433-7, 2009	Retrospective study.
Raimondi, Francesco, Spera, Anna Maria, Sellitto, Maria, Landolfo, Francesca, Capasso, Letizia, Amino acid-based formula as a rescue strategy in feeding very-low-birth-weight infants with intrauterine growth restriction, Journal of Pediatric Gastroenterology and Nutrition, 54, 608-12, 2012	Study design not relevant; case-control.
Rassin, D. K., Gaull, G. E., Raiha, N. C., Heinonen, K., Milk protein quantity and quality in low-birth-weight infants. IV. Effects on tyrosine and phenylalanine in plasma and urine, The Journal of pediatrics, 90, 356-60, 1977	Intervention not relevant.
Reynolds,R.M., Bass,K.D., Thureen,P.J., Achieving positive protein balance in the immediate postoperative period in neonates undergoing abdominal surgery, Journal of Pediatrics, 152, 63-67, 2008	Study design not relevant; non-random allocation.
Rhodes, P. G., Reddy, N. S., Downing, G., Carlson, S. E., Effects of different levels of intravenous alpha-linolenic acid and supplemental breast milk on red blood cell docosahexaenoic acid in very low birth-weight infants, Journal of Pediatric Gastroenterology & Nutrition, 13, 67-71, 1991	No relevant outcomes.
Rivera, A., Jr., Bell, E. F., Bier, D. M., Effect of intravenous amino acids on protein metabolism of preterm infants during the first three days of life, Pediatric Research, 33, 106-11, 1993	Glucose vs glucose plus amino acids; glucose dosage unclear. No outcomes of interest reported.
Rivera, A., Jr., Bell, E. F., Stegink, L. D., Ziegler, E. E., Plasma amino acid profiles during the first three days of life in infants with respiratory distress syndrome: effect of parenteral amino acid supplementation, The Journal of pediatrics, 115, 465-8, 1989	Glucose vs glucose plus amino acids; unclear glucose dosage.
Roberts, S. A., Ball, R. O., Filler, R. M., Moore, A. M., Pencharz, P. B., Phenylalanine and tyrosine metabolism in neonates receiving	Intervention not relevant.

Study	Reason for Exclusion
parenteral nutrition differing in pattern of amino acids, Pediatric research, 44, 907-14, 1998	
Roberts, S. A., Ball, R. O., Moore, A. M., Filler, R. M., Pencharz, P. B., The effect of graded intake of glycyl-L-tyrosine on phenylalanine and tyrosine metabolism in parenterally fed neonates with an estimation of tyrosine requirement, Pediatric research, 49, 111-9, 2001	Study does not match eligibility criteria - relevant outcomes specified in the protocol are not reported.
Rosenthal, M., Sinha, S., Laywood, E., Levene, M., A double blind comparison of a new paediatric amino acid solution in neonatal total parenteral nutrition, Early human development, 15, 137-46, 1987	Intervention not relevant; infants received similar dosages.
Rubecz, I., Mestyan, J., Energy metabolism and intravenous nutrition of premature infants. I. The responses of oxygen consumption, respiratory quotient and substrate utilization to infusion of aminosol-glucose, Biology of the Neonate, 23, 45-58, 1973	Combination treatment.
Sann, L., Ruitton, A., Mathieu, M., Bourgeois, J., Genoud, J., Effect of intravenous L-alanine administration on plasma glucose, insulin and glucagon, blood pyruvate, lactate and beta-hydroxybutyrate concentrations in newborn infants. Study in term and preterm newborn infants, Acta Paediatrica Scandinavica, 67, 297-302, 1978	Non-RCT. Intervention not relevant.
Savich, R. D., Finley, S. L., Ogata, E. S., Intravenous lipid and amino acids briskly increase plasma glucose concentrations in small premature infants, American journal of perinatology, 5, 201-5, 1988	Lipid vs lipid plus amino acids; lipid infusion at same dosage.
Schroder, H., Paust, H., Plasma amino acids in supplementary parenteral nutrition of preterm infants. Effect of different quantities of amino acid infusion and comparison with enteral feeding, Acta Paediatrica Scandinavica, 75, 302-7, 1986	Non-RCT.
Shah, P., Shah, V., Arginine supplementation for prevention of necrotising enterocolitis in preterm infants, Cochrane Database of Systematic Reviews, (3), 2007	Cochrane review - studies compare L-arginine, arginine or glutamine vs placebo or no treatment.
Soghier, L. M., Brion, L. P., Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates, The Cochrane database of systematic reviews, CD004869, 2006	Intervention not relevant.
Stein, J., Boehles, H. J., Blumenstein, I., Goeters, C., Schulz, R., Amino acids - Guidelines on Parenteral Nutrition, Chapter 4, German medical science : GMS e-journal, 7, 2009	Non-RCT.
Struijs, Mc, Schaible, T, Elburg, Rm, Debauche, C, Beest, H, Tibboel, D, Efficacy and safety of a parenteral amino acid solution containing alanyl-glutamine versus standard solution in infants: a first-in-man randomized double-blind trial,	Similar dose/regimens used for both intervention groups.

