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Glutamine supplementation to prevent morbidity and mortality in preterm infants (Review)

Moe-Byrne T, Brown JVE, McGuire W

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[Intervention Review]

Glutamine supplementation to prevent morbidity and mortality in preterm infants

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A B S T R A C T

Background

Glutamine is a conditionally essential amino acid. Endogenous biosynthesis may be insufficient for tissue needs in states of metabolic stress. Evidence exists that glutamine supplementation improves clinical outcomes in critically ill adults. It has been suggested that glutamine supplementation may also benefit preterm infants.

Objectives

To determine the effects of glutamine supplementation on mortality and morbidity in preterm infants.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group. This included searches of the Cochrane Central Register of Controlled Trials (CENTRAL, 2015, Issue 12), MEDLINE, EMBASE and Maternity and Infant Care (to December 2015), conference proceedings and previous reviews.

Selection criteria

Randomised or quasi-randomised controlled trials that compared glutamine supplementation versus no glutamine supplementation in preterm infants at any time from birth to discharge from hospital.

Data collection and analysis

We extracted data using the standard methods of the Cochrane Neonatal Review Group, with separate evaluation of trial quality and data extraction by two review authors. We synthesised data using a fixed-effect model and reported typical relative risk, typical risk difference and weighted mean difference.

Main results

We identified 12 randomised controlled trials in which a total of 2877 preterm infants participated. Six trials assessed enteral glutamine supplementation and six trials assessed parenteral glutamine supplementation. The trials were generally of good methodological quality. Meta-analysis did not find an effect of glutamine supplementation on mortality (typical relative risk 0.97, 95% confidence interval 0.80 to 1.17; risk difference 0.00, 95% confidence interval -0.03 to 0.02) or major neonatal morbidities including the incidence of invasive infection or necrotising enterocolitis. Three trials that assessed neurodevelopmental outcomes in children aged 18 to 24 months and beyond did not find any effects.

Authors' conclusions

The available trial data do not provide evidence that glutamine supplementation confers important benefits for preterm infants.

PLAIN LANGUAGE SUMMARY

Glutamine supplementation to prevent morbidity and mortality in preterm infants

Review question: In preterm infants, does glutamine supplementation reduce the risk of death or disability?

Background: Glutamine is an important nutrient for growth and development and may be especially important in protecting preterm infants from infections and gut problems that cause death and disability. We sought evidence that giving preterm infants extra glutamine improves important outcomes.

Study characteristics: We found 12 randomised controlled trials (enrolling 2877 infants in total). The trials were generally of good methodological quality.

Key results: These trials did not provide strong or consistent evidence that glutamine supplementation affected the risk of death, serious infection or bowel disease, or longer term development.

Conclusions: Glutamine supplementation is not likely to be beneficial for preterm infants.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Population: Preterm infants
Intervention: Glutamine supplementation ¶
Comparison: No supplementation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with no supplementation	**Risk with Glutamine supplementation**			
Death prior to hospital discharge	Study population		RR 0.97 (0.80 to 1.17)	2877 (12 RCTs)	⊕⊕⊕⊕ HIGH
	123 per 1000	119 per 1000 (98 to 144)			
	Moderate				
	80 per 1000	78 per 1000 (64 to 94)			
Neurodevelopmental impairment	Study population		RR 1.07 (0.59 to 1.92)	72 (1 RCT)	⊕⊕◯◯ LOW [1]
	375 per 1000	401 per 1000 (221 to 720)			
	Moderate				
	375 per 1000	401 per 1000 (221 to 720)			
Invasive infection	Study population		RR 0.94 (0.86 to 1.04)	2815 (11 RCTs)	⊕⊕⊕◯ MODERATE [2,3]
	368 per 1000	346 per 1000 (316 to 383)			
	Moderate				

	364 per 1000	342 per 1000 (313 to 379)			
Necrotising enterocolitis	Study population		RR 0.83 (0.66 to 1.06)	2849 (11 RCTs)	⊕⊕⊕◯ MODERATE [2,3]
	95 per 1000	79 per 1000 (63 to 101)			
	Moderate				
	72 per 1000	59 per 1000 (47 to 76)			

¶ Enteral or parenteral route
[1] Total sample size= 72
[2] Unexplained heterogeneity
[3] Funnel plot asymmetry

BACKGROUND

Glutamine is the most abundant amino acid in plasma and muscle in humans (Bergström 1974). Under normal conditions glutamine is the preferred respiratory fuel for rapidly proliferating cells such as enterocytes and lymphocytes (Windmueller 1982; Newsholme 1985). It is a regulator of acid-base balance via ammonium, as well as an important precursor of nucleic acids, nucleotides, amino sugars and protein (Krebs 1980).

Description of the intervention

Endogenous biosynthesis of glutamine may be insufficient for tissue needs in states of metabolic stress. In these situations glutamine appears to be "conditionally essential" (Lacey 1990). Glutamine is abundant in human milk, but present only in much lower levels in infant formula and not present in standard parenteral nutrition solutions. It has been suggested that glutamine supplementation may benefit preterm infants.

How the intervention might work

In animal models of experimental enterocolitis, glutamine supplementation has been associated with reduced mucosal damage, improved nitrogen balance, lower rates of sepsis and higher levels of survival (Klimberg 1990; Rombeau 1990). In studies in adult humans, glutamine supplementation has been shown to attenuate gut atrophy in the fasting state, maintain ATP levels in oxidant injured cells, preserve immune cellularity of the gastrointestinal tract during prolonged parenteral feeding and reduce post-operative deterioration in gastrointestinal permeability and mucosal integrity (O'Dwyer 1989; Hinshaw 1990; Alverdy 1992; van der Hulst 1993). Parenteral glutamine in adults is well tolerated metabolically and appears to have no toxic effects (Ziegler 1990). The findings of systematic reviews of randomised controlled trials in adult surgical or critically ill patients suggest that glutamine supplementation reduces infectious complications and duration of hospital stay and may reduce mortality (Wischmeyer 2008; Avenell 2009). Systematic reviews of randomised controlled trials found that patients undergoing bone marrow transplantation who receive parenteral nutrition with glutamine versus standard parenteral nutrition have fewer episodes of invasive infection (Crowther 2009; Murray 2009). Larger trials of glutamine supplementation in these populations are ongoing.

Why it is important to do this review

Given the findings in studies with adult participants, it is reasonable to hypothesise that glutamine supplementation in preterm infants (particularly very preterm infants) might enhance gastrointestinal mucosal integrity, thus improving enteral feed tolerance, growth and development. Enhanced gastrointestinal barrier function and lymphocyte production might reduce the rate of late-onset invasive infection or necrotising enterocolitis (NEC), and so reduce mortality and adverse neurodevelopmental outcomes.

OBJECTIVES

Our objective was to determine the effects of glutamine supplementation on mortality and morbidity in preterm infants. We prespecified subgroup analyses of enteral and parenteral glutamine supplementation because evidence from systematic reviews of these interventions in adults suggests different effect sizes for various outcomes (Avenell 2009).

METHODS

Criteria for considering studies for this review

Types of studies

We included controlled trials using random or quasi-random participant allocation. Due to the nature of the intervention, we excluded cross-over trials.

Where trials were reported as abstracts only, we aimed to include them provided there was sufficient information to assess eligibility. We contacted the authors requesting further information if we could not decide after reading the abstract.

Types of participants

We included preterm infants (gestational age < 37 weeks) admitted to neonatal intensive or special care units or comparable settings after birth. Where participants in a trial included both term and preterm infants, we sought subgroup data from the report or from the authors.

