# Higher versus lower protein intake in formula-fed low birth weight infants (Review)

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[Intervention Review]

# Higher versus lower protein intake in formula-fed low birth weight infants

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## ABSTRACT

### Background

The ideal quantity of dietary protein for formula-fed low birth weight infants < 2.5 kilograms is still a matter of controversy and debate. In premature infants, the protein intake must be sufficient to achieve normal growth without negative effects such as acidosis, uremia, and elevated levels of circulating amino acids (e.g. phenylalanine levels). This systematic review evaluates the benefits and risks of higher (>= 3.0 g/kg/day) versus lower (< 3.0 g/kg/day) protein intakes during the initial hospital stay of formula-fed preterm infants < 2.5 kilograms.

### Objectives

To determine whether higher (>= 3.0 g/kg/day) versus lower (< 3.0 g/kg/day) protein intakes during the initial hospital stay of formula-fed preterm infants < 2.5 kilograms result in improved growth and neurodevelopmental outcomes without evidence of short and long-term morbidity.

### Search strategy

Two review authors searched MEDLINE (1966 - May 2005), CINAHL (1982 - May 2005), PubMed (1966 - May 2005), EMBASE (1980 - May 2005), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2005), abstracts, conferences and symposia proceedings from Society of Pediatric Research, and American Academy of Pediatrics. Cross references were reviewed independently for additional relevant titles and abstracts for articles up to fifty years old.

### Selection criteria

Randomized controlled trials contrasting levels of formula protein intakes as low (< 3.0 g/kg/day), high (=> 3.0 g/kg/day but < 4.0 g/kg/day), or very high protein intake (=> 4.0 g/kg/day) during hospitalization of neonates less than 2.5 kilograms at birth who were formula-fed. Studies were not included if infants received partial parenteral nutrition during the study period or were fed formula as a supplement to human milk. Given the small number of studies that met all inclusion criteria, studies in which nutrients other than protein also varied (> 10% relative difference) were added in a post-facto analysis.

**Data collection and analysis**

Two review authors used standard methods of the Cochrane Collaboration and of the Cochrane Neonatal Review Group to independently assess trial eligibility and quality, and extracted data. In a 3-arm trial where two groups fell within the same predesignated protein intake group, weighted means and pooled standard deviations were calculated.

**Main results**

The literature search identified 37 studies, of which five met all the inclusion criteria. All five studies compared low (< 3.0 g/kg/day) to high protein intakes (=> 3.0 g/kg/day but < 4.0 g/kg/day). The overall analysis revealed an improved weight gain (WMD 2.36 g/kg/day, 95% CI 1.31, 3.40) and higher nitrogen accretion (WMD 143.7 mg/kg/day, 95% CI 128.7, 158.8) in infants receiving formula with higher protein content while other nutrients were kept constant. None of the studies reported IQ or Bayley scores at 18 months or later. No significant differences were seen in rates of necrotizing enterocolitis, sepsis or diarrhea.

Of three studies included in the post-facto analysis, only one could be included in the meta-analysis. The post-facto analysis revealed further improvement in all growth parameters in infants receiving formula with higher protein content (weight gain: WMD 2.53 g/kg/day, 95% CI 1.62, 3.45, linear growth: WMD 0.16 cm/week, 95% CI 0.03, 0.30, and head growth: WMD 0.23, 95% CI 0.12, 0.35). There was no significant difference (WMD 0.25, 95% CI -0.20, 0.70) in the concentration of plasma phenylalanine between the high and low protein intake groups. One study (Goldman 1969) in the post-facto analysis documented a significantly increased incidence of low IQ scores, below 90, in infants of birth weight less than 1300 grams who received a very high protein intake (6 to 7.2 g/kg/day).

**Authors' conclusions**

This systematic review suggests that higher protein intake (=> 3.0 g/kg/day but < 4.0 g/kg/day) from formula accelerates weight gain. Based on increased nitrogen accretion rates, this most likely indicates an increase in lean body mass. Although accelerated weight gain is considered to be a positive effect, increase in other outcome measures examined may represent a negative or ambivalent effect. These include elevated blood urea nitrogen levels and increased metabolic acidosis. Limited information was available regarding the impact of higher formula protein intakes on long term outcomes such as neurodevelopmental abnormalities. As determined in this review, existing research literature on this topic is not adequate to make specific recommendations regarding the provision of very high protein intake (> 4.0 g/kg/day) from formula.

## PLAIN LANGUAGE SUMMARY

**Higher versus lower protein intake in formula-fed low birth weight infants**

Dietary protein is needed for normal growth and development. The protein intake required for growth of the low birth weight infant has been estimated by the growth rate of the fetus to be 3.5 to 4 g/kg/day. Controlling the amount is particularly important in low birth-weight babies (less than 2.5 kg) fed with formula. Too much protein can raise blood urea and amino acid (phenylalanine) levels and cause metabolic acidosis, which may harm neurodevelopment. Too low protein intakes may limit the growth of these infants. The review authors searched the medical literature to identify studies that compared protein intakes: between 3 and 4.0 g of protein per kg of infant body weight in a day versus less than 3.0 g/kg/day or greater than 4.0 g/kg/day by low birth-weight infants fed on formula during their initial hospital stay. Increased protein intake resulted in a greater weight gain of around 2 g/kg/day. Based on increased body incorporation of nitrogen, this was associated with increased lean body mass. The present conclusion was based on five studies changing only the protein content of the formula and supported by three additional studies that also made changes in other nutrients. There was no significant difference in the concentration of plasma phenylalanine between infants fed with high or low protein content formula. The differences in protein content among comparison groups in some of the individual trials were small and the formulas differed substantially across studies; some studies included healthier and more mature premature infants. The study periods varied from eight days to two years so there was limited information on long-term outcomes. Existing research is not adequate to make specific recommendations regarding formula with protein content more than 4.0 g/kg/day.

## BACKGROUND

Good nutrition is essential for optimal growth and development in the preterm infant (Raiha 2001). Protein is an important component of adequate nutrition as it provides essential amino acids required for protein synthesis, which is necessary for growth. Hence, the quantity of protein is an important consideration ( Raiha 2001). The protein requirement for preterm infants can be estimated in two ways: estimates based on the protein intake of breast fed infants or estimates based on theoretical calculations (the factorial approach). A preterm infant fed own mother's milk receives approximately 1.4 g/100 ml (Gomella 1999) or about 2.5 g/kg/day of protein (Carlson 1998). The factorial approach is a theory-based calculation that sums the requirements for growth and those for replacement of inevitable losses in urine, feces, and skin (Fomon 1991). It is difficult to estimate requirements for protein intake in premature infants since they may have a high rate of protein turnover and breakdown (Pencharz 1981) as a result of either immaturity or illness (Hay 1996; Kalhan 2000). Preterm infants have a very rapid rate of growth and protein accretion. Ziegler and Fomon estimated the protein intake required for preterm infant growth and nitrogen accretion based on the factorial approach using the "reference fetus" (Ziegler 1976; Ziegler 1981) to be 4 g/kg/day of enteral protein for infants with a birth weight of less than 1200 grams, and 3.5 g/kg/day for infants with a birth weight of 1200 to 1800 grams (AAP 1998). Formulas currently available for preterm infants in North America contain 3 g of protein per 100 kcal. If energy intakes are maintained at the recommended range (CPS 1995), formula fed infants would receive about 3.2 to 4.2 g/kg/day of protein. There is a disparity between what is provided in own mother's milk compared to the estimated protein intake based on the factorial approach using the Ziegler-Fomon reference and what is contained in preterm formula.

Putative benefits of higher protein intake include adequacy of protein for growth of lean tissue, bone and blood constituents, turnover of tissues, synthesis of hormones and enzymes, and maintenance of oncotic pressure (Fomon 1993). In an animal study, higher protein intake was shown to accelerate maturation of the renal tubules (Jakobsson 1990). Deficiency of protein in infants leads to growth failure, and, when extreme, can lead to edema and lower resistance to infection (Nayak 1989).

Putative risks of higher protein intake include increased concentrations of amino acids, hydrogen ions, and urea as a result of the immaturity of amino acid metabolic pathways in preterm infants (Senterre 1983). Premature infants may not be able to handle higher protein intakes efficiently and hence metabolic acidosis and higher plasma levels of amino acids such as tyrosine and phenylalanine concentrations may result (Micheli 1999). Theoretically, these metabolic changes could lead to mental retardation. Additionally, adaptive responses of endocrine and metabolic homeostasis resulting from early nutrition may lead to 'metabolic programming', which alters long-term outcomes of chronic diseases. Renal hypertrophy accompanied by a significant rise in kidney tissue and circulating insulin-like growth factor-1 has been reported secondary to high protein intake (Murray 1993). High protein intake in early life may increase the risk of obesity (Rolland-Cachera 1995; Scaglioni 2000) and other pathologies later in life (Rolland-Cachera 1995) such as diabetes mellitus (Raiha 2001). Therefore, long-term consequences of early nutrition need to be considered.

Sufficient energy and other nutrients are needed to allow protein to be used for anabolism (Kashyap 1994) rather than as a fuel source. When energy availability is limited, nitrogen balance and protein utilization for tissue synthesis is limited. When protein is used for energy, the amino groups are cleaved and converted primarily to urea, which is excreted, while the carbon skeleton enters the citric acid cycle to be used as the energy source. When protein is used as an energy source, optimal protein synthesis cannot occur (Kashyap 1994). Consequently, protein intake needs to be evaluated in relation to the energy intake in order to make a direct comparison of alleged benefits and risks of higher protein intake.

Protein intake also needs to be evaluated in relation to other nutrients, as differences in other nutrients may influence infant growth rates (Castillo-Duran 2003; Musoke 2001). If studies vary both protein and other nutrients at the same time, it is not possible to attribute the findings solely to the difference in protein intake. If formulas vary more than 10% in any constituent other than protein, a direct comparison of outcomes may not be valid.

A related Cochrane review by Kuschel and Harding (Kuschel 2000) concluded that protein supplementation of human milk in relatively well preterm infants offers certain short term benefits including increases in weight gain, linear growth and head growth. Although urea levels were higher in patients receiving protein supplementation, this was thought to reflect adequate rather than excessive dietary protein intake. The long-term effects and adverse effects of protein supplementation of human milk could not be evaluated in Kuschel and Harding's systematic review (Kuschel 2000) due to an absence of relevant data.

The balance between supposed benefits and risks of higher protein intake for formula-fed low birth weight infants < 2.5 kilograms remains unclear.

## OBJECTIVES

To determine whether higher (>= 3.0 g/kg/day) versus lower (< 3.0 g/kg/day) protein intakes during the initial hospital stay of formula-fed preterm infants < 2.5 kilograms results in improved growth and neurodevelopmental outcomes without evidence of short and long-term morbidity.

To examine the following distinctions in protein intakes:

a) Low protein intake if the amount was less than 3.0 g/kg/day

b) High protein intake if the amount was equal to or greater than 3.0 g/kg/day, but less than 4.0 g/kg/day

c) Very high protein intake if the amount was equal to or greater than 4.0 g/kg/day

If the reviewed studies combined alterations of protein and energy, subgroup analyses were to be carried out for the planned categories of protein intake according to the following predefined energy intake categories:

a) Low energy intake, less than 105 kcal/kg/day

b) Medium energy intake, greater than or equal to 105 kcal/kg/day and less than or equal to 135 kcal/kg/day

c) High energy intake, greater than 135 kcal/kg/day

Since the Ziegler-Fomon reference fetus estimates different protein requirements for infants based on their birth weights, subgroup analyses were to be undertaken for the following birth weight categories:

a) < 800 grams

b) 800 to 1199 grams

c) 1200 to 1799 grams

d) 1800 to 2499 grams

# METHODS

## Criteria for considering studies for this review

### Types of studies

Randomized controlled trials. Quasi-randomized trials were not considered.