Study	Reason for Exclusion
Clinical nutrition (Edinburgh, Scotland), 32, 331-7, 2013	
Tan, M., Abernethy, L., Cooke, R., Improving head growth in preterm infants - A randomised controlled trial II: MRI and developmental outcomes in the first year, Archives of Disease in Childhood: Fetal and Neonatal Edition, 93, f342-f346, 2008	Hyperalimented vs standard PN; different doses of dextrose, protein and fat per day.
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.
te Braake, Frans W. J., van den Akker, Chris H. P., Wattimena, Darcos J. L., Huijmans, Jan G. M., van Goudoever, Johannes B., Amino acid administration to premature infants directly after birth, The Journal of pediatrics, 147, 457-61, 2005	Outcomes not reported in sufficient detail for analysis.
te Braake, F. W. J., Schierbeek, H., De Groof, K., Vermes, A., Longini, M., Buonocore, G., Van Goudoever, J. B., Glutathione synthesis rates after amino acid administration directly after birth in preterm infants, American Journal of Clinical Nutrition, 88, 333-339, 2008	Study does not match eligibility criteria - dextrose only compared to dextrose plus amino acids.
Thakur, A., Kansal, B. K., Saini, A., Kler, N., Garg, P., Modi, M., Soni, A., Saluja, S., Effect of aggressive versus standard nutritional regime on growth of extremely low birth weight infants-A randomized controlled trial, Journal of Pediatric Gastroenterology and Nutrition, 66, 1089, 2018	Abstract only.
Thompson,S.W., McClure,B.G., Tubman,T.R.J., A randomized, controlled trial of parenteral glutamine in ill, very low birth-weight neonates, Journal of Pediatric Gastroenterology and Nutrition, 37, 550-553, 2003	Infants received similar dosage/regimen.
Thornton, L., Griffin, E., Evaluation of a taurine containing amino acid solution in parenteral nutrition, Archives of Disease in Childhood, 66, 21-25, 1991	Non-RCT.
Thureen, P. J., Anderson, A. H., Baron, K. A., Melara, D. L., Hay, W. W., Jr., Fennessey, P. V., Protein balance in the first week of life in ventilated neonates receiving parenteral nutrition, The American journal of clinical nutrition, 68, 1128-35, 1998	No comparison group.
Thureen, P. J., Melara, D., Fennessey, P. V., Hay Jr, W. W., Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period, Pediatric Research, 53, 24-32, 2003	Study does not match eligibility criteria - outcomes not relevant or data unusable. Blood urea nitrogen concentration was measured but remained similar between groups. Degree of acidosis determined by base deficit (mean base deficit from blood gas measurements during the study were -3.4 - 0.6 versus -4.1 - 0.7 mEq/L in the LAA versus HAA intake groups, respectively).