Types of interventions

Glutamine supplementation versus no supplementation, administered by the parenteral or enteral route, in addition to a standard nutrition regime.

Types of outcome measures

Studies were included in the review regardless of whether they reported all outcome measures. If a study did not report these outcomes we requested further information from the trial authors.

Primary outcomes

1. Death prior to hospital discharge.
2. Neurodevelopment:
   i) Neurodevelopmental outcomes assessed using validated tools at ≥ 12 months post term.
   ii) Classifications of disability, including non-ambulant cerebral palsy, developmental delay and auditory and visual impairment.
   iii) Cognitive and educational outcomes at ≥ 5 years: intelligence quotient and indices of educational achievement measured using a validated tool (including school examination results).

Secondary outcomes

1. Invasive infection during hospital admission as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, urine or from a normally sterile body space (number of participants per group with one or more episodes).
2. NEC during hospital admission including at least two of the following features:
   i) Pneumatosis coli on abdominal radiograph.
   ii) Abdominal distension/abdominal radiograph with gaseous distension or frothy appearance of bowel lumen (or both).
   iii) Blood in stool.
   iv) Lethargy, hypotonia or apnoea (or combination of these).
3. Growth during the trial period: weight gain (g/day or g/kg/day), linear growth (mm/week), head growth (mm/week), skinfold thickness growth (mm/week).
4. Days from birth to establish full enteral tube feeds (at least 150 ml/kg/day), independently of parenteral fluids or nutrition.
5. Days from birth to discharge to home from hospital.

Search methods for identification of studies

We used the standard search strategy of the Cochrane Neonatal Review Group.

Electronic searches

We searched: the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (OvidSP), Maternity and Infant Care (OvidSP), MEDLINE & MEDLINE in process (OvidSP) and PubMed (until December 2015 updated from previous search in November 2011) using the combination of text words and MeSH terms described in Appendix 1. We did not apply language restrictions. Search filters were applied in EMBASE, MEDLINE and PubMed to limit retrieval to clinical trials.

We searched Clinical Trials.gov, metaRegister of Controlled Trials (mRCT), and the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing and completed trials.

Searching other resources

We examined the reference lists of studies identified as potentially relevant. We also searched the abstracts from the annual meetings of the Pediatric Academic Societies (1993 to 2015), the European Society for Pediatric Research (1995 to 2014), the UK Royal College of Paediatrics and Child Health (2000 to 2015) and the Perinatal Society of Australia and New Zealand (2000 to 2014). We considered trials reported only as abstracts to be eligible if sufficient information was available, from the report or from contact with the authors, to fulfil the inclusion criteria.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group.

Selection of studies

Two review authors screened the titles and abstracts of all studies identified by the search. We assessed the full texts of any potentially eligible reports and excluded those studies that did not meet all of the inclusion criteria. We discussed any disagreements until consensus was achieved.

Data extraction and management

We used a data collection form to aid extraction of relevant information from each included study. One author extracted the data and a second author checked the extracted data. Any disagreements were discussed until consensus was achieved. We contacted the investigators for further information if data from the trial reports were insufficient.

Assessment of risk of bias in included studies

We used the criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of any included trials. Two authors conducted the assessment of risk of bias. We resolved disagreements by discussion. We requested additional information from the trial authors to clarify methodology and results if necessary.

We made explicit judgements about whether studies were at high risk of bias across four domains according to the criteria suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

1. Random sequence generation - we categorised the method used to generate the allocation sequence as having:
   - low risk - any truly random process, e.g. random number table, computer random number generator;
   - high risk - any non-random process, e.g. odd or even date of birth, hospital or clinic record number; or
   - unclear risk - no or unclear information provided.

2. Allocation concealment - we categorised the method used to conceal the allocation sequence as having:

- low risk - e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes;
- high risk - open random allocation, e.g. unsealed or non-opaque envelopes, alternation, assignment determined by date of birth; or
- unclear risk - no or unclear information provided.

3. Blinding - we assessed blinding of participants, clinicians and caregivers, and outcome assessors separately for different outcomes and categorised the methods as having:

- low risk;
- high risk; or
- unclear risk.

4. Incomplete outcome data - we described the completeness of data, including attrition and exclusions from the analysis for each outcome, and any reasons for attrition or exclusion, where reported. We assessed whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we planned to reinstate missing data in the analyses. We categorised completeness as having:

- low risk: ≤ 10% missing data;
- high risk: > 10% missing data; or
- unclear risk: no or unclear information provided.

Quality of evidence

We assessed the quality of evidence for the main comparisons at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011a). This methodological approach considers evidence from randomised controlled trials as high quality that may be downgraded based on consideration of any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. (Guyatt 2011a). The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades: 1) High: We are very confident that the true effect lies close to that of the estimate of the effect; 2) Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; 3) Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; 4) Very Low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect (Schünemann 2013).

Two review authors independently assessed the quality of the evidence found for outcomes identified as critical or important for clinical decision making: mortality and invasive infection.

In cases where we considered the risk of bias arising from inadequate concealment of allocation, randomised assignment, complete follow-up or blinded outcome assessment to reduce our confidence in the effect estimates, we downgraded the quality of evidence accordingly (Guyatt 2011b). Consistency was evaluated by similarity of point estimates, extent of overlap of confidence intervals and statistical criteria including measurement of heterogeneity (I^2). The quality of evidence was downgraded when inconsistency across studies results was present being large and unexplained (some studies suggest important benefit and others no effect or harm without a clinical explanation) (Guyatt 2011d). Precision was assessed according with the 95% confidence interval around the pooled estimation (Guyatt 2011c). When trials were conducted in populations other than the target population, we downgraded the quality of evidence because of indirectness (Guyatt 2011e).

The pooled estimates of the effects and 95% confidence intervals (CI) with explicit judgments for each of the above aspects assessed were entered into the Guideline Development Tool, the software used to create Summary of Findings (SoF) tables (GRADEpro 2008). All judgements involving the assessment of the study characteristics described above were explained in foot notes or comments in the SoF table.

Measures of treatment effect

We calculated relative risk (RR) and risk difference (RD) for dichotomous data and weighted mean difference (WMD) for continuous data, with respective 95% confidence intervals (CI). We determined the number needed to treat for benefit (NNTB) or harm (NNTH) for a statistically significant difference in the RD.

Dealing with missing data

We requested outcome data from the trial investigators when these were unavailable in the report. Specifically, we sought unpublished data on the primary outcomes and on the incidence of NEC and invasive infection for all trials. Further information on methodology, especially with regard to the assessment of the risk of bias, was also requested from authors if necessary. The tables 'Characteristics of included studies' report which information was obtained from authors.

Assessment of heterogeneity

We examined the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots if more than one trial was included in a meta-analysis. We calculated the I^2 statistic for each analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than sampling error. If substantial heterogeneity was detected ($I^2 > 50\%$), we explored the possible causes (for example, differences in study design, participants, interventions, or completeness of outcome assessments).

Assessment of reporting biases

We inspected a funnel plot for asymmetry if more than ten trials were included in a meta-analysis.

Data synthesis

We used a fixed-effect model for meta-analyses.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

1. Route of administration of glutamine supplementation: enteral versus parenteral glutamine administration.
2. Trial setting (country): low- and middle-income versus high-income countries (see: http://data.worldbank.org/about/country-classifications)

R E S U L T S

Description of studies

See: Included studies; Excluded studies.

Results of the search

The updated search identified one new eligible trial (Pawlik 2012). One publication of relevant follow-up data from van den Berg 2005 was identified and included in this review (de Kieviet 2012). Several other publications of follow-up data were also identified by the searches but were excluded as they did not report any of our prespecified outcomes in addition to data already included in this review.