### Types of participants

Infants who weighed less than 2.5 kilograms at birth, whether appropriate or small-for-gestational age (AGA or SGA), and were studied during their initial hospital stay. They were exclusively fed formula and did not receive parenteral nutrition during the study.

### Types of interventions

The interventions comprised different levels of protein intake during the initial hospital stay, that were categorized as follows: low protein intake if the amount was less than 3.0 g/kg/day, high protein intake if the amount was equal to or greater than 3.0 g/kg/day, but less than 4.0 g/kg/day, or very high protein intake if the amount was equal to or greater than 4.0 g/kg/day. Contrasting levels of protein intake were compared over varied periods of time.

### Types of outcome measures

- Primary Outcomes

a) Growth parameters including weight gain (g/kg/day or g/day), linear growth (cm/week), and head growth (cm/kg/week or cm/week), expressed either in absolute terms or relative to intrauterine standards or Centre for Disease Control growth charts once the infant is term corrected age
b) Nitrogen utilization as reflected by blood urea (mmol/l)
c) Nitrogen accretion, expressed either in absolute terms, g/kg/day, or relative to fetal accretion rate
d) IQ scores and Bayley score at 18 months, and/or later
e) Abnormal phenylalanine levels
f) Growth failure (weight for age < 10% based in intrauterine standards or Centre for Disease Control growth charts once the infant is term corrected age)

- Secondary Outcomes

a) Decreased gastric motility (number of episodes of abdominal distension experienced per day)
b) Days to full feedings (days from initiation of feedings to achievement of 120 cc/kg/day)
c) Feeding intolerance (number of feeding interruptions related to feeding intolerance experienced per day)
d) Necrotizing enterocolitis (Bell's Stage II or greater)
e) Metabolic acidosis (pH, base excess)
f) Serum albumin (g/l)
g) Sepsis (number of babies who developed confirmed sepsis-positive blood culture and the organism(s) identified)
h) Diarrhea (number of babies who developed episodes of stools considered to have abnormal water loss)

## Search methods for identification of studies

Computerized searches were conducted by two review authors up to May 2005. A number of databases were searched including MEDLINE back to 1966, CINAHL back to 1982, PubMed back to 1966, EMBASE back to 1980, and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2005). MeSH headings including infant, newborn, low birth weight, small for gestational age, very low birth weight, premature, amino acids, dietary proteins, milk proteins, milk, infant food, food, formulated and text words including formula and protein were used for the computerized searches. Abstracts, conferences and symposia proceedings from Society of Pediatric Research, and American Academy of Pediatrics were also identified. Cross-references were reviewed independently for additional relevant titles and abstracts for articles up to fifty years old. Experts were also contacted to identify other studies relevant to the area. There were no language restrictions.

## Data collection and analysis

All articles retrieved from the complete search were assessed for relevance independently by the two review authors. Randomized controlled trials testing contrasting levels of formula protein intakes during initial hospital stay were considered if they meet the following criteria for relevance:

- Study participants were less than 2.5 kilograms at birth
- Study participants were not receiving parenteral nutrition at time of randomization
- Study participants were exclusively formula-fed
- Energy, Na, K, P, Zn or essential fatty acid intakes did not differ significantly (no more than 10% relative concentration)

Given the small number of trials that met all the criteria, and some larger and important studies that met the first three but not the last criteria, the three review authors decided to include these studies in a post-facto analysis of the primary outcomes, to provide the readers with a more comprehensive and clinical relevant systematic review.

If all of the protein intake groups within a study fell inside one of the predesignated protein intake criteria, then this study was excluded. The articles that met all relevance criteria were assessed for methodological quality using the following criteria: blinding of randomization, blinding of intervention, complete follow-up and blinding of outcome measurement. Each criteria was rated as yes, no or don't know. Data were extracted independently by both review authors. Differences were resolved by discussion and consensus of the three review authors. Efforts were made to contact investigators for data, additional information and/or clarification regarding eight studies (Bhatia 1991; Hillman 1994; Kashyap 1986; Mimouni 1989; Nichols 1966; Svenningsen 1982; Thom 1984; Wauben 1995).

A standardized statistical method was used to handle three-arm trials where two groups fell within one predesignated protein intake group (Rosner 2000). For meta-analysis, weighted mean differences (WMD) and 95% confidence intervals are reported for continuous variables, and typical estimates for relative risk and risk difference and 95% confidence intervals are reported for categorical outcomes. A statistical test for heterogeneity ($I^2$ test) included in the graphical output of Cochrane Reviews was used to assess variability in treatment effects being evaluated in the different trials. Fixed effects models were assumed.

# RESULTS

## Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

The literature search identified 37 studies of which 12 were non-randomized controlled studies. The 25 randomized studies were scrutinized for criteria of relevance. Fourteen studies were excluded for the following reasons:

(a) In six studies the protein intake groups within a study fell inside one of the predesignated protein intake criteria

(b) In six studies the intervention being examined was different from that proposed in this systematic review (e.g. the studies examining quality of protein)

(c) In one study infants received parenteral nutrition during the study period

(d) In one study the experimental protocol was modified during the study period. Details for reasons for exclusion are listed in the Table "Characteristics of Excluded Studies".

Five studies (Bhatia 1991; Hillman 1994; Kashyap 1986; Svenningsen 1982; Wauben 1995) met all the inclusion criteria. Three studies (Goldman 1969; Kashyap 1988; Raiha 1976) differed in one or more nutrients by more than 10% in either direction; however, they were included in a post-facto analysis for the primary outcomes. Details of the studies that met the inclusion criteria and those which were included for the post-facto analysis are presented in the table "Characteristics of Included Studies". Three studies (Mimouni 1989; Nichols 1966; Thom 1984) await assessment.

**STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA**

Bhatia 1991 randomized 26 AGA and SGA infants with birthweight less than 1550 grams who were assigned to one of three formulas that were identical in composition except for the protein content. Three infants were withdrawn from the study. Infants were given study formula when they were tolerating 60 kcal/kg/day of a standard premature infant formula. The study formulas were continued for two weeks after the intake reached 100 kcal/kg/day. Growth, biochemical parameters, necrotizing enterocolitis, and neonatal behavior were assessed. Data for two groups in the high protein category were combined in this review.

Hillman 1994 randomized 27 infants weighing less than 1500 grams at birth in three weight group strata (< 1000 grams, 1000 to 1250 grams, 1250 to 1500 grams) to one of three study formulas, before initiation of feedings in the first week of life. All infants completed two and four week assessments of growth, biochemical parameters, and bone mineral content, however, 14 of the 27 infants were discharged prior to the six week assessment. Data for two groups in the high protein category were combined in this review.

Kashyap 1986 randomly assigned 34 AGA and SGA low birthweight infants weighing 900 to 1750 grams at birth to receive one of three formulas. One group of nine infants received increased energy intakes, so they were not included in this review. Growth, biochemical parameters, necrotizing enterocolitis, diarrhea, and nutrient balance were assessed. Data on energy expenditure and energy balance were collected in a subset of infants in this study

and published by Schulze 1987.

Svenningsen 1982 randomly allocated 48 AGA and SGA very low birthweight and premature infants in the third week of life to one of three groups. One group received human milk and was not eligible for this review. The other two groups received formulas with or without the addition of a commercial product "protinpur" to produce either high or low protein intake. Svenningsen 1982a reported long-term follow-up growth parameters and neurodevelopmental outcomes up to two years of age.

Wauben 1995 randomly allocated 16 healthy AGA premature infants between 28 and 35 weeks gestational age to two formulas with differing protein content and conducted a modified three-day protein and energy balance study. The study began once infants were receiving full enteral feedings of 160 cc/kg/day.

**STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS**

Goldman 1969 randomly assigned 304 AGA and SGA infants with birthweight less than 2000 grams in three birthweight strata, < 1000 grams, 1000 to 1499 grams, and 1500 to 2000 grams to two study formulas. Infants > 1000 grams were further stratified based on gender, and twins were assigned separately. Infants were followed from the first few days of life until 2200 grams was achieved. The study compared high (3.0 - 3.6 g/kg/day) versus very high (6.0 - 7.2 g/kg/day) protein intakes. The higher protein formula had 17% higher concentration of minerals. Growth, biochemical and neurological parameters were assessed. Two separate papers (Goldman 1971, 1974) of the same study reported neurodevelopmental outcomes at three and five to seven years of life.

Kashyap 1988 randomly assigned 50 AGA and SGA low birthweight infants weighing 900 to 1750 grams at birth to receive one of three formulas until study end when the infants reached 2200 grams. One group of 15 infants who received increased energy intakes was not included in this review. Formula of the high protein groups had 14% more potassium, 15% more calcium and 20% more magnesium compared to the low protein group. Growth, biochemical parameters, necrotizing enterocolitis, and nutrient balance were assessed prior to study end when the infants reached 2200 grams.

Raiha 1976 randomly assigned 106 AGA infants with birthweight 2100 grams or less to one of four isocaloric formulas that varied in both quantity (2.25 and 4.5 g/kg/day) and type (whey:casein ratios) of protein in the first week of life. Infants were grouped into three categories: 28 to 30 weeks, 31 to 33 weeks, and 34 to 36 weeks. Potassium varied 17%, calcium 15%, and phosphorus 12% in relative concentration in the whey predominant formulas between the low and very high protein groups. Sodium varied 28% and magnesium 12% in relative concentration in the casein predominant formulas. Study formulas were provided until hospital discharge. Three separate papers on this study have been published (Rassin 1977, 1977, and Gaull 1977) reporting different outcomes.

## Risk of bias in included studies

Infants were allocated to assigned treatment by randomization in all studies included in this review. Only two studies (Bhatia 1991; Hillman 1994) reported adequate concealment of allocation and blinding of randomization. Six studies (Bhatia 1991; Goldman 1969; Hillman 1994; Kashyap 1986; Kashyap 1988; Raiha 1976) reported that the intervention was blinded to caregivers and/or investigator(s). Two studies (Bhatia 1991; Raiha 1976) reported blinding of outcome. Only one study reported an intention-to-treat analysis (Wauben 1995).

## Effects of interventions

HIGH VERSUS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

(1) PRIMARY OUTCOMES

**01 Growth Parameters**

**01 Weight gain (g/kg/day)**

Bhatia 1991 and Svenningsen 1982 found no significant differences in weight gain between groups. However, Hillman 1994, Kashyap 1986, and Wauben 1995 found that infants receiving high protein intakes had significantly greater weight gain. The overall analysis revealed a significant difference in weight gain (WMD 2.36 g/kg/day, 95% CI 1.31, 3.40) in favour of the high protein group.

**02 Linear growth (cm/week)**

Kashyap 1986 found that infants receiving high protein intakes had significantly greater linear growth while Svenningsen 1982 observed no significant difference between the groups. The overall analysis did not reveal a significant difference (WMD 0.16 cm/week, 95% CI -0.02, 0.34).