Study	Reason for Exclusion
Torer, B., Hanta, D., Ozdemir, Z., Cetinkaya, B., Gulcan, H., An aggressive parenteral nutrition protocol improves growth in preterm infants, Turkish Journal of Pediatrics, 57, 236-241, 2015	Study does not match eligibility criteria - retrospective study.
Tubman, T. R. J., Thompson, S. W., McGuire, W., Glutamine supplementation to prevent morbidity and mortality in preterm infants, The Cochrane database of systematic reviews, CD001457, 2008	Cochrane review on glutamine supplementation; relevant references checked.
Tubman, T. R., Thompson, S. W., Glutamine supplementation for prevention of morbidity in preterm infants, The Cochrane database of systematic reviews, CD001457, 2001	Cochrane review on glutamine supplementation; relevant references checked.
Uauy,R., Mize,C., Argyle,C., McCracken,G.,Jr., Metabolic tolerance to arginine: implications for the safe use of arginine salt-aztreonam combination in the neonatal period, Journal of Pediatrics, 118, 965-970, 1991	Intervention not relevant.
Vaidya, U. V., Bhave, S. A., Pandit, A. N., Parenteral nutrition (PN) in the management of very low birth weight (VLBW) babies--a randomized controlled trial, Indian pediatrics, 32, 165-70, 1995	Study does not match eligibility criteria - PN compared to conventional intravenous fluid therapy with no AA (AA versus no AA).
Van Den Akker, C. H. P., Te Braake, F. W. J., Schierbeek, H., Rietveld, T., Wattimena, D. J. L., Bunt, J. E. H., Van Goudoever, J. B., Albumin synthesis in premature neonates is stimulated by parenterally administered amino acids during the first days of life, American Journal of Clinical Nutrition, 86, 1003-1008, 2007	Study does not match eligibility criteria - No relevant comparison. Glucose versus glucose plus amino acids.
Van Goudoever, J. B., Sulkers, E. J., Timmerman, M., Huijmans, J. G., Langer, K., Carnielli, V. P., Sauer, P. J., Amino acid solutions for premature neonates during the first week of life: the role of N-acetyl-L-cysteine and N-acetyl-L-tyrosine, JPEN. Journal of parenteral and enteral nutrition, 18, 404-8, 1994	Interventions not relevant; different AA compositions administered at similar dosage.
van Lingen, R. A., van Goudoever, J. B., Luijendijk, I. H., Wattimena, J. L., Sauer, P. J., Effects of early amino acid administration during total parenteral nutrition on protein metabolism in pre-term infants, Clinical science (London, England : 1979), 82, 199-203, 1992	Study does not match eligibility criteria - Glucose, fat and AA versus glucose and fat only (AA versus no AA).
Vanek, V. W., Matarese, L. E., Robinson, M., Sacks, G. S., Young, L. S., Kochevar, M., A.S.P.E.N. position paper: Parenteral nutrition glutamine supplementation, Nutrition in Clinical Practice, 26, 479-494, 2011	Guideline.
Vanhorebeek, Ilse, Verbruggen, Sascha, Casaer, Michael P., Gunst, Jan, Wouters, Pieter J., Hanot, Jan, Guerra, Gonzalo Garcia, Vlasselaers, Dirk, Joosten, Koen, Van den Berghe, Greet, Effect of early supplemental parenteral nutrition in the paediatric ICU: a pre-planned observational study of post-randomisation treatments in the PEPaNIC trial,	Population not relevant - paediatric not neonatal.