The trial NCT00213668 was identified by our search of trial registers. Contact with the trial coordinator revealed that this trial has been completed, however no publication of relevant outcomes could be identified. NCT01263041 was also identified by our searches as potentially relevant. We were unable to determine who is responsible for this trial and hence do not know the current status of this trial. These trials may be included in an update of this review as results become available.

Included studies

We included 12 trials that fulfilled the eligibility criteria; nine single-centre studies (Lacey 1996; Neu 1997; Thompson 2003; Bober-Olesiñska 2005; van den Berg 2005; Korkmaz 2007; Mohamad Ikram 2011; Sevastiadou 2011; Pawlik 2012), one trial in two centres (Wang 2010) and two larger multi-centre trials (Vaughn 2003; Poindexter 2004).

Participants

A total of 2877 preterm infants participated in the included trials; 2082 (72%) of these infants participated in the two largest trials (Vaughn 2003; Poindexter 2004). All participating infants were of very or extremely low birth weight and were recruited to a trial within the first few days of postnatal life.

Intervention

Six trials assessed the effect of parenteral glutamine supplementation (Lacey 1996; Thompson 2003; Poindexter 2004; Bober-Olesiñska 2005; Wang 2010; Mohamad Ikram 2011). The other six trials examined the effect of enteral glutamine supplementation (Neu 1997; Vaughn 2003; van den Berg 2005; Korkmaz 2007; Sevastiadou 2011; Pawlik 2012).

Outcomes

Reported outcomes included mortality, the incidence of invasive infection, NEC, the duration of parenteral nutrition administration, time taken to establish full enteral nutrition, rate of weight gain and length of hospital admission. Poindexter 2004 and van den Berg 2005 reported neurodevelopmental outcomes at 18 and 24 months post term, respectively. van den Berg 2005 reported neurodevelopmental and cognitive outcomes at seven to eight years of age.

Excluded studies

See: Characteristics of excluded studies.

Risk of bias in included studies

Allocation

Eight trials reported adequate allocation concealment methods (randomisation in central pharmacy, computer generated sequence in sealed opaque envelopes; Neu 1997; Thompson 2003; Vaughn 2003; Poindexter 2004; Bober-Olesiñska 2005; van den Berg 2005; Wang 2010; Mohamad Ikram 2011). Two trials were likely to be "quasi-randomised" and did not report concealment of allocation (Lacey 1996; Korkmaz 2007). Two trial reports did not describe the randomisation and allocation procedure (Sevastiadou 2011; Pawlik 2012).

Blinding

All apart from two trial reports described the methods used for blinding of caregivers and investigators (Korkmaz 2007; Pawlik 2012).

Incomplete outcome data

Nine trials achieved complete or near-complete levels of follow-up and reported intention-to-treat analyses (Neu 1997; Thompson 2003; Vaughn 2003; Poindexter 2004; Bober-Olesiñska 2005; van den Berg 2005; Wang 2010; Sevastiadou 2011; Pawlik 2012). Two trials did not report the drop out rate (Korkmaz 2007; Mohamad Ikram 2011). Lacey 1996 reported post-recruitment withdrawal of nearly 50% of participants, mainly due to non-compliance with protocol.

Effects of interventions

See: **Summary of findings for the main comparison** Glutamine supplementation to prevent morbidity and mortality in preterm infants

Glutamine supplementation versus no supplementation (parenteral or enteral route)

Primary outcomes

Death prior to hospital discharge (Analysis 1.1)

None of the individual studies nor a meta-analyses of data from all trials showed a statistically significant difference (typical RR 0.97, 95% CI 0.80 to 1.17; typical RD 0.00, 95% CI -0.03 to 0.02; 12 studies, 2877 infants; Analysis 1.1). There was no evidence of statistical heterogeneity or funnel plot asymmetry (Figure 1).

Figure 1. Funnel plot of comparison: 1 Glutamine supplementation versus no supplementation, outcome: 1.1 Death prior to hospital discharge.
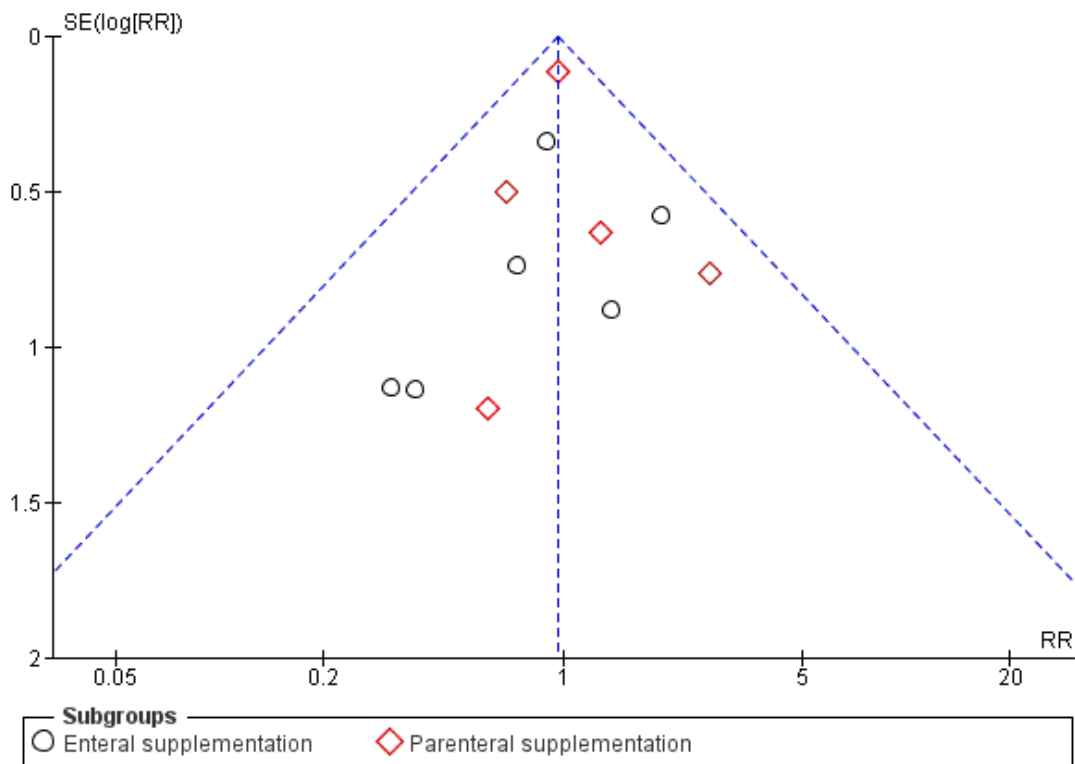
Neurodevelopment (Analysis 1.2)

Poindexter 2004 conducted follow-up assessments of about 89%

of the surviving infants at 18 to 22 months post term. This included neurological examination and developmental assessment

using Bayley Scales of Infant Development II (BSID-II) Mental, Motor and Behavior Rating Scales. The investigators reported that they did not find any statistically significant differences between the groups for any of the outcomes assessed but numerical data are not published or yet available. Thirty month follow-up on all of these infants was also planned. We could not find these data for inclusion in this review. They will be included in a future update if they become available.

van den Berg 2005 reported neurodevelopmental outcomes for infants aged two years post term. Outcomes assessed included the mental development index (MDI) and psychomotor development index (PDI) subscales of the BSID-II, incidence of cerebral palsy and visual and hearing impairment. No significant differences between the glutamine and the control groups were reported for any of these individual outcomes or for a composite of neurodevelopmental impairment consisting of any of the following: MDI ≤ 85, PDI ≤ 85, cerebral palsy, blindness in one or both eyes or hearing loss requiring amplification (RR 1.07, 95% CI 0.59 to 1.92; RD 0.03, 95% CI -0.20 to 0.25; 1 study, 72 infants; Analysis 1.2).

van den Berg 2005 reported follow-up assessments of 68 children aged 7 to 8 years. Four of these children had serious motor (n = 2), hearing (n = 1), or visual (n = 1) difficulties which prevented them from participating; it is not known if these children received glutamine or placebo. Of the remaining 64 children, 30 had received glutamine after birth and 34 had received placebo. The trial did not show any significant differences in intelligence quotient, processing speed, attention level, working memory and parent- and teacher-rated behavioural outcomes.