**03 Head growth (cm/week)**

Kashyap 1986 found that infants receiving high protein intakes had significantly greater head growth. Bhatia 1991, Hillman 1994, and Svenningsen 1982 reported no significant difference in head growth. However, data were missing so these three studies were not included in the meta-analysis.

**02 Nitrogen Utilization**

**01 Blood urea nitrogen (mg/dl)**

Bhatia 1991, Kashyap 1986 and Svenningsen 1982 report higher blood urea nitrogen levels among infants receiving high protein intakes. Svenningsen 1982 did not find a significant difference in blood urea nitrogen at the third and fifth week of life, although at seven weeks levels were significantly higher among the infants receiving higher protein intakes (third week p = 0.85, fifth week p = 0.375, and seventh week p = 0.0005). Blood urea nitrogen levels were measured by Svenningsen 1982 at different time points than the other studies, so this study was not included in the meta-analysis. When data from the two studies that measured blood

urea nitrogen at the two week point were combined, significantly higher levels were noted in infants in the high protein intakes group (WMD 1.92 mg/dl, 95%CI 1.00, 2.84) compared to the low protein group.

**03 Nitrogen Balance**

**01 Nitrogen accretion (mg/kg/day)**

Kashyap 1986 and Wauben 1995 reported statistically significant higher protein accretion in the high protein formula groups. The meta-analysis revealed significantly higher nitrogen accretion (WMD 143.7 mg/kg/day, 95% CI 128.7, 158.8) in infants receiving formula with high protein content compared to infants on the low protein formula. Of note, there was significant heterogeneity of treatment effect; consequently the data need to be interpreted prudently.

**04 IQ Score and Bayley Score at 18 months, and/or Later**

No study primarily addressed these outcomes, however, Bhatia 1991 and Svenningsen 1982 reported neurodevelopmental outcomes for infants enrolled in their studies. Bhatia 1991 assessed behavior in a subset of 15 infants within five days of completing the feeding study. The infants were approximately 36 to 37 weeks at the time of testing. A certified child psychologist, blinded to feeding history of the infants, administered the Neonatal Behavior Assessment Scale. Infants receiving formula with higher protein intakes performed significantly better on the orientation (p = 0.0003), habituation (p = 0.003), and autonomic stability (p = 0.01) clusters of the neonatal behavior assessment scale. There were no differences between groups in the remaining behavioral clusters, motor (p = 0.7), range of state (p = 0.5) and regulation of state ( p= 0.29). Svenningsen 1982 reported no significant differences in neurodevelopmental outcomes up to two years of age. They assessed developmental performance indicators such as sitting, standing, walking and talking at 5 - 6, 10 - 11, 14 - 18 and 24 months of age on 46 of the 48 infants enrolled in the study. At 10 - 14 months, an audiometric test was also performed. The instruments used for these assessments were not stated.

**05 Phenylalanine Levels**

**01 Plasma phenylalanine concentration (umol/dl)**

Bhatia 1991 and Kashyap 1986 tested phenylalanine levels and found no significant difference between low and high protein formula groups. Bhatia 1991 measured phenylalanine concentration at the end of the two week study period. Kashyap 1986 monitored plasma amino acid concentrations before feedings were started, and weekly once the target intake was achieved. Different approaches were used to report data so a meta-analysis could not be undertaken.

**06 Growth Failure**

No study addressed outcomes using this term.

**(2) SECONDARY OUTCOMES**

01 Decreased Gastric Motility (number of episodes of abdominal distension)

No study addressed this outcome.

**02 Days to Full Feedings (from initiation of feedings to achievement of 120 cc/kg/day)**

Kashyap 1986 defined full intake as 180 cc/kg/day, which was maintained throughout the study. There were no significant differences between groups with respect to the age at which feedings were started and age at which full feeding was attained. None of the other studies included information describing when full feedings were achieved.

**03 Feeding Intolerance (number of episodes per day)**

No study addressed this outcome.

**04 Necrotizing Enterocolitis (Bell's Stage II or greater)**

Svenningsen 1982 and Wauben 1995 reported no incidence of necrotizing enterocolitis in either the high or the low protein intake groups. However, it is uncertain what criteria was used to define necrotizing enterocolitis in these studies. For the purpose of this systematic review, necrotizing enterocolitis was defined as Bell's Stage II or greater. The overall analysis showed no significant effect of protein intake on necrotizing enterocolitis (typical risk difference 0.00, 95%CI -0.12, 0.12).

**05 Metabolic Acidosis (pH, base excess)**

Kashyap 1986 reported blood acid-base status and found pH and base excess to be within normal limits for all infants enrolled in the study regardless of group assignment.

**06 Serum Albumin (g/l)**

Kashyap 1986 reported albumin as approximately 3 g/dl, while Hillman 1994 and Svenningsen 1982 reported albumin as 3 mg/dl and 30 g/ml, respectively. We attempted to clarify the units with the latter two authors without success. Hillman 1994 measured albumin values at four and six weeks of age. Svenningsen 1982 measured albumin levels at approximately zero, two and four weeks of study. The values reported for each time period were not significantly different between the low and high protein formula groups. Kashyap 1986 reported prealbumin (mg/dl) (i.e. transthyretin) levels and found a significant difference between the low and high protein formula groups, favouring the high protein formula group. A meta-analysis could not be undertaken given the discrepancy in the units used to report findings and differences in time frames used for measuring serum albumin.

**07 Sepsis: Incidence, Number of Episodes**

Although Svenningsen 1982 states that there was no difference in the rate of septicaemia between groups, supporting data was not provided. Additionally, it is uncertain what constituted septicaemia (e.g. positive blood culture or positive cerebrospinal fluid). Hillman 1994 indicates that five of the 27 infants enrolled in their study failed to complete at least four weeks of study either because the infant became unwell (e.g. sepsis) or the infant was transferred to another hospital. The exact number of infants who developed infection was not specified.

**08 Diarrhea (Number of Episodes Per Day Per Baby)**

Kashyap 1986 addressed the outcome of diarrhea using a categorical rather than continuous level of measurement. Kashyap 1986 indicated that of the seven infants withdrawn from the study (n = 34 infants), one developed diarrhea. This infant belonged in the group which differed in energy intake rather than protein intake and, therefore, was not included in this review.

**SUBGROUP ANALYSES**

**01 Stratification Based on Energy Intake**

No study addressed this outcome.

**02 Distinction in Birth Weight Categories**

Although Hillman 1994 randomly assigned infants enrolled in their study within three overlapping weight group strata (< 1000 grams, 1000 to 1250 grams, and 1250 to 1500 grams), data were not presented for each weight category, but rather were based on protein group assignment. No other study reported data for birth weight categories. Consequently, subgroup analyses for the birth weight categories were not undertaken.

**VERY HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)**

No study addressed this outcome

**VERY HIGH VS HIGH PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)**

No study addressed this outcome.

**POST-FACTO ANALYSIS**

**HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)**

**(1) PRIMARY OUTCOMES**

**01 Growth Parameters**

**01 Weight gain (g/kg/day)**

Kashyap 1988 found weight gain to be significantly lower in the low protein intake formula group. Inclusion of this study in the overall analysis revealed improvement in weight gain (WMD 2.53 g/kg/day, 95% CI 1.62, 3.45), beyond that in the a priori analysis, in infants receiving formula with high protein content.

**02 Linear growth (cm/week)**

Kashyap 1988 and Svenningsen 1982 found no significant difference in linear growth between groups. These findings differed from Kashyap 1986's study that noted a significant increase in linear growth in infants receiving higher protein intakes. The inclusion of the Kashyap 1988 study in the meta-analysis revealed a significant difference (WMD 0.16 cm/week, 95% 0.03, 0.30), with greater linear growth with high protein intakes compared to low protein intakes.

**03 Head growth (cm/week)**

Kashyap 1988 found that infants receiving high protein intakes had a significantly greater head growth (p = 0.027). With the inclusion of this study, a meta-analysis revealed a significantly greater head growth among the high protein intakes group (WMD 0.23 cm/week, 95% 0.12, 0.35) compared to the low protein intake group.

**02 Nitrogen Utilization**

**01 Blood urea nitrogen (mg/dl)**

Kashyap 1988 found significantly higher blood urea nitrogen levels with increased protein intakes. These findings are consistent with Svenningsen 1982 and Bhatia 1991. Kashyap 1986 reported low levels of blood urea nitrogen in all groups, but levels were significantly lower in the low protein group. Since Kashyap 1986 and Kashyap 1988 both report results that were measured weekly, a meta-analysis was possible of both of these studies. A significant increase in blood urea nitrogen levels was evident in the high protein intake group (WMD 3.22 mg/dl, 95% CI 2.48, 3.96). Of note, there was significant heterogeneity of treatment effect; consequently the data need to be interpreted with caution.

**03 Nitrogen Balance**

**01 Nitrogen accretion (mg/kg/day)**

Kashyap 1988 found that protein intake exerted a positive effect on nitrogen retention. These findings are consistent with those of Kashyap 1986 and Wauben 1995. With inclusion of this study, the meta-analysis continued to show significantly higher nitrogen accretion (WMD 112.6, 95% CI 101.4, 123.8) in infants receiving formula with higher protein content. There was significant heterogeneity of treatment effect; consequently the data need to be interpreted with caution.

**04 IQ Score and Bayley Score at 18 months, and/or Later**

No study addressed this outcome.

**05 Phenylalanine Levels**

**01 Plasma phenylalanine concentration (umol/dl)**

Kashyap 1988 found no significant difference in concentration of plasma phenylalanine between infants fed high versus low protein intakes. When data from this study were included with those of Kashyap 1986, the meta-analysis showed no significant difference (WMD 0.25, 95% CI -0.20, 0.70) in the concentration of plasma phenylalanine between groups.

**06 Growth Failure**

No study addressed this outcome

**VERY HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)**

**(1) PRIMARY OUTCOMES**

**01 Growth Parameters**

**01 Weight gain (g/week)**

Raiha 1976 reported rate of weight gain in g/week measured from the time birth weight was regained to 2400 grams based on gestational age category. There were no significant differences in the rate of weight gain between the low and very high protein intake groups in any gestational age group.

**02 Linear growth (cm/week)**

Raiha 1976 reported rate of growth in crown-rump length (cm/week) from time of regaining birth weight to attainment of 2400 grams based on gestational age category. There were no significant differences between the low and very high protein intake groups in any gestational age strata.

**03 Head growth (cm/week)**
Raiha 1976 reported no significant differences in rate of growth of head circumference from time of regaining birth weight to 2400 grams between the low and very high protein intake groups in any gestational age group. No numerical data were documented.

**02 Nitrogen Utilization**
**01 Blood urea nitrogen (mg/dl)**
Raiha 1976 reported a significant difference in blood urea nitrogen levels between the infants fed very high versus low protein formulas when data from the three gestational ages were combined. Blood urea nitrogen levels varied directly with the quantity of protein in the diet; levels were greater than the normal range in infants receiving very high protein intakes. They report progressive elevation in blood urea nitrogen levels and metabolic acidosis in two infants receiving very high protein intakes, one on the whey predominant (5%) and one on the casein predominant (5%) formulas. Graphical data were presented rather than numerical values.