Study	Reason for Exclusion
The Lancet. Respiratory medicine, 5, 475-483, 2017	
Vlaardingerbroek, H., Roelants, J. A., Rook, D., Dorst, K., Schierbeek, H., Vermes, A., Vermeulen, M. J., van Goudoever, J. B., van den Akker, C. H. P., Adaptive regulation of amino acid metabolism on early parenteral lipid and high-dose amino acid administration in VLBW infants - A randomized, controlled trial, Clinical Nutrition, 33, 982-990, 2014	Study does not match eligibility criteria - no outcomes of interest as specified in the protocol are reported.
Vlaardingerbroek, H., Schierbeek, H., Rook, D., Vermeulen, M. J., Dorst, K., Vermes, A., van Goudoever, J. B., van den Akker, C. H. P., Albumin synthesis in very low birth weight infants is enhanced by early parenteral lipid and high-dose amino acid administration, Clinical Nutrition, 35, 344-350, 2016	Follow-up of the RCT, Vlaardingerbroek 2013 which is already included. Study does not report any additional outcomes of interest. Amino acid intake reported as combined parenteral and enteral intake.
Vlaardingerbroek, Hester, Schierbeek, Henk, Rook, Denise, Vermeulen, Marijn J., Dorst, Kristien, Vermes, Andras, van Goudoever, Johannes B., van den Akker, Chris H. P., Albumin synthesis in very low birth weight infants is enhanced by early parenteral lipid and high-dose amino acid administration, Clinical nutrition (Edinburgh, Scotland), 35, 344-50, 2016	Outcomes not relevant - hepatic albumin synthesis.
Wang, Y., Cai, W., Tao, Y. X., Tang, Q. Y., Feng, Y., Wu, J., Glutamine supplementation in preterm infants receiving parenteral nutrition leads to an early improvement in liver function, Asia Pacific Journal of Clinical Nutrition, 22, 530-536, 2013	Starting doses of amino acids appear similar; starting at 1.0 to 1.5 g/kg/day and advanced or weaned, depending on enteral nutrition.
Weiler, Hope A., Fitzpatrick-Wong, Shirley C., Schellenberg, Jeannine M., Fair, Denise E., McCloy, Ursula R., Veitch, Rebecca R., Kovacs, Heather R., Seshia, Mary M., Minimal enteral feeding within 3 d of birth in prematurely born infants with birth weight < or = 1200 g improves bone mass by term age, The American journal of clinical nutrition, 83, 155-62, 2006	Study does not match eligibility criteria - Does not report relevant comparisons. Parenteral AA is compared with minimal enteral feeding.
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	No relevant outcomes.
Whitby, T., McGowan, P., Turner, M. A., Morgan, C., Concentrated parenteral nutrition solutions and central venous catheter complications in preterm infants, Archives of disease in childhood. Fetal and neonatal edition, 100, F250-2, 2015	Follow-up of the included RCT, Morgan 2014. Study does not match eligibility criteria - early onset sepsis reported only as percentage. Data not useable.
Wright, Kelly, Ernst, Kimberly D., Gaylord, Mark S., Dawson, Joan P., Burnette, Tara M., Increased incidence of parenteral nutrition-associated cholestasis with aminosyn PF compared to trophamine, Journal of perinatology	Retrospective study.

Study	Reason for Exclusion
: official journal of the California Perinatal Association, 23, 444-50, 2003	
Yang, J., Chang, S. S. Y., Poon, W. B., Relationship between Amino Acid and Energy Intake and Long-Term Growth and Neurodevelopmental Outcomes in Very Low Birth Weight Infants, Journal of Parenteral and Enteral Nutrition, 40, 820-826, 2016	Cohort study.
Yang, Sami, Lee, Byong Sop, Park, Hye-Won, Choi, Yong-Sung, Chung, Sung-Hoon, Kim, Ji-Hee, Kim, Ellen Ai-Rhan, Kim, Ki-Soo, Effect of high vs standard early parenteral amino acid supplementation on the growth outcomes in very low birth weight infants, JPEN. Journal of parenteral and enteral nutrition, 37, 327-34, 2013	Non-RCT.
Yip, L., Dart, R. C., Hurlbut, K. M., Intravenous administration of oral N-acetylcysteine, Critical Care Medicine, 26, 40-3, 1998	Non-RCT.
Zarif, M. A., Pildes, R. S., Szanto, P. B., Vidyasagar, D., Cholestasis associated with administration of L-amino acids and dextrose solutions, Biology of the Neonate, 29, 66-76, 1976	Not an RCT.
Zlotkin, S. H., Anderson, G. H., Sulfur balances in intravenously fed infants: Effects of cysteine supplementation, American Journal of Clinical Nutrition, 36, 862-867, 1982	Intervention not relevant.
Zlotkin, S. H., Buchanan, B. E., Amino acid intake and urinary zinc excretion in newborn infants receiving total parenteral nutrition, The American journal of clinical nutrition, 48, 330-4, 1988	Cohort study.

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:

What is the optimal target dosage for amino acids in preterm and term babies who are receiving parenteral nutrition and neonatal care?

What is the optimal way (starting dose and approach to increment, if employed) to achieve this target dosage for amino acids?

No research recommendation was made for this review. [TBC]