Secondary outcomes

Invasive infection (Analysis 1.3)

Data were available from eleven trials (Lacey 1996; Neu 1997; Thompson 2003; Vaughn 2003; Poindexter 2004; Bober-Olesińska 2005; van den Berg 2005; Korkmaz 2007; Mohamad Ikram 2011; Sevastiadou 2011; Pawlik 2012). Two trials found a statistically significant lower incidence in infants who received glutamine (van den Berg 2005; Sevastiadou 2011), but none of the other trials nor a meta-analysis of all of the data found a statistically significant difference (typical RR 0.94, 95% CI 0.86 to 1.04; typical RD -0.02, 95% CI -0.06 to 0.01; 11 studies, 2815 infants; Analysis 1.3). There was evidence of statistical heterogeneity (I^2 = 58%) and funnel plot asymmetry (Figure 2).

Figure 2.   Funnel plot of comparison: 1 Glutamine supplementation versus no supplementation, outcome: 1.3 Invasive infection.
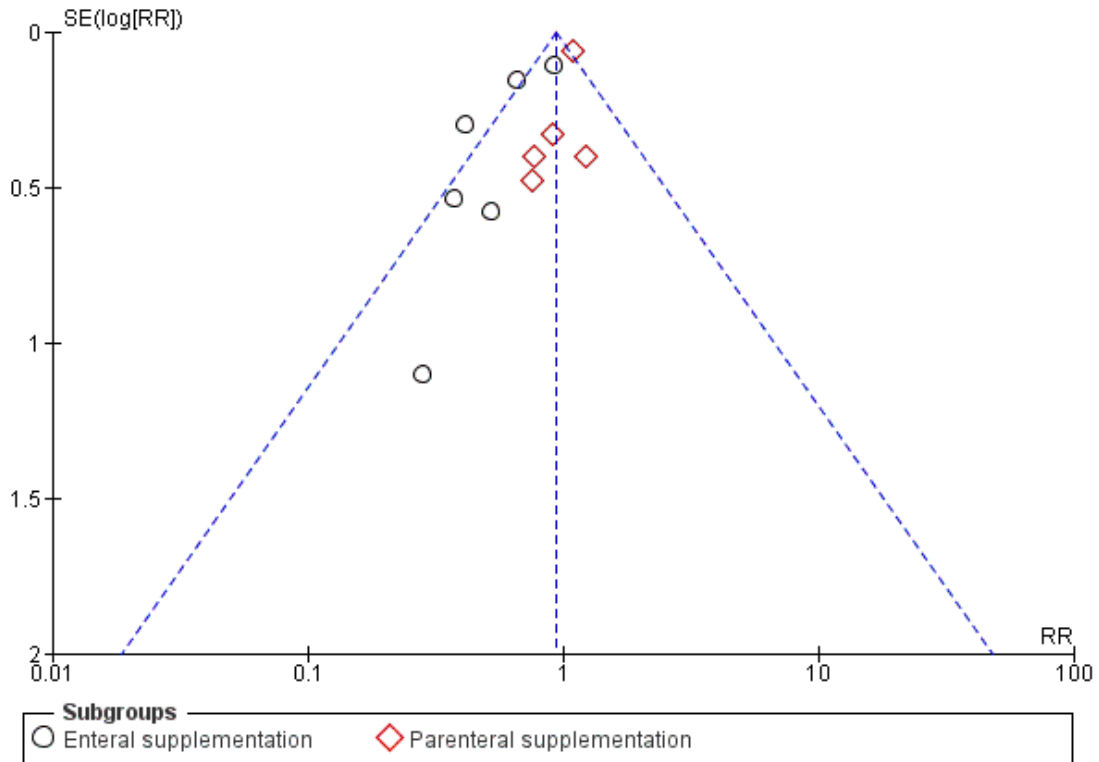
Necrotising enterocolitis (Analysis 1.4)

None of the eleven individual studies that reported this outcome found a statistically significant difference (Lacey 1996; Neu 1997; Thompson 2003; Vaughn 2003; Poindexter 2004; Bober-Olesiñska 2005; van den Berg 2005; Korkmaz 2007; Mohamad Ikram 2011; Sevastiadou 2011; Pawlik 2012). Meta-analysis did not reveal a statistically significant difference (typical RR 0.83, 95% CI 0.66 to 1.06; typical RD -0.02, 95% CI -0.04 to 0.00; 11 studies, 2879 infants; Analysis 1.4). There was some evidence of statistical heterogeneity (I² = 31%), as well as funnel plot asymmetry (Figure 3).

Figure 3. Funnel plot of comparison: 1 Glutamine supplementation versus no supplementation, outcome: 1.4 Necrotising enterocolitis.
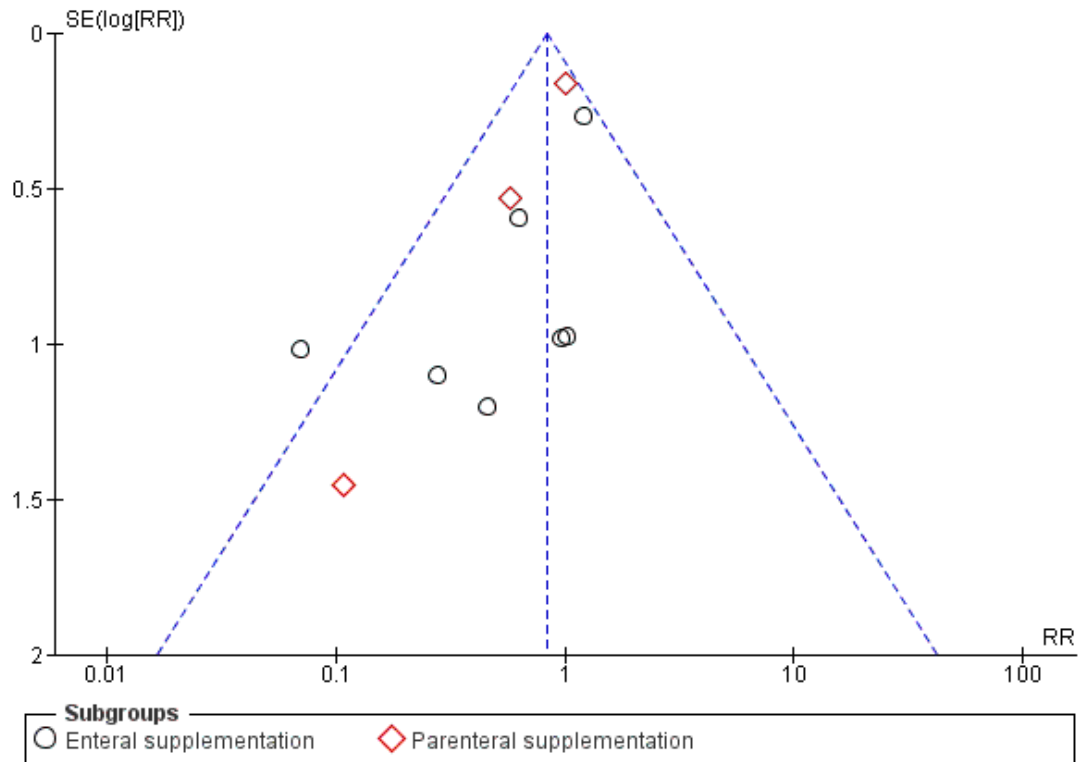
Growth during the trial period (Analysis 1.5)