**03 Nitrogen Balance**
**01 Nitrogen accretion (mg/kg/day)**
No study addressed this outcomes
**04 IQ Score and Bayley Score at 18 months, and/or Later**
No study addressed this outcome
**05 Phenylalanine Levels**
**01 Plasma phenylalanine concentration (umol/dl)**
Raiha 1976 found that infants fed formula providing higher protein intakes had higher concentrations of plasma phenylalanine, particularly among the infants fed the casein predominant formulas when data from the three gestational ages were combined.
**06 Growth Failure**
No study addressed outcomes using this term.
**VERY HIGH VS HIGH PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)**
**(1) PRIMARY OUTCOMES**
**01 Growth Parameters**
**01 Weight gain (g/kg/day)**
Goldman 1969 did not report weight gain (g/kg/day), but rather number of days from regaining birth weight to 2200 grams. Based on regression curves calculated for infants < 1500 grams and > 1500 grams, more infants in the very high protein intake group took longer than the calculated period of time to reach 2200 grams ($p<0.01$).
**02 Linear growth (cm/week)**
No study addressed this outcome.

**03 Head growth (cm/Week)**
No study addressed this outcome.
**02 Nitrogen Utilization**
**01 Blood urea nitrogen (mg/dl)**
No study addressed this outcome.
**03 Nitrogen Balance**
**01 Nitrogen accretion (mg/kg/day)**
No study addressed this outcome.

**04 IQ Score and Bayley Score at 18 months, and/or Later**
Two separate papers on the study by Goldman 1969 (Goldman 1971, 1974) reported incidence of low Stanford-Binet test scores in infants at three and five to seven years of life, respectively. Of the 80% of infants of the original study who were assessed at three years (corrected and chronological age), there was a similar incidence of IQ scores below 90 among infants fed the very high and the high protein formulas. Of the 81% of infants of the original study who were assessed at five to seven years, they report a similar incidence of IQ scores below 90 in both groups. At both the three year and the five to seven year evaluation, a significantly higher incidence of IQ scores below 90 is reported among the infants of birth weight below 1300 grams who received very high protein intakes compared to those who were fed the high protein intakes.
**05 Phenylalanine Levels**
**01 Plasma phenylalanine concentration (umol/dl)**
No study addressed this outcome.
**06 Growth Failure**
No study addressed outcomes using this term.

## DISCUSSION

Although a large number of studies (n = 37) were located, upon close inspection only five studies (Bhatia 1991; Hillman 1994; Kashyap 1986; Svenningsen 1982; Wauben 1995) were found to be suitable for inclusion in this systematic review. The majority of studies were excluded because they did not compare sufficiently different protein intakes or they examined a different intervention (e.g. studies examining quality of protein). Methodological limitations of the included trials that may have introduced bias and, therefore, pose a threat to the validity of the analysis, are as follows:

(a) only two studies (Bhatia 1991; Hillman 1994) had adequately concealed allocation

(b) the differences in protein content among comparison groups in some of the individual trials may be too small (range 0.56 to 1.36 g/kg/day) to illustrate the potential effect of changes in protein intakes

(c) the formulas differed substantially across the studies

(d) the duration of the interventions and/or study periods varied from eight days (Wauben 1995) to two years (Svenningsen 1982)

(e) the characteristics of participants varied across studies with some studies including healthier and more mature premature infants.

These limitations may explain some of the differences in treatment effects and the statistical heterogeneity evident in measures of weight gain and nitrogen accretion.

In order for this review to be comprehensive and more clinically relevant, studies that varied in nutrient content other than protein were included in a post-facto analysis. Three studies (Goldman 1969; Kashyap 1988; Raiha 1976) were considered, although only one of these studies (Kashyap 1988) could be included in the meta-analysis.

Weight gain (g/kg/day) was the most commonly reported outcome. There was an overall increase in weight gain in infants randomized to the high protein intake group compared to the low protein intake group (WMD 2.36 g/kg/day, 95% CI 1.31, 3.40 for the overall analysis and WMD 2.53 g/kg/day, 95% CI 1.62, 3.45 for post-facto analysis). The most desirable level of protein intake is that which contributes to infant growth at the infant's predetermined genetic potential without negative consequences. The ideal composition of weight gain of the preterm infant is not known. It is generally considered that the lower lean tissue and higher fat gain of these infants relative to the fetus may not be desirable (Schulze 1987). There was significantly greater nitrogen accretion (WMD 143.7, 95% CI 128.7, 158.8 for the overall analysis, and WMD 112.6, 95% CI 101.4, 123.8 for post-facto analysis) in infants randomized to the high protein intake groups. This greater nitrogen accretion suggests that some or all of the increment in weight is due to gains in lean body mass. These findings indicate that higher protein intakes may help correct the non-optimal body composition seen in preterm infants at term adjusted age (Atkinson 2000). There was statistical heterogeneity in nitrogen accretion, hence the data need to be interpreted cautiously. Potential sources of heterogeneity might include clinical diversity (e.g. variability in participants, intervention and outcomes), and methodological variability (e.g. differences in trial design).

Two studies (Kashyap 1986; Kashyap 1988) attempted to determine if utilization of protein was enhanced by higher energy intakes. These studies compared a medium energy intake (120 kcal/kg/day) with a high energy intake (142 kcal/kg/day). Kashyap 1986 found that the higher energy intake did not enhance protein utilization. This was evident from similarities noted between groups in amounts of nitrogen retention, albumin, prealbumin as well as concentrations of blood urea nitrogen and most plasma amino acids. In contrast, in a later study, Kashyap 1988 reported improvements in nitrogen retention and blood urea nitrogen levels with a higher energy intake.

Three studies reported that blood urea nitrogen levels were higher among those infants who were fed high protein intakes compared to those fed low protein intakes (Bhatia 1991; Kashyap 1986; Svenningsen 1982). Although detectable, some of these differences may not be clinically significant. Three studies (Bhatia 1991; Kashyap 1986; Kashyap 1988) reported no significant differences in phenylalanine levels between low and high protein intake groups. The inclusion of the two Kashyap studies in the post-facto meta-analysis resulted in no significant difference (WMD 0.25, 95% CI -0.20, 0.75) in the concentration of plasma phenylalanine between the high low protein intake groups.

While the Kashyap studies (Kashyap 1986; Kashyap 1988) reported acid-base status to be within normal limits, others raised concerns regarding metabolic acidosis among infants on high protein intakes (Raiha 1976; Svenningsen 1982). Raiha 1976 noted that infants receiving very high protein intakes (4.5 g/kg/day) developed metabolic acidosis that resolved once the infants were removed from the study and fed breast milk. In the Svenningsen 1982 study, late metabolic acidosis occurred in 25% and 7%, respectively, of infants in the high and low protein intake groups. It is possible that the supplement "protinpur" that they added to their low protein formula to prepare the high protein formula had a poor biological value.

Very high protein intakes may be poorly tolerated in infants with very low birth weights and extreme prematurity. Studies have not adequately evaluated short- and long-term adverse sequelae of very high protein intakes. The maximal utilizable protein limits for infants in different weight and gestational age categories are unknown. In recent years, preterm infant formulas used in North America have changed such that if infants are fed at energy intakes that exceed 133 kcal/kg/day, protein intakes will exceed 4 g/kg/day. In this systematic review, only two studies (Goldman 1969; Raiha 1976) in the post-facto analysis assessed protein intakes above 4.0 g/kg/day. The quantity of protein intake in these studies was 4.5 g/kg/day (Raiha 1976) and 6 to 7.2 g/kg/day (Goldman 1969). Their findings could not be included in the meta-analysis since the comparisons made within these studies were unique.

Other potential adverse effects of high protein intake were assessed by reporting neurodevelopmental outcomes, days to full feedings, necrotizing enterocolitis, sepsis, and diarrhea. However, limited information could be obtained regarding these potential risks. Although a meta-analysis was carried out for necrotizing enterocolitis, the findings presented should be interpreted cautiously because: (a) there remains uncertainty about the definition of necrotizing enterocolitis used by some studies, and (b) of the small number of infants in the two groups; N = 49 receiving high protein intake and N = 38 receiving low protein intake.

Neurodevelopmental outcomes of early nutrition were evaluated

by three studies (Bhatia 1991; Svenningsen 1982; Goldman 1969) included in this systematic review. Svenningsen 1982 did not report the tool used. Bhatia 1991 used the Neonatal Behavioral Assessment scale that has known psychometric properties, but has been validated for use only in term infants up to two months of life (Brazelton 1995). Bhatia 1991's results suggested improvements in some of the parameters of neurodevelopmental outcome with high protein intakes compared to low intakes. Goldman 1969, who administered the Stanford-Binet test at three and five to seven years of age noted a significant increase in the incidence of low IQs among infants with birthweights < 1300 g who were fed very high protein intakes of 6 to 7.2 g/kg/day during their initial hospitalization.

# AUTHORS' CONCLUSIONS

## Implications for practice

This systematic review suggests that weight gain and nitrogen accretion can be promoted by regulating protein intake in "healthy" formula-fed preterm infants. The American Academy of Pediatrics (AAP 1998) and the Canadian Pediatric Society (CPS 1995) recommend 3 - 4 g/kg/day of protein for preterm infants. Increased levels of blood urea nitrogen and metabolic acidosis may occur in some infants who receive protein intakes above three but less than 4 g/kg/day. This review determined that there were benefits in weight gain and nitrogen accretion without any clear risks associated with this intake. The exact protein intake that safely promotes optimal growth and development of low birth weight infants remains uncertain.

## Implications for research

Future research should determine the precise protein requirements of preterm infants according to birth weight and gestational age. Moreover, there are unanswered research questions regarding protein requirements according to postnatal age and the presence of both short-term and long-term growth and neurodevelopmental morbidities. The question of whether there are clinically significant risks to moderately elevated blood urea nitrogen and metabolic acidosis warrants study. Given the current state of evidence, protein intakes above 4 g/kg/day should be considered experimental.

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**Kalhan 2000**
Kalhan SC, Iben S. Protein metabolism in the extremely low-birth weight infant. *Clinics in Perinatology* 2000;**27**:23–56.

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Kashyap S, Schulze KF, Ramakrishnan R, Dell RB, Heird WC. Evaluation of a mathmatical model for predicting the relationship between protein and energy intakes of low-birth-weight infants and the rate and composition of weight gain. *Pediatric Research* 1994; **35**:704–12.

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composition of weight gain in low birth weight infants fed diets of different protein and energy content. *Journal of Pediatrics* 1987; **110**:753–9.

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**Svenningsen 1982a**

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Zeigler EE, Biga RL, Fomon SJ. Nutritional requirements of the premature infant. In: Suskind RM editor(s). *Textbook of Pediatric Nutrition*. New York: Raven Press, 1981:29–39.