Meta-analysis of data from three trials did not reveal a statistically significant difference in the rate of weight gain in grams/day during the study period (WMD 0.59, 95% CI -1.42 to 2.59; Analysis 1.5) There was evidence of statistical heterogeneity ($I^2 = 40\%$) (Analysis 1.5). Four trials reported no statistically significant differences in the rate of weight gain or mean weight at the end of the trial period but did not provide data that could be included in meta-analyses (Neu 1997; Vaughn 2003; Poindexter 2004; van den Berg 2005). Korkmaz 2007 reported that the rate of gain in weight and length and head circumference was higher in the glutamine group than controls up to the end of the 120 day intervention period, but numerical data (including number of participants assessed at each monthly interval) were not available for inclusion in the meta-

analysis.

Days from birth to establish full enteral feeds (Analysis 1.6)

Data were available from seven studies (Lacey 1996; Thompson 2003; Poindexter 2004; van den Berg 2005; Korkmaz 2007; Wang 2010; Mohamad Ikram 2011). Thompson 2003 reported a statistically significant shorter time to full enteral nutrition in the glutamine group while the other studies did not find any significant differences. Meta-analysis of data from all of these trials showed a statistically significant difference between glutamine and control groups in days to full enteral feeds (WMD -1.68, 95% CI -2.88 to -0.48; Analysis 1.6). Statistical heterogeneity was not evident ($I^2 = 13\%$), nor was funnel plot asymmetry (Figure 4).

Figure 4. Funnel plot of comparison: 1 Glutamine supplementation versus no supplementation, outcome: 1.6 Time to full enteral nutrition (days).
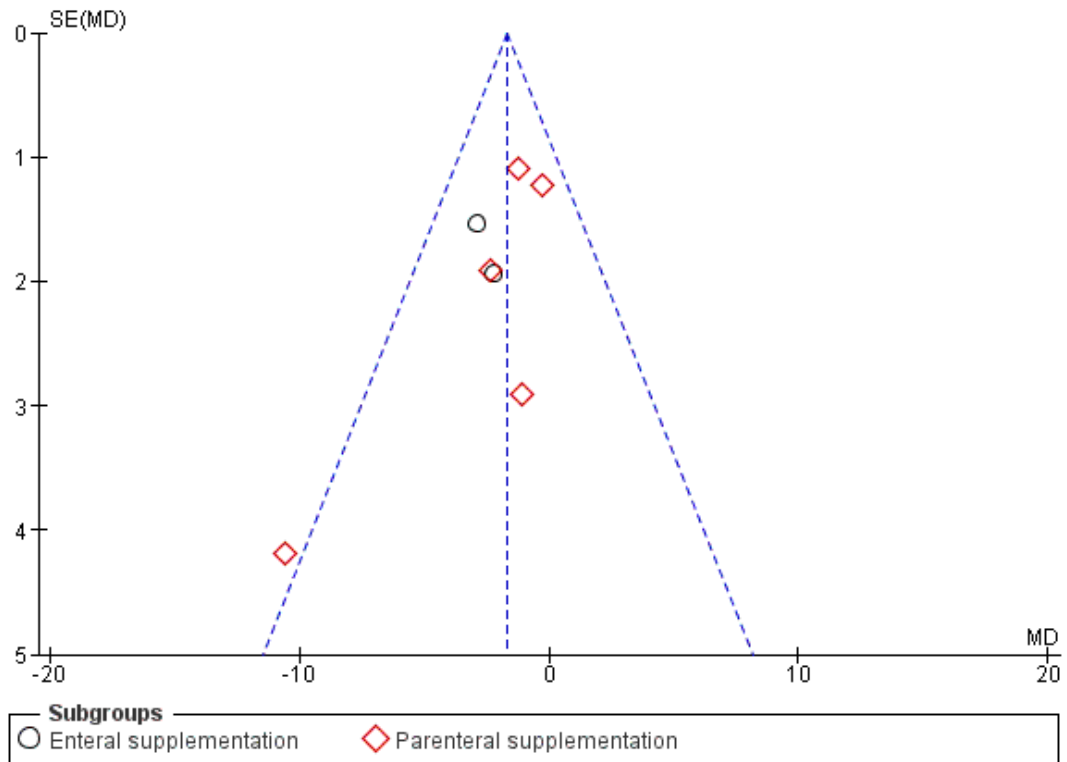
Days from birth to discharge to home from hospital (Analysis 1.7)

Data were available from eight trials (Lacey 1996; Thompson 2003; Vaughn 2003; Poindexter 2004; van den Berg 2005; Korkmaz 2007; Wang 2010; Mohamad Ikram 2011). None of the trials nor a meta-analysis of all data found a statistically significant difference between the glutamine and the control group in days from birth to discharge to home in days (WMD -0.85, 95% CI -3.39 to 1.70; Analysis 1.7). Statistical heterogeneity was not evident (I^2 = 0%), nor was funnel plot asymmetry (Figure 5).

Figure 5. Funnel plot of comparison: 1 Glutamine supplementation versus no supplementation, outcome: 1.7 Duration of hospital stay (days).
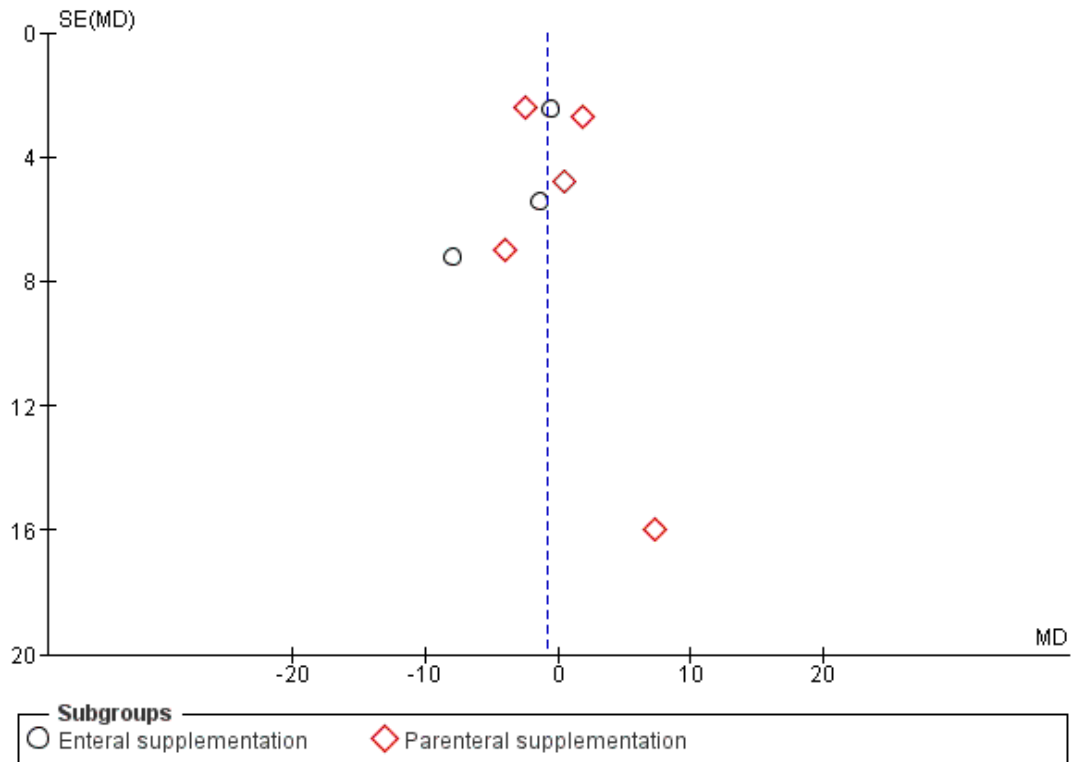
Subgroup analyses

Enteral glutamine supplementation

Six trials examined the effect of enteral glutamine supplementation (Neu 1997; Vaughn 2003; van den Berg 2005; Korkmaz 2007; Sevastiadou 2011; Pawlik 2012). Meta-analysis of the available data did not show statistically significant effects on mortality or NEC (Analysis 1.1; Analysis 1.4).

Meta-analysis showed a statistically significant lower incidence of invasive infection in the enteral glutamine supplemented group (typical RR 0.76, 95% CI 0.64 to 0.89; typical RD -0.09, 95% CI -0.14 to -0.04; NNTB 11, 05% CI 7 to 25; 6 studies, 1095 infants) (Analysis 1.3). The meta-analysis contained substantial statistical heterogeneity ($I^2 = 56\%$) which remained in a sensitivity analysis in which the quasi-randomised trial was omitted (Korkmaz 2007). Meta-analysis of data from two trials (van den Berg 2005; Korkmaz 2007) showed a statistically significant difference in time to reach full enteral feeds (WMD -2.63 days, 95% CI -4.99 to -0.27) (Analysis 1.6). Meta-analysis of three trials (Vaughn 2003; van den

Berg 2005; Korkmaz 2007) did not find a statistically significant difference in duration of hospital stay (Analysis 1.7).

Parenteral glutamine supplementation

Six trials examined the effect of parenteral glutamine supplementation (Lacey 1996; Thompson 2003; Poindexter 2004; Bober-Olesińska 2005; Wang 2010; Mohamad Ikram 2011). Meta-analyses did not detect any statistically significant effects on mortality, incidence of invasive infection, incidence of NEC, rate of weight gain, time to full enteral nutrition, or duration of hospital stay (Analysis 1.1; Analysis 1.3; Analysis 1.5; Analysis 1.6; Analysis 1.7). Substantial heterogeneity was not evident in any of these meta-analyses.

Low- or middle-income countries (Analyses 2.1-2.6)

Three of the trials were undertaken in middle-income countries: Turkey (Korkmaz 2007), Malaysia (Mohamad Ikram 2011), and China (Wang 2010). Meta-analyses did not detect any statistically significant effects on mortality (Analysis 2.1), incidence of invasive

infection (Analysis 2.2), NEC (Analysis 2.3), rate of weight gain (Analysis 2.4), time to full enteral feeds (Analysis 2.5), or duration of hospital stay (Analysis 2.6). Statistical heterogeneity was not evident in any of these meta-analyses.

DISCUSSION

Summary of main results

The major finding of this review of 12 randomised controlled trials is that glutamine supplementation does not have a statistically significant effect on mortality in preterm infants. The narrow 95% CI around the estimate of effect suggests that a modest but clinically important difference has not been missed. Data from three of the trials also indicate that glutamine supplementation does not have an important effect on neurodevelopmental outcomes. With regard to secondary outcomes, we did not find evidence of an effect on major neonatal morbidities including the rate of invasive infection and the incidence of NEC.

In a pre-specified subgroup analysis, we found that enteral (but not parenteral) glutamine supplementation resulted in a statistically significant reduction in the incidence of invasive infection.

However, the meta-analysis contained substantial heterogeneity not explained by variation in study design and methodological quality (randomised versus quasi-randomised). In a meta-analysis of two trials, enteral glutamine supplementation resulted in a 2.6 days reduction in the time taken to achieve full enteral nutrition. Given the potential clinical importance of these findings, further evaluation of enteral glutamine supplementation may be merited as advocated by van Zwol 2011. Currently, two trials of enteral glutamine supplementation in preterm infants are ongoing and their findings may be incorporated into an update of this review (NCT00213668; NCT01263041).

Quality of the evidence

The interpretation of the review findings is limited by the existence of methodological weaknesses associated with the potential for bias in some of the trials (Figure 6). The main concern is lack of evidence of methods to preserve allocation concealment in four of the trials (Lacey 1996; Korkmaz 2007; Sevastiadou 2011; Pawlik 2012). However, in general the trials were of good quality and analyses with quasi-randomised trials omitted did not alter statistical heterogeneity or the overall size of the treatment effects.

Figure 6. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

The other methodological limitation present in one of the trials was incomplete outcome assessment (Lacey 1996). This trial reported post-recruitment withdrawal of nearly 50% of participants, mainly due to non-compliance with protocol issues. Intention-to-treat re-analysis was not possible. Removal of this trial in sensitivity analyses did not affect the level of heterogeneity or size of treatment effect.

Potential biases in the review process

The main concern with the review process is the possibility that the findings are subject to publication and other reporting biases; in other words, that there may be a greater availability of data for inclusion in meta-analyses from trials which reported statistically significant or clinically important effects (Hopewell 2007a; Hopewell 2007b; Hopewell 2009). We attempted to minimise this threat by searching the proceedings of the major international perinatal conferences to identify trial reports that were not published in full form in academic journals (Young 2011). However, we cannot be sure that other trials have not been undertaken but not reported, and the concern remains that such trials are less likely than published trials to have detected statistically significant or clinically important effects. Some of the meta-analyses that we performed demonstrated funnel plot asymmetry consistent with possible publication or reporting bias (Figure 2).

Agreements and disagreements with other studies or reviews

The biologically plausible effects of glutamine supplementation relate to its role in the repair and growth of rapidly dividing cells. This action is consistent with the evidence of benefit of glutamine supplementation in critically ill adult patients (Wischmeyer 2008; Avenell 2009). Although the population of preterm infants who participated in the trials identified in this review were all of very low birth weight (and of extremely low birth weight in the largest trial), it may be that any benefits of glutamine supplementation are confined to those infants who are critically ill, for example with severe gastrointestinal disease such as NEC. Glutamine supplementation may be beneficial in the recovery phase of these illnesses when infants are severely metabolically compromised and glutamine availability is rate-limiting for tissue repair (Brown 2014). Additionally, many of the participating infants in the included trials may not have been truly glutamine-deficient as they received glutamine from breast milk, or received glutamate (a precursor for glutamine) from milk, formula, or parenteral nutrition.

AUTHORS' CONCLUSIONS

Implications for practice

The available data from randomised controlled trials suggests that the routine use of glutamine supplementation does not have an important effect on mortality or neonatal morbidity in preterm infants. Some limited evidence exists that enteral glutamine supplementation reduces the time to reach full enteral nutrition and the rate of late-onset invasive infection in preterm infants; this finding should be interpreted with caution because of the potential for bias in the included trials.