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Bhatia 1991**

| | |
|---|---|
| Methods | RCT: Numbered envelopes.<br>Blinding of randomization: Yes<br>Blinding of intervention: Yes (medical and nursing staff)<br>Complete follow-up: No<br>Blinding of outcome: Yes (to psychologist)<br>Three of 26 patients (12%) were withdrawn for provision of human milk and necrotizing enterocolitis.<br>Eight of 23 patients (22%) lost to follow-up. |
| Participants | 26 infants<br>Inclusion criteria: BW < 1500 g, no major congenital anomalies, no congestive heart failure, oxygen requirements < 40% on study entry, no supplemental oxygen on day 1 of study.<br>Study entry: when infants reached 60 kcal/kg/d.<br>Study day 1: enteral intake reached 100 kcal/kg/d within 21 days of life.<br>To stay in study: enteral feeding to begin by 14 days of age, and infant to achieve enteral intake of 100 kcal/kg/d by 21 days of life. |
| Interventions | High protein intake: 3.8 g/kg/day (n=8) and 3.1 g/kg/day (n=8). Data for these two groups were combined in this review.<br>Low protein intake: 2.6 g/kg/day (n=7). |
| Outcomes | Weight, length, head circumference, skin-fold thickness, serum total protein, pre-albumin, retinol-binding protein, urea nitrogen, plasma amino acids, and Neonatal Behavior Assessment Scale (orientation, habituation, stability, regulation, range and motor) in subset of infants (n=18, 69%) within 5 days of completing the feeding study. |
| Notes | Did not mention total parenteral nutrition.<br>Carbohydrates added to make the energy level identical between formulas. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Goldman 1969**

| | |
|---|---|
| Methods | RCT: Random sequence.<br>Infants assigned within the following birth weight groups: < 1000 g, 1000 to 1499 g male, 1000 to 1499 g female, 1500 to 2000 g male, 1500 to 2000 g female, and twins.<br>Blinding of randomization: Can't tell<br>Blinding of intervention: Yes (physician, nurses and others)<br>Complete follow-up: No<br>Blinding of outcome: No (one physician aware of code for translation and did assessments of infants)<br>Five infants (1.6%) were withdrawn from the study: 2 infants (0.7%) in the low protein intake group died due to apneic episodes, 2 infants (1.3%) in the high protein group and 1 infant (0.7%) in the low protein intake group were withdrawn from the study after they developed diarrhea. |
| Participants | 304 infants < 2000 g birthweight<br>Inclusion criteria: no major congenital anomalies, intestinal obstruction, or Rh disease.<br>Exclusion criteria: infants more than 3 days of age on admission to the nursery and infants who died in the first few days of life. |
| Interventions | Very high protein intake: 6 to 7.2 g/kg/day (n=152). High protein intake: 3 to 3.6 g/kg/day (n=152).<br>Formulas differed in nutrient content; very high protein formula was 17% higher in minerals.<br>Feeding initiated within 72 hours after birth with the initial two feedings of 5% dextrose water. Formula increased gradually to 150 to 180ml/kg/day. |
| Outcomes | Axilla temperature, weight, edema, lethargy, nipple feeding efforts, cyanosis, central nervous system symptoms, apnea, abdominal distention, diarrhea and serum albumin.<br>Goldman 1971 reported outcomes at 3 years of life: physical abnormalities, incidence of strabismus, and Stanford-Binet test of IQ.<br>Goldman 1974 reported 5-7 year follow-up outcomes on survivors (81%): interval history, physical exam, Stanford-Binet IQ, and strabismus. |
| Notes | Study took place prior to routine use of parenteral nutrition. |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Goldman <1300 g**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Goldman <1300 g** (*Continued*)

| *Risk of bias* | | |
|---|---|---|
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | D - Not used |

**Goldman =>1300-1700g**

| Methods | | |
|---|---|---|
| Participants | | |
| Interventions | | |
| Outcomes | | |
| Notes | | |
| *Risk of bias* | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | D - Not used |

**Goldman =>1701-2000g**

| Methods | | |
|---|---|---|
| Participants | | |
| Interventions | | |
| Outcomes | | |
| Notes | | |
| *Risk of bias* | | |
| **Item** | **Authors' judgement** | **Description** |
| Allocation concealment? | Unclear | D - Not used |

**Hillman 1994**

| | |
|---|---|
| Methods | RCT: Infants randomly assigned, by a previously generated random assignment table, to one of three formulas before initiation of feeding.<br>Infants assigned within three wt group strata: < 1000 g, 1000 to 1250 g, 1250 to 1500 g.<br>Blinding of randomization: Yes<br>Blinding of intervention: Can't tell<br>Complete follow-up: No<br>Blinding of outcome: Can't tell<br>Five infants (19%) failed to complete at least 4 weeks of study as a result of: transfer to other hospitals, NEC, sepsis, and respiratory deterioration. These 5 infants were equally distributed between groups and replaced in their formula assignment by five additional infants.<br>High attrition at 6-weeks - only 13 of 27 infants remaining in study.<br>27 infants assessed at 2, and 4 weeks and 13 infants assessed at 6 weeks of age. |
| Participants | 27 infants < 1500 g<br>Inclusion criteria: breathing room air, off total parenteral nutrition and diuretics. |
| Interventions | High protein intake: 3.6 g/kg/day (n=9); 3.2 g/kg/day (n=9). Data for these two groups were combined in this review.<br>Low protein intake: 2.8 g/kg/day (n=9).<br>Formulas had identical nutrient content except for protein.<br>Infants enrolled when taking total fluid intake enterally. Infants assessed at 2-week intervals while receiving study formula. |
| Outcomes | Weight gain (birth to 30 days of age), growth of length and head circumference, time to discharge, serum calcium, phosphorus and magnesium, bone mineral content, bone width, serum albumin, parathyroid hormone levels, urinary calcium/creatinine ratio, phosphorus/creatinine ratio, aminoaciduria, beta 2-microglobulins and N-acetylglucosamine. |
| Notes | Infants could not be on total parenteral nutrition at the time of enrolment.<br>Unclear when infants were switched from study to "regular" formula.<br>In several infants the aminoaciduria persisted after change to standard formula was made. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Yes | A - Adequate |

**Kashyap 1986**

| | |
|---|---|
| Methods | RCT: State infants randomly assigned.<br>Blinding of randomization: Can't tell<br>Blinding of intervention: Yes (investigators and nurses)<br>Complete follow-up: No<br>Blinding of outcome: Can't tell<br>Seven infants (21% - 2 in group 1, 2 in group 2, and 3 in group 3) were withdrawn for: medical conditions (e.g. PDA) that limited intake (3 infants), NEC (2 infants), diarrhea (1 infant) and stool or urine collection inadequate (1 infant). |
| Participants | 34 LBW infants weighing between 900 to 1750 g at birth, with gestational ages between 27 and 37 weeks, met the following inclusion criteria: no gastrointestinal tract disease, or pulmonary disease severe enough to produce acidosis or necessitate prolonged ventilatory assistance.<br>27 infants completed study, 9 in each group. |
| Interventions | High protein intake: 3.6 g/kg/day (n=9).<br>Low protein intake: 2.2 g/kg/day (n=9).<br>Formulas had identical nutrient content except for protein.<br>As soon as enteral feedings were tolerated, the assigned formula was started. Formula increased until intake of 180cc/kg/day reached and this was maintained throughout study period (until infants reached 2200g). |
| Outcomes | Weight, length, head circumference, triceps and subscapular skin fold thickness, nutrient balance (N, Na, K, Cl, Ca & P), blood urea nitrogen, albumin and transthyretin, acid-base status, alkaline phosphatase, and plasma amino acids levels.<br>Secondary analysis of this study published by Schulze 1987, which reported the following outcomes: metabolizable energy, energy expenditure, and stored energy. |
| Notes | Does not mention total parenteral nutrition. However, Schulze states that monitoring began when full feedings were tolerated. Full feedings was not defined.<br>Carbohydrates and fat were both altered to make the formulas isocaloric. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Kashyap 1988**

| | |
|---|---|
| Methods | RCT: Assigned randomly<br>Blinding of randomization: Can't tell<br>Blinding of intervention: Yes (investigators and nurses)<br>Complete follow-up: No<br>Blinding of outcome: Can't tell<br>Six infants (12%) (2 in Group 1, 1 in Group 2 and 3 in Group 3) were withdrawn for: medical conditions (e.g. PDA) that limited intake (2 infants), NEC (2 infants), failed to tolerate 180cc/kg/day (1 infant) and severe gastroesophageal reflux (1 infant). |

**Kashyap 1988** (*Continued*)

| | |
|---|---|
| Participants | 50 LBW infants weighing between 900 to 1750 g at birth.<br>Inclusion criteria: no gastrointestinal disease, renal disease or pulmonary disease. |
| Interventions | High protein intake: 3.8 g/kg/day (n=15).<br>Low protein intake: 2.8 g/kg/day (N=14).<br>Formulas varied with K 14% higher in high protein formula and Ca and Mg, 15% and 20% higher, respectively, in the low protein formula.<br>The assigned formula was started as soon as enteral feedings were tolerated. Formula increased until intake of 180cc/kg/day reached and this was maintained throughout study period (until infants reached 2200g). |
| Outcomes | Weight, length, head circumference, triceps and subscapular skin fold thickness, nutrient balance (N, Na, K, Cl, Ca & P), blood urea nitrogen, albumin and transthyretin, acid-base status and alkaline phosphatase, plasma amino acids, nutrient retention, energy balance, and composition of weight gain. |
| Notes | Both carbohydrates and fat in the formulas were altered to make formulas isocaloric. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Raiha 1976**

| | |
|---|---|
| Methods | RCT: Assigned randomly<br>Blinding of randomization: Can't tell<br>Blinding of intervention: Yes<br>Complete follow-up: No<br>Blinding of outcome: Yes<br>Three infants (3%) were dropped from the study during the first 3 days due to respiratory problems. All of the other infants were in the study for at least 3 weeks. Two infants were withdrawn at 3 and 3.5 weeks due to progressive metabolic acidosis and "progressive nitrogen retention". |
| Participants | 106 infants<br>Inclusion criteria: free of physical abnormality or obvious disease, gestational ages between 28 and 36 weeks, birth weight of < 2100 g and size appropriate for gestational age. |
| Interventions | Very high protein intake: 4.5 g/kg/day (N=41).<br>Low protein intake: 2.3 g/kg/day (n=43).<br>Whey:casein ratios were either 40:60 or 82:18. Whey based formula: K (17%), Ca (15%), and P (12%) were higher in the high protein intake formula.<br>Casein based formula: Na (28%) and Mg (12%) were higher in the lower protein intake formula.<br>Feedings began before 24 hours of age and volume increased gradually until infant reached 150cc/kg/day providing 2.3 or 4.5g/kg/day of protein. This intake was maintained until infants reached 2400g. |
| Outcomes | Weight (reported as initial weight loss, rate of gain from regained birth weight to 2400g, time from birth to regained BW, time from regained BW to 2400g, time from birth to 2400g), vomiting, edema, |

**Raiha 1976** (*Continued*)

| | |
|---|---|
| | hypoglycemia, acid-base studies, mean temperature, linear and head circumference growth, BUN, serum ammonia, urine osmolality, albumin.<br>4 Publications from same study.<br>2nd publication by Rassin 1977 reported selected aliphatic amino acids in plasma and urine.<br>3rd publication by Gaul 1977 reported levels of sulfur amino acids in plasma and urine.<br>4th publication by Rassin 1977 reported levels of tyrosine and phenylalanine in plasma and urine. |
| Notes | Study took place prior to routine use of parenteral nutrition.<br>Lactose content varied to keep formulas isocaloric. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Raiha 28-30 weeks**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | D - Not used |

**Raiha 31-33 weeks**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

***Risk of bias***

**Raiha 31-33 weeks** (*Continued*)

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | D - Not used |

**Raiha 34-36 weeks**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | D - Not used |

**Svenningsen 1982**

| | |
|---|---|
| Methods | RCT: No details<br>Blinding of randomization: Can't tell.<br>Blinding of intervention: Can't tell<br>Complete follow-up: No<br>Blinding of outcome: Can't tell<br>One death in the human milk fed group. One infant in the high protein group was lost to follow-up. |
| Participants | 48 VLBW and preterm infants (n=18 in human milk group).<br>No inclusion/exclusion criteria. |
| Interventions | High protein intake: 3.2 g/kg/day (n=16).<br>Low protein intake: 2.6 g/kg/day (n=14).<br>Formulas had identical nutrient content except for protein.<br>TFI = 170cc/kg/d |
| Outcomes | Mean wt, body length, head circumference, albumin, Urea-N, and metabolic acidosis.<br>2nd study (n=46 by Svenningsen 1982) reported the long-term follow-up growth parameters until 2 years of age and neurodevelopmental outcomes at 6 months, 1 and 2 years of age. Also measured B-haemoglobin and B-hematocrit on capillary samples. |
| Notes | Birth to 2nd wk - IV glucose, electrolytes, and some on parenteral nutrition (note: some infants given pooled human milk).<br>Infants not randomized until the third week of life. |