Implications for research

Follow-up of infants who participated in the trials identified in this review might provide further data on the effect of this intervention on growth through later childhood, specifically later neurodevelopmental outcomes. Further evaluation of routine parenteral glutamine supplementation in preterm infants is unlikely to be considered a research priority, but this review does provide some support for further trials of enteral glutamine supplementation to be undertaken (van Zwol 2011). It may also be appropriate to focus research effort on assessing the effect of glutamine supplementation as a treatment for preterm infants with severe gastrointestinal disease (Brown 2014).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bober-Olesińska 2005

Methods	Randomised controlled trial
Participants	55 very low birth weight infants
Interventions	Treatment: glutamine dipeptide added to standard parenteral nutrition solution to make 20% of total amino acid content (n = 25) Control: no added glutamine (n = 30)
Outcomes	Invasive infection and rate of NEC
Notes	Abstract in English. Article in Polish. Further information received courtesy of Dr Bober-Olesińska

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of intervention and outcome measurement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up assessment

Korkmaz 2007

Methods	Quasi-randomised controlled trial
Participants	69 very low birth weight infants (appropriate birth weight for gestational age) Exclusion criteria: congenital malformations, chromosomal abnormalities, inherited metabolic diseases, receipt of enteral feeding for < 1 week or mechanical ventilation for > 4 weeks, those developing post-haemorrhagic hydrocephalus after grade III to IV intra-ventricular haemorrhage
Interventions	Treatment: enteral glutamine supplementation (300 mg/kg/day) between 8-120 days after birth (n = 36) Control: sterile water (n = 33)

Korkmaz 2007 (*Continued*)

Outcomes	Growth parameters (weight, length, head circumference, left upper mid-arm circumference, left mid-thigh circumference during trial period (4 months)) Incidence of invasive infection Time to full enteral nutrition Duration of hospital stay
Notes	Data on mortality and NEC incidence supplied by trial investigators Setting: Neonatal Intensive Care Unit and neonatal follow-up clinic of Hacettepe University, Ihsan Dogramaci Children's Hospital, Anakara, Turkey (early 2000s)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised allocation of participants according to the order of admission
Allocation concealment (selection bias)	High risk	Quasi-randomised allocation of participants according to the order of admission
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported, number presumed to be followed up: 36 and 33

Lacey 1996

Methods	Randomised controlled trial
Participants	78 infants aged < 4 days, receiving parenteral nutrition for < 3 days Must have met > 5 of the following criteria: birth weight < 1500 g, gestational age < 32 weeks, 5-minute Apgar score < 6, need for > 21% oxygen, need for ventilatory assistance, low blood pressure for age, suspected intraventricular haemorrhage, presence of patent ductus arteriosus, presence of umbilical, arterial and venous catheters and birth weight < 1000 g
Interventions	Treatment: glutamine added to parenteral nutrition solution (n = 38) Control: parenteral nutrition without added glutamine (n = 39)
Outcomes	Time to full enteral feeds, duration of administration of parenteral nutrition, duration of mechanical ventilation, average weight gain per day, duration of hospital stay
Notes	Glutamine was added to parenteral nutrition at concentrations of between 15% and 25% weight per volume of the amino acid mix. The protocol specified that participating infants should continue to receive parenteral nutrition for at least seven days

Lacey 1996 (*Continued*)

| | | Setting: Brigham and Women's Hospital, Boston, USA (early 1990s) |

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	First four infants allocated to intervention group and subsequent participants allocated by "balanced assignment" - unclear if this was concealed, may be quasi-randomisation
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, nursing staff and dieticians blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Of the 78 infants originally enrolled, 34 were subsequently excluded for the following reasons: insufficient time on parenteral nutrition (8 treated and 8 control), surgery or transfer (1 treated and 3 control), development of NEC (2 treatment and 2 control) or death (5 treatment and 4 control). One was excluded as a "statistical outlier" (allocation not stated). We have not been able to re-analyse the outcomes for all of the enrolled infants (intention-to-treat)

Mohamad Ikram 2011

Methods	Randomised controlled trial
Participants	154 newborn infants aged < 72 hours and receiving parenteral nutrition Exclusion criteria: chromosomal abnormalities or inborn metabolism errors, those born from consanguineous marriage and those anticipated to require < 48 hours parenteral nutrition
Interventions	Treatment: 20% glutamine solution added to standard parenteral nutrition (n = 76) Control: standard parenteral nutrition (n = 78)
Outcomes	Mortality, invasive infection, NEC, time to full enteral nutrition, time to discharge
Notes	Trial included term and preterm infants, subgroup data for preterm infants were provided by authors Setting: Neonatal Intensive Care Unit at Hospital Universiti Sains, Malaysia

Risk of bias

Mohamad Ikram 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly permuted blocks
Allocation concealment (selection bias)	Low risk	Randomisation sequence was generated by a person who was not directly involved in recruitment or care of the infants
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators and treating staff blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow up assessment

Neu 1997

Methods	Randomised controlled trial
Participants	68 newborn infants (birth weight 500 - 1250 grams, gestational age 24 - 32 weeks) aged < 3 days Exclusion criteria: congenital anomalies of gastrointestinal tract, NEC, major surgery, breast fed infants, infants considered nonviable Duration: 3 - 30 days of life
Interventions	Treatment: enteral glutamine added to commercial preterm formula feed (n = 35) Control: no added glutamine (n = 33)
Outcomes	Mortality, invasive infection, NEC, duration of hospital stay
Notes	The intervention group received 0.08 g/kg/day of glutamine at the start of the study (day 3), increasing to 0.31 g/kg/day by day 13. Glutamine supplementation was stopped on day 30. All infants received the same level of parenteral nutrition (without added glutamine) while enteral feeds were being advanced Setting: Neonatal Intensive Care Unit, Shands Hospital at University of Florida, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Sealed envelopes

Neu 1997   (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	All investigators and caregivers blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 68 infants enrolled, 27 were withdrawn from the study for the following reasons: transfer (1 treated and 1 control), illness or intolerance of enteral feeding (9 treated and 16 control). All but the two infants who were transferred from the study centre were included in the analysis whether they were able to adhere completely to the feeding protocol or not

Pawlik 2012

Methods	Randomised controlled trial
Participants	106 very low birth weight infants
Interventions	Treatment: glutamine/amino acid solution added to usual human milk or formula (n = 50) Control: human milk or formula without added glutamine (n = 56)
Outcomes	Feeding intolerance, NEC, intestinal perforation, sepsis, mortality
Notes	Paper published in Polish with only the abstract and some outcome data available in English. Despite contacting the authors, no further details could be obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methological details were not reported in the abstract. This table will be updated if further details are made available to us by the authors
Allocation concealment (selection bias)	Unclear risk	Methological details were not reported in the abstract.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Methological details were not reported in the abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Methological details were not reported in the abstract.