**Svenningsen 1982** (*Continued*)

| | |
|---|---|
| | Formulas were made isocaloric, however, energy source not specified.<br>End of 2nd wk - all fed per orally with human milk.<br>Definition of Septicemia - unclear. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

**Wauben 1995**

| | |
|---|---|
| Methods | RCT: Infants randomly allocated by use of a computer-created randomization table.<br>Blinding of randomization: Can't tell<br>Blinding of intervention: No<br>Complete follow-up: Yes<br>Blinding of outcome: No (personal communication July 10, 2003). |
| Participants | 16 appropriate for gestational age "healthy" infants between 28 and 35 weeks.<br>Personal communication July 10, 2003 - Eligible infants 1000 to 2500g, AGA, and no history of NEC. |
| Interventions | High protein intake: 3.1 g/kg/day (n=8).<br>Low protein intake: 2.7 g/kg/day (n=8).<br>Nutrient intakes other than protein and energy were not reported.<br>Study started when the infants were receiving full enteral feeding (TFI=160cc/kg/d).<br>Study period 10 days: 2 days for adaptation to the study formula, 8 days for observation. |
| Outcomes | Protein accretion, weight gain, energy and protein balance. |
| Notes | |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Allocation concealment? | Unclear | B - Unclear |

Status as of May 2005 of Additional Data Requested From Authors

Bhatia 1991

Provided data on length, head circumference and blood urea nitrogen levels. Data on length and head circumference was not reported in a manner that would permit inclusion in this systematic review. Last correspondence August 14, 2003.

Hillman 1994

Awaiting information on head circumference, length, and incidence of Stage II NEC or greater. Last correspondence Sept 3, 2003

Kashyap 1986, 1988

Provided data on age when level of plasma amino acids were assessed, criteria for diagnosis of NEC, and clarification for units of measurement for blood urea nitrogen. Last correspondence June 30, 2004.

Raiha 1976

Provided data on phenylalanine levels. Last correspondence October 27, 2004
Svenningsen 1982
Awaiting information on length, head circumference, pH, base deficit, and neurodevelopmental outcomes.
Awaiting clarification regarding definition of Septicemia. Last correspondence January 24, 2004
Wauben 1995
Provided data on NEC and clarified that all infants enrolled in the study were <2.5kg and there was no blinding of investigators. Last correspondence July 9, 2003

## Characteristics of excluded studies *[ordered by study ID]*

| | |
|---|---|
| Bell 1986 | Compared intakes of protein whereby groups fell within the same predesignated high protein intake group (3.4 and 3.9 g/kg/day). |
| Darling 1985 | Not the intervention of interest - formulas differed in quality of protein (different ratio of whey-casein and casein hydrolysate). |
| Davidson 1967 | Experimental protocol was modified during the study period (see page 700). Selective exclusion of infants based on review of clinical course (done prior to deciphering feeding code). |
| Fairey 1997 | Compared intakes of protein whereby groups fell within the same predesignated high protein intake group (3.1 and 3.7 g/kg/day). |
| Fewtrell 1997 | Compared intakes of protein whereby groups fell within the same predesignated high protein intake group (3.6 and 3.9 g/kg/day). |
| Greer 1988 | Both protein intakes fell in the same predesignated criteria of low protein intake (2.8 and 2.9 g/kg/day). |
| Lucas 1990 | Infants received parenteral nutrition during the study period. |
| Mihatsch 2001 | Not the intervention of interest - comparing high lactose vs negligible lactose. Did not meet all criteria of relevance - infants on study formula and total parenteral nutrition. |
| Moro 1984 | Not the intervention of interest. Protein intake was the same in comparison groups. |
| Picaud 2001 | Not the intervention of interest, as compared quality of protein (partially hydrolyzed versus standard formula). |
| Siripoonya 1989 | Not the intervention of interest as compared quality of protein (special care formula versus standard whey-predominate formula). |
| Spencer 1992 | Compared intakes of protein whereby groups fell within the same predesignated low protein intake group (2.9 and 2.95 g/kg/day). |
| Szajewska 2001 | Compared intakes of protein whereby groups fell within the same predesignated high protein intake group (3.3 and 3.8 g/kg/day). |

(*Continued*)

| | |
|---|---|
| van Goudoever 2000 | Not intervention of interest as compared normal energy versus low energy formula. Compared intakes of protein whereby groups fell within the same predesignated high protein intake group (3.3 and 3.3 g/kg/day). |

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Mimouni 1989**

| | |
|---|---|
| Methods | Not known |
| Participants | Not known |
| Interventions | Not known |
| Outcomes | Not known |
| Notes | |

**Nichols 1966**

| | |
|---|---|
| Methods | Not known |
| Participants | Not known |
| Interventions | Not known |
| Outcomes | Not known |
| Notes | |

**Thom 1984**

| | |
|---|---|
| Methods | Not known |
| Participants | Not known |
| Interventions | Not known |
| Outcomes | Not known |
| Notes | |

## DATA AND ANALYSES

### Comparison 1. HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Growth Parameters | 5 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 1.1 Weight gain (g/kg/day) | 5 | 114 | Mean Difference (IV, Fixed, 95% CI) | 2.36 [1.31, 3.40] |
| 1.2 Linear growth (cm/week) | 2 | 48 | Mean Difference (IV, Fixed, 95% CI) | 0.16 [-0.02, 0.34] |
| 1.3 Head growth (cm/week) | 1 | 18 | Mean Difference (IV, Fixed, 95% CI) | 0.37 [0.16, 0.58] |
| 2 Nitrogen Utilization | 2 | 41 | Mean Difference (IV, Fixed, 95% CI) | 1.92 [1.00, 2.84] |
| 2.1 Blood urea nitrogen (mg/dl) | 2 | 41 | Mean Difference (IV, Fixed, 95% CI) | 1.92 [1.00, 2.84] |
| 3 Nitrogen Balance | 2 | 34 | Mean Difference (IV, Fixed, 95% CI) | 143.73 [128.70, 158.77] |
| 3.1 Nitrogen accretion (mg/kg/day) | 2 | 34 | Mean Difference (IV, Fixed, 95% CI) | 143.73 [128.70, 158.77] |
| 4 Phenylalanine Levels | 2 | 41 | Mean Difference (IV, Fixed, 95% CI) | 0.34 [-0.27, 0.96] |
| 4.1 Plasma phenylalanine concentration (umol/dl) | 2 | 41 | Mean Difference (IV, Fixed, 95% CI) | 0.34 [-0.27, 0.96] |
| 5 Necrotizing Enterocolitis | 2 | 46 | Risk Difference (M-H, Fixed, 95% CI) | Not estimable |
| 5.1 NEC (Bell's Stage II or greater) comparing high and low protein intakes (same micronutrient content) | 2 | 46 | Risk Difference (M-H, Fixed, 95% CI) | Not estimable |
| 6 Metabolic Acidosis (pH, Base Excess) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 6.1 pH | 1 | 18 | Mean Difference (IV, Fixed, 95% CI) | 0.01 [-0.02, 0.04] |
| 6.2 Base excess (mEq/L) | 1 | 18 | Mean Difference (IV, Fixed, 95% CI) | -0.20 [-2.43, 2.03] |
| 7 Serum Albumin (g/l) | 1 | 18 | Mean Difference (IV, Fixed, 95% CI) | 44.0 [23.59, 64.41] |
| 7.1 Serum prealbumin (g/L) | 1 | 18 | Mean Difference (IV, Fixed, 95% CI) | 44.0 [23.59, 64.41] |
| 8 Sepsis | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.44 [0.04, 4.32] |
| 8.1 Septicemia | 1 | 30 | Risk Ratio (M-H, Fixed, 95% CI) | 0.44 [0.04, 4.32] |
| 9 Diarrhea | 1 | 18 | Risk Difference (M-H, Fixed, 95% CI) | Not estimable |
| 9.1 Diarrhea Episodes (Babies with one or more episodes of diarrhea) | 1 | 18 | Risk Difference (M-H, Fixed, 95% CI) | Not estimable |

**Comparison 4. HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Growth Parameters | 6 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 1.1 Weight gain (g/kg/day) | 6 | 143 | Mean Difference (IV, Fixed, 95% CI) | 2.53 [1.62, 3.45] |
| 1.2 Linear growth (cm/week) | 3 | 77 | Mean Difference (IV, Fixed, 95% CI) | 0.16 [0.03, 0.30] |
| 1.3 Head growth (cm/week) | 2 | 47 | Mean Difference (IV, Fixed, 95% CI) | 0.23 [0.12, 0.35] |
| 2 Nitrogen Utilization | 2 | 47 | Mean Difference (IV, Fixed, 95% CI) | 3.22 [2.48, 3.96] |
| 2.1 Blood urea nitrogen (mg/dl) | 2 | 47 | Mean Difference (IV, Fixed, 95% CI) | 3.22 [2.48, 3.96] |
| 3 Nitrogen Balance | 3 | 63 | Mean Difference (IV, Fixed, 95% CI) | 112.57 [101.37, 123.77] |
| 3.1 Nitrogen accretion (mg/kg/day) | 3 | 63 | Mean Difference (IV, Fixed, 95% CI) | 112.57 [101.37, 123.77] |
| 4 Phenylalanine Levels | 2 | 47 | Mean Difference (IV, Fixed, 95% CI) | 0.25 [-0.20, 0.70] |
| 4.1 Plasma phenylalanine concentration (umol/dl) | 2 | 47 | Mean Difference (IV, Fixed, 95% CI) | 0.25 [-0.20, 0.70] |

**Comparison 5. VERY HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Growth Parameters | 3 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 1.1 Weight gain (g/week) | 3 | 84 | Mean Difference (IV, Fixed, 95% CI) | -6.47 [-19.05, 6.11] |
| 1.2 Linear growth (cm/week) | 3 | 84 | Mean Difference (IV, Fixed, 95% CI) | -0.03 [-0.10, 0.04] |
| 2 Phenylalanine Levels | 1 | 84 | Mean Difference (IV, Fixed, 95% CI) | 3.15 [1.31, 4.99] |
| 2.1 Plasma phenylalanine concentration (umol/dl) | 1 | 84 | Mean Difference (IV, Fixed, 95% CI) | 3.15 [1.31, 4.99] |

**Comparison 6. VERY HIGH VS HIGH PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)**

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Low IQ or Bayley Score at 18 months and/or Later | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 IQ score < 90 at 3 years of age based on chronological age | 1 | 47 | Risk Ratio (M-H, Fixed, 95% CI) | 0.30 [0.14, 0.64] |
| 1.2 IQ score < 90 at 3 years of age based on corrected age | 1 | 216 | Risk Ratio (M-H, Fixed, 95% CI) | 0.70 [0.46, 1.08] |

| | | | | |
|---|---|---|---|---|
| 1.3 IQ score < 90 at 5 years of age | 1 | 49 | Risk Ratio (M-H, Fixed, 95% CI) | 0.31 [0.15, 0.66] |

## Analysis 1.1. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 1 Growth Parameters.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 1 Growth Parameters

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Weight gain (g/kg/day) | | | | | | | |
| Bhatia 1991 | 16 | 20.3 (2.31) | 7 | 18.9 (1.2) | | 52.7 % | 1.40 [ -0.04, 2.84 ] |
| Hillman 1994 | 18 | 17.4 (3.6) | 9 | 12.9 (5.3) | | 7.4 % | 4.50 [ 0.66, 8.34 ] |
| Kashyap 1986 | 9 | 18.3 (2.8) | 9 | 13.9 (2.8) | | 16.3 % | 4.40 [ 1.81, 6.99 ] |
| Svenningsen 1982 | 16 | 13.8 (4.1) | 14 | 13.3 (3.9) | | 13.3 % | 0.50 [ -2.37, 3.37 ] |
| Wauben 1995 | 8 | 16.45 (3.51) | 8 | 11.54 (3.15) | | 10.2 % | 4.91 [ 1.64, 8.18 ] |
| **Subtotal (95% CI)** | **67** | | **47** | | | **100.0 %** | **2.36 [ 1.31, 3.40 ]** |
| Heterogeneity: $Chi^2$ = 9.25, df = 4 (P = 0.06); $I^2$ =57% | | | | | | | |
| Test for overall effect: Z = 4.42 (P < 0.00001) | | | | | | | |
| 2 Linear growth (cm/week) | | | | | | | |
| Kashyap 1986 | 9 | 1.21 (0.32) | 9 | 0.94 (0.19) | | 53.6 % | 0.27 [ 0.03, 0.51 ] |
| Svenningsen 1982 | 16 | 1.02 (0.38) | 14 | 0.99 (0.35) | | 46.4 % | 0.03 [ -0.23, 0.29 ] |
| **Subtotal (95% CI)** | **25** | | **23** | | | **100.0 %** | **0.16 [ -0.02, 0.34 ]** |
| Heterogeneity: $Chi^2$ = 1.74, df = 1 (P = 0.19); $I^2$ =42% | | | | | | | |
| Test for overall effect: Z = 1.75 (P = 0.081) | | | | | | | |
| 3 Head growth (cm/week) | | | | | | | |
| Kashyap 1986 | 9 | 1.22 (0.28) | 9 | 0.85 (0.15) | | 100.0 % | 0.37 [ 0.16, 0.58 ] |
| **Subtotal (95% CI)** | **9** | | **9** | | | **100.0 %** | **0.37 [ 0.16, 0.58 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 3.49 (P = 0.00048) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 17.70, df = 2 (P = 0.00), $I^2$ =89% | | | | | | | |

### Analysis 1.2. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 2 Nitrogen Utilization.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

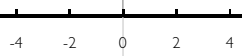
Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 2 Nitrogen Utilization

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Blood urea nitrogen (mg/dl) | | | | | | | |
| Bhatia 1991 | 16 | 9.85 (1.53) | 7 | 7.62 (1.64) | | 41.4 % | 2.23 [ 0.80, 3.66 ] |
| Kashyap 1986 | 9 | 3.1 (1.45) | 9 | 1.4 (1.13) | | 58.6 % | 1.70 [ 0.50, 2.90 ] |
| **Total (95% CI)** | **25** | | **16** | | | **100.0 %** | **1.92 [ 1.00, 2.84 ]** |

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² =0.0%

Test for overall effect: Z = 4.09 (P = 0.000042)




### Analysis 1.3. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 3 Nitrogen Balance.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 3 Nitrogen Balance

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Nitrogen accretion (mg/kg/day) | | | | | | | |
| Kashyap 1986 | 9 | 422.2 (21.7) | 9 | 267.9 (12) | | 86.2 % | 154.30 [ 138.10, 170.50 ] |
| Wauben 1995 | 8 | 348 (30) | 8 | 270 (50) | | 13.8 % | 78.00 [ 37.59, 118.41 ] |
| **Total (95% CI)** | **17** | | **17** | | | **100.0 %** | **143.73 [ 128.70, 158.77 ]** |

Heterogeneity: Chi² = 11.80, df = 1 (P = 0.00059); I² =92%

Test for overall effect: Z = 18.73 (P < 0.00001)

### Analysis 1.4. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 4 Phenylalanine Levels.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

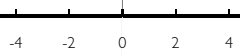
Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 4 Phenylalanine Levels

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Plasma phenylalanine concentration (umol/dl) | | | | | | | |
| Bhatia 1991 | 16 | 4.8 (1.3) | 7 | 4.5 (0.7) | | 56.5 % | 0.30 [ -0.52, 1.12 ] |
| Kashyap 1986 | 9 | 6.4 (0.6) | 9 | 6 (1.3) | | 43.5 % | 0.40 [ -0.54, 1.34 ] |
| **Total (95% CI)** | **25** | | **16** | | | **100.0 %** | **0.34 [ -0.27, 0.96 ]** |

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.87); I² =0.0%

Test for overall effect: Z = 1.09 (P = 0.28)




### Analysis 1.5. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 5 Necrotizing Enterocolitis.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 5 Necrotizing Enterocolitis

| Study or subgroup | High n/N | Low n/N | Risk Difference M-H,Fixed,95% CI | Weight | Risk Difference M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 NEC (Bell's Stage II or greater) comparing high and low protein intakes (same micronutrient content) | | | | | |
| Svenningsen 1982 | 0/16 | 0/14 | | 65.1 % | 0.0 [ -0.12, 0.12 ] |
| Wauben 1995 | 0/8 | 0/8 | | 34.9 % | 0.0 [ -0.21, 0.21 ] |
| **Total (95% CI)** | **24** | **22** | | **100.0 %** | **0.0 [ -0.12, 0.12 ]** |

Total events: 0 (High), 0 (Low)

Heterogeneity: Chi² = 0.0, df = 1 (P = 1.00); I² =0.0%

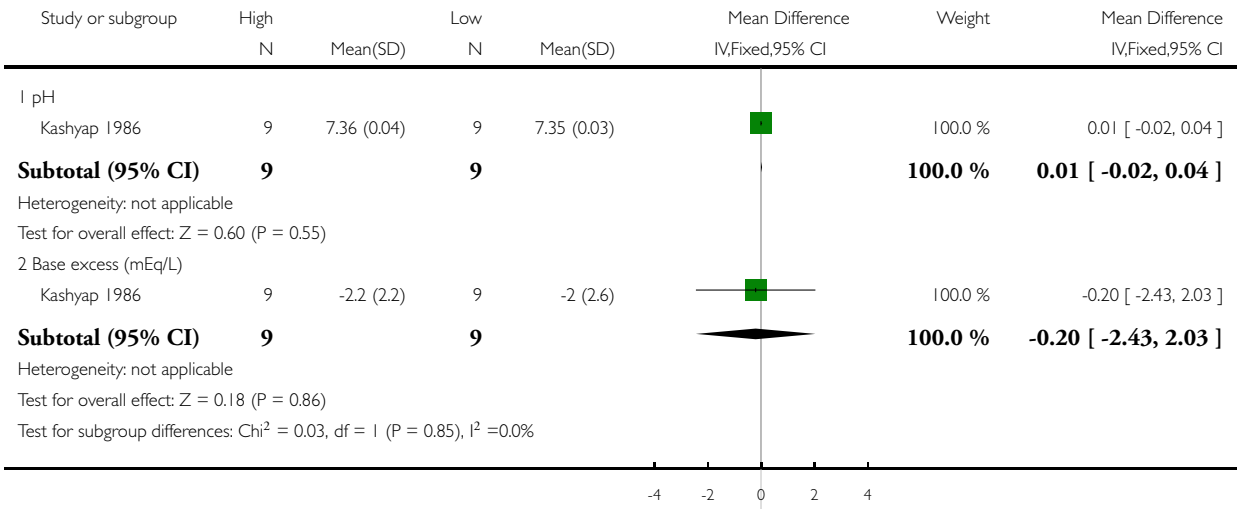
Test for overall effect: Z = 0.0 (P = 1.0)

### Analysis 1.6. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 6 Metabolic Acidosis (pH, Base Excess).

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 6 Metabolic Acidosis (pH, Base Excess)

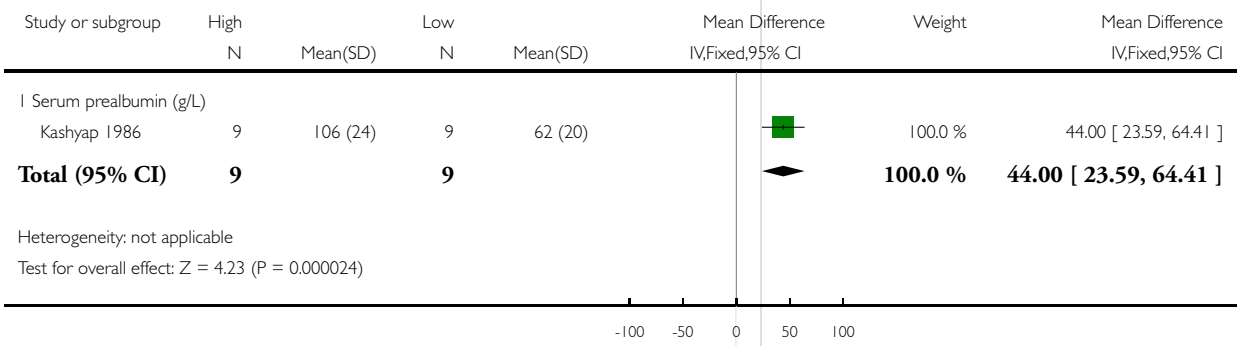



### Analysis 1.7. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 7 Serum Albumin (g/l).

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 7 Serum Albumin (g/l)



## Analysis 1.8. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 8 Sepsis.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 8 Sepsis

| Study or subgroup | High n/N | Low n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Septicemia | | | | | |
| Svenningsen 1982 | 1/16 | 2/14 | | 100.0 % | 0.44 [ 0.04, 4.32 ] |
| **Total (95% CI)** | **16** | **14** | | **100.0 %** | **0.44 [ 0.04, 4.32 ]** |
| Total events: 1 (High), 2 (Low) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.71 (P = 0.48) | | | | | |


## Analysis 1.9. Comparison 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA), Outcome 9 Diarrhea.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 1 HIGH VS LOW PROTEIN INTAKE (RESTRICTED TO STUDIES MEETING ALL A PRIORI INCLUSION CRITERIA)

Outcome: 9 Diarrhea

| Study or subgroup | High n/N | Low n/N | Risk Difference M-H,Fixed,95% CI | Weight | Risk Difference M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Diarrhea Episodes (Babies with one or more episodes of diarrhea) | | | | | |
| Kashyap 1986 | 0/9 | 0/9 | | 100.0 % | 0.0 [ -0.19, 0.19 ] |
| **Total (95% CI)** | **9** | **9** | | **100.0 %** | **0.0 [ -0.19, 0.19 ]** |
| Total events: 0 (High), 0 (Low) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.0 (P = 1.0) | | | | | |

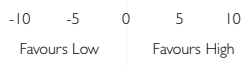
## Analysis 4.1. Comparison 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 1 Growth Parameters.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 1 Growth Parameters

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Weight gain (g/kg/day) | | | | | | | |
| Bhatia 1991 | 16 | 20.3 (2.31) | 7 | 18.9 (1.2) | | 40.2 % | 1.40 [ -0.04, 2.84 ] |
| Hillman 1994 | 18 | 17.4 (3.6) | 9 | 12.9 (5.3) | | 5.6 % | 4.50 [ 0.66, 8.34 ] |
| Kashyap 1986 | 9 | 18.3 (2.8) | 9 | 13.9 (2.8) | | 12.4 % | 4.40 [ 1.81, 6.99 ] |
| Kashyap 1988 | 15 | 19.1 (3.2) | 14 | 16 (1.8) | | 23.7 % | 3.10 [ 1.23, 4.97 ] |
| Svenningsen 1982 | 16 | 13.8 (4.1) | 14 | 13.3 (3.9) | | 10.1 % | 0.50 [ -2.37, 3.37 ] |
| Wauben 1995 | 8 | 16.45 (3.51) | 8 | 11.54 (3.15) | | 7.8 % | 4.91 [ 1.64, 8.18 ] |
| **Subtotal (95% CI)** | **82** | | **61** | | | **100.0 %** | **2.53 [ 1.62, 3.45 ]** |
| Heterogeneity: Chi² = 9.71, df = 5 (P = 0.08); I² =48% | | | | | | | |
| Test for overall effect: Z = 5.44 (P < 0.00001) | | | | | | | |
| 2 Linear growth (cm/week) | | | | | | | |
| Kashyap 1986 | 9 | 1.21 (0.32) | 9 | 0.94 (0.19) | | 29.4 % | 0.27 [ 0.03, 0.51 ] |
| Kashyap 1988 | 15 | 1.21 (0.34) | 14 | 1.04 (0.18) | | 45.1 % | 0.17 [ -0.03, 0.37 ] |
| Svenningsen 1982 | 16 | 1.02 (0.38) | 14 | 0.99 (0.35) | | 25.5 % | 0.03 [ -0.23, 0.29 ] |
| **Subtotal (95% CI)** | **40** | | **37** | | | **100.0 %** | **0.16 [ 0.03, 0.30 ]** |
| Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 2.43 (P = 0.015) | | | | | | | |
| 3 Head growth (cm/week) | | | | | | | |
| Kashyap 1986 | 9 | 1.22 (0.28) | 9 | 0.85 (0.15) | | 31.0 % | 0.37 [ 0.16, 0.58 ] |
| Kashyap 1988 | 15 | 1.15 (0.25) | 14 | 0.98 (0.11) | | 69.0 % | 0.17 [ 0.03, 0.31 ] |
| **Subtotal (95% CI)** | **24** | | **23** | | | **100.0 %** | **0.23 [ 0.12, 0.35 ]** |
| Heterogeneity: Chi² = 2.46, df = 1 (P = 0.12); I² =59% | | | | | | | |
| Test for overall effect: Z = 3.94 (P = 0.000083) | | | | | | | |
| Test for subgroup differences: Chi² = 25.43, df = 2 (P = 0.00), I² =92% | | | | | | | |



### Analysis 4.2. Comparison 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 2 Nitrogen Utilization.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

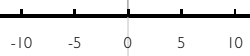
Comparison: 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 2 Nitrogen Utilization

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Blood urea nitrogen (mg/dl) | | | | | | | |
| Kashyap 1986 | 9 | 2.9 (1.18) | 9 | 1.2 (0.84) | | 61.0 % | 1.70 [ 0.75, 2.65 ] |
| Kashyap 1988 | 15 | 8.1 (2.3) | 14 | 2.5 (0.4) | | 39.0 % | 5.60 [ 4.42, 6.78 ] |
| **Total (95% CI)** | **24** | | **23** | | | **100.0 %** | **3.22 [ 2.48, 3.96 ]** |

Heterogeneity: Chi² = 25.47, df = 1 (P<0.00001); I² =96%

Test for overall effect: Z = 8.55 (P < 0.00001)




### Analysis 4.3. Comparison 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 3 Nitrogen Balance.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 3 Nitrogen Balance

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Nitrogen accretion (mg/kg/day) | | | | | | | |
| Kashyap 1986 | 9 | 422.2 (21.7) | 9 | 267.9 (12) | | 47.8 % | 154.30 [ 138.10, 170.50 ] |
| Kashyap 1988 | 15 | 419.6 (30.6) | 14 | 345.8 (12.3) | | 44.6 % | 73.80 [ 57.03, 90.57 ] |
| Wauben 1995 | 8 | 348 (30) | 8 | 270 (50) | | 7.7 % | 78.00 [ 37.59, 118.41 ] |
| **Total (95% CI)** | **32** | | **31** | | | **100.0 %** | **112.57 [ 101.37, 123.77 ]** |

Heterogeneity: Chi² = 48.83, df = 2 (P<0.00001); I² =96%

Test for overall effect: Z = 19.71 (P < 0.00001)

### Analysis 4.4. Comparison 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 4 Phenylalanine Levels.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 4 HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 4 Phenylalanine Levels

| Study or subgroup | High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Plasma phenylalanine concentration (umol/dl) | | | | | | | |
| Kashyap 1986 | 9 | 6.4 (0.6) | 9 | 6 (1.3) | | 23.1 % | 0.40 [ -0.54, 1.34 ] |
| Kashyap 1988 | 15 | 6.4 (0.8) | 14 | 6.2 (0.6) | | 76.9 % | 0.20 [ -0.31, 0.71 ] |
| **Total (95% CI)** | **24** | | **23** | | | **100.0 %** | **0.25 [ -0.20, 0.70 ]** |

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² =0.0%

Test for overall effect: Z = 1.07 (P = 0.28)


### Analysis 5.1. Comparison 5 VERY HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 1 Growth Parameters.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 5 VERY HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 1 Growth Parameters

| Study or subgroup | Very High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Weight gain (g/week) | | | | | | | |
| Raiha 28-30 weeks | 13 | 148 (41) | 14 | 158 (35) | | 19.0 % | -10.00 [ -38.86, 18.86 ] |
| Raiha 31-33 weeks | 14 | 164 (17) | 15 | 176 (33) | | 44.2 % | -12.00 [ -30.93, 6.93 ] |
| Raiha 34-36 weeks | 14 | 175 (28) | 14 | 173 (28) | | 36.8 % | 2.00 [ -18.74, 22.74 ] |
| **Subtotal (95% CI)** | **41** | | **43** | | | **100.0 %** | **-6.47 [ -19.05, 6.11 ]** |
| Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² =0.0% | | | | | | | |
| Test for overall effect: Z = 1.01 (P = 0.31) | | | | | | | |
| 2 Linear growth (cm/week) | | | | | | | |
| Raiha 28-30 weeks | 13 | 0.5 (0.12) | 14 | 0.5 (0.1) | | 64.4 % | 0.0 [ -0.08, 0.08 ] |


(*Continued* . . . )

(. . . *Continued*)

| Study or subgroup | Very High N | Mean(SD) | Low N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Raiha 31-33 weeks | 14 | 0.48 (0.18) | 15 | 0.65 (0.26) | | 17.2 % | -0.17 [ -0.33, -0.01 ] |
| Raiha 34-36 weeks | 14 | 0.53 (0.23) | 14 | 0.54 (0.19) | | 18.4 % | -0.01 [ -0.17, 0.15 ] |
| **Subtotal (95% CI)** | **41** | | **43** | | | **100.0 %** | **-0.03 [ -0.10, 0.04 ]** |

Heterogeneity: $Chi^2 = 3.43$, df = 2 (P = 0.18); $I^2 = 42\%$

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: $Chi^2 = 1.01$, df = 1 (P = 0.32), $I^2 = 1\%$


## Analysis 5.2. Comparison 5 VERY HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 2 Phenylalanine Levels.

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 5 VERY HIGH VS LOW PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 2 Phenylalanine Levels

| Study or subgroup | Very High N | Mean(SD) | High N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Plasma phenylalanine concentration (umol/dl) | | | | | | | |
| Raiha 1976 | 41 | 9.65 (5.41) | 43 | 6.5 (2.68) | | 100.0 % | 3.15 [ 1.31, 4.99 ] |
| **Total (95% CI)** | **41** | | **43** | | | **100.0 %** | **3.15 [ 1.31, 4.99 ]** |

Heterogeneity: not applicable

Test for overall effect: Z = 3.36 (P = 0.00079)

**Analysis 6.1. Comparison 6 VERY HIGH VS HIGH PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS), Outcome 1 Low IQ or Bayley Score at 18 months and/or Later.**

Review: Higher versus lower protein intake in formula-fed low birth weight infants

Comparison: 6 VERY HIGH VS HIGH PROTEIN INTAKE (ADDING STUDIES COMPARING FORMULAS WITH DIFFERENCES IN OTHER NUTRIENTS)

Outcome: 1 Low IQ or Bayley Score at 18 months and/or Later

| Study or subgroup | High n/N | Very High n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 IQ score < 90 at 3 years of age based on chronological age | | | | | |
| Goldman <1300 g | 6/26 | 16/21 | | 100.0 % | 0.30 [ 0.14, 0.64 ] |
| **Subtotal (95% CI)** | **26** | **21** | | **100.0 %** | **0.30 [ 0.14, 0.64 ]** |
| Total events: 6 (High), 16 (Very High) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.16 (P = 0.0016) | | | | | |
| 2 IQ score < 90 at 3 years of age based on corrected age | | | | | |
| Goldman 1969 | 26/111 | 35/105 | | 100.0 % | 0.70 [ 0.46, 1.08 ] |
| **Subtotal (95% CI)** | **111** | **105** | | **100.0 %** | **0.70 [ 0.46, 1.08 ]** |
| Total events: 26 (High), 35 (Very High) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.60 (P = 0.11) | | | | | |
| 3 IQ score < 90 at 5 years of age | | | | | |
| Goldman <1300 g | 6/26 | 17/23 | | 100.0 % | 0.31 [ 0.15, 0.66 ] |
| **Subtotal (95% CI)** | **26** | **23** | | **100.0 %** | **0.31 [ 0.15, 0.66 ]** |
| Total events: 6 (High), 17 (Very High) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.07 (P = 0.0021) | | | | | |


## WHAT'S NEW

Last assessed as up-to-date: 10 October 2005.

| | | |
|---|---|---|
| 27 October 2008 | Amended | Converted to new review format. |

## HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 1, 2006

| | | |
|---|---|---|
| 11 October 2005 | New citation required and conclusions have changed | Substantive amendment |

## CONTRIBUTIONS OF AUTHORS

S. Premji (SSP) and T. Fenton (TRF) - wrote protocol, searched for trials, selected studies, extracted data, wrote review.

SSP - input data into RevMan, performed data-analyses

TRF - corresponded with authors, double checked data entry

R. Sauve (RSS) - principal investigator on the intramural support, facilitated consensus decision making, revised review

Premji SS, Fenton TR, Sauve RS

## DECLARATIONS OF INTEREST

None

## SOURCES OF SUPPORT


### Internal sources

- Perinatal Funding Competition, Canada.
- Alberta Children's Hospital, Canada.

### External sources

- No sources of support supplied


## INDEX TERMS

## Medical Subject Headings (MeSH)

Child Development [*physiology]; Dietary Proteins [*administration & dosage]; Infant, Low Birth Weight [*growth & development]; Infant, Newborn; Infant Formula [*chemistry]; Randomized Controlled Trials as Topic

## MeSH check words

Humans