Poindexter 2004

Methods	Randomised controlled trial
Participants	1433 extremely low birth weight infants enrolled within 72 hours of birth Exclusion criteria: major congenital anomalies, congenital non-bacterial infection, terminal illness, decision made not to provide full intensive care and support Duration: birth to 120 days
Interventions	Treatment: 20% glutamine added to standard parenteral nutrition solution (n = 721) Control: no added glutamine (n = 712)
Outcomes	Primary: Composite outcome of death or late-onset sepsis Secondary: Number of episodes of late-onset invasive infection, rate of NEC, duration of mechanical ventilation, length of hospital stay, measures of feeding tolerance and intolerance, duration of parenteral nutrition, growth parameters
Notes	Setting: 15 neonatal care centres in the USA (1999-2001)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated by data coordination centre
Allocation concealment (selection bias)	Low risk	Hospital pharmacists allocated infants to control or glutamine group
Blinding (performance bias and detection bias) All outcomes	Low risk	The caregivers were not aware whether participating infants received glutamine-supplemented or non-supplemented parenteral nutrition
Incomplete outcome data (attrition bias) All outcomes	Low risk	One baby (glutamine) lost to follow-up

Sevastiadou 2011

Methods	Randomised controlled trial
Participants	101 formula fed preterm infants, birth weight < 2 kg, gestational age < 34 weeks Exclusion criteria: congenital or chromosomal anomalies, severe hypotension, severe perinatal distress, abdominal distention, signs of early NEC Duration: 3 - 30 days
Interventions	Treatment: 10% glutamine solution, administered enterally 3x daily (n = 51), dosage adjusted to actual weight (0.3 g/kg/day) Control: isocaloric "caloreen" (glucose polymer) supplementation (n = 50)
Outcomes	Measures of intestinal permeability

Sevastiadou 2011 (*Continued*)

Notes	Unpublished invasive infection and NEC data provided by authors Setting: Neonatal Intensive Care Unit at Alexandra Regional General Hospital, Greece (2007-8)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Nursing staff blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	25 participants exited the study after randomisation (16 in control group: 4 died, in 12 urine collection failed; 9 in glutamine group: 3 died, in 6 urine collection failed)

Thompson 2003

Methods	Randomised controlled trial
Participants	35 very low birth weight infants with a need for mechanical ventilation or more than 40% oxygen enrolled on day one of postnatal life Exclusion criteria: renal or hepatic dysfunction, suspected congenital anomalies of the gastrointestinal tract, lethal congenital anomalies
Interventions	Treatment: 2.5% glutamine solution given along with standard parenteral nutrition (n = 17), increased to maximum of 3 g/kg/day Control: sterile water with no added glutamine (n = 18)
Outcomes	Time to full enteral feeds, number of episodes of sepsis, rate of weight gain, measures of feeding tolerance and intolerance, rate of NEC
Notes	Infants in the intervention group received a solution of 2.5% L-glutamine given as a separate but simultaneous infusion with the remainder of the parenteral nutrition. The glutamine comprised approximately 16% of total amino acids. Control infants received an infusion of water indistinguishable in appearance to the glutamine solution. Parenteral nutrition and glutamine supplementation was discontinued when enteral feeding exceeded 80% of total energy requirements Setting: Regional Neonatal Unit in Royal Maternity Hospital, Belfast, UK (late 1990s)

Risk of bias

Thompson 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Four-block randomisation sequence generated off-site
Allocation concealment (selection bias)	Low risk	Hospital pharmacists randomly allocated one solution to be control and one to be glutamine supplemented
Blinding (performance bias and detection bias) All outcomes	Low risk	Main researcher, medical and nursing staff blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 infants in the glutamine group and 2 in the control group died

van den Berg 2005

Methods	Randomised controlled trial
Participants	107 very low birth weight or very preterm infants Exclusion criteria: major congenital or chromosomal anomalies, death or transfer to another hospital within 48 hrs of birth, admission from extra regional hospital Duration: 3 - 30 days of life
Interventions	Treatment: enteral glutamine supplementation to breast milk or formula (up to 0.3 g/kg/day; n = 54), after two weeks the dosage was adjusted to actual weight of the infants Control: placebo (alanine) in breast milk or formula (n = 53)
Outcomes	Primary: time to full enteral feeding Secondary: other variables of feeding tolerance, NEC, days of no enteral feeding, incidence of serious infection, growth, need for mechanical ventilation, age at discharge, death *Neurodevelopmental outcomes* Cognitive development, cerebral palsy, blindness and hearing loss were assessed at 24 months corrected age. Out of the 107 infants initially randomised, 88 were eligible for 2 year follow-up. Data were available for 72 infants (glutamine: n = 40, control: n = 32) On follow-up at age 7 to 8 years, 68 children were assessed. Four of these children had serious motor (n = 2), hearing (n = 1), or visual (n = 1) difficulties which hindered them from participation. It is not known if these children received glutamine or placebo. Parents and teachers completed questionnaires addressing any behavioural problems at home or in school, respectively. The following cognitive and motor measures were also assessed: the Wechsler Intelligence Scale for Children to assess intellectual development, the Movement Assessment Battery for Children to assess motor development, and an adapted version of the Attention Network Test to assess orienting, executive, and alerting attention

van den Berg 2005 *(Continued)*

Notes	After randomisation 5 infants were excluded due to clinical complications, therefore glutamine group n = 52, control n = 50 Setting: Level III Neonatal Intensive Care Unit of VU University Medical Centre, Amsterdam, The Netherlands

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation table based on blocks of four
Allocation concealment (selection bias)	Low risk	Sealed code batch numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, parents, medical and nursing staff were not aware which solution infants received
Incomplete outcome data (attrition bias) All outcomes	High risk	17 (glutamine) and 11 (control) infants were lost to follow-up

Vaughn 2003

Methods	Randomised controlled trial
Participants	649 newborn infants with birth weight 500 - 1250 grams Exclusion criteria: major chromosomal or congenital anomalies, high probability of death within 3 days, diagnosed with NEC within 7 days after birth Duration: between 7 days and 36 weeks
Interventions	Treatment: 5 ml/kg of 3% glutamine solution given enterally 12-hourly for the first 28 days (n = 314); dosage not adjusted to weight Control: sterile water with no added glutamine (n = 335)
Outcomes	Primary: Number of infants with positive blood cultures from 7 days to 36 weeks postmenstrual age Secondary: Number of episodes of sepsis, measures of growth, rates of other neonatal morbidities including NEC, and length of hospital stay
Notes	Glutamine/control solution given at the same time but separate from milk feeds Setting: 20 neonatal care centres in the USA (late 1990s)

Risk of bias

Bias	Authors' judgement	Support for judgement

Vaughn 2003 (*Continued*)

Random sequence generation (selection bias)	Low risk	Blocks of 10 for each of 3 birth weight strata
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Caregivers were not aware which solution infants received
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although 105 (56 treated and 49 control) infants left the study before completing a full course of treatment due to death (39), transfer to another hospital (24), NEC (24), meeting exclusion criteria after enrolment (12), discharge home (2) and parental request (4), outcome analyses in the published report and in this review are intention-to-treat

Wang 2010

Methods	Randomised controlled trial
Participants	28 very low birth weight infants receiving parenteral nutrition for at least 7 days Exclusion criteria: pre-existing renal or hepatic dysfunction, congenital errors of metabolism, major chromosomal disease, cytomegalovirus infection, viral hepatitis, congenital or acquired immune deficiency
Interventions	Intervention: parenteral glutamine 0.3 g/kg/day added to parenteral nutrition Control: no glutamine (6% amino acid)
Outcomes	Time to full enteral nutrition, weight gain, head circumference, length of hospitalisation, days on ventilator
Notes	Data on invasive infection, NEC, time to full enteral nutrition, and duration of hospital stay were requested from the authors (not available May 2014) Setting: two neonatal care centres in China (mid-late 2000s)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unique randomisation code
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, parents, physicians, nurses blinded

Wang 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	n = 4 from control group and n = 2 from glutamine group were withdrawn

NEC = necrotising enterocolitis

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

Study	Reason for exclusion
Barbosa 1999	No preterm infants
Li 2007	Not a randomised controlled trial
Strujis 2013	Term infants, average gestational age 37 weeks

Characteristics of ongoing studies *[ordered by study ID]*

NCT00213668

Trial name or title	Effect of Glutamine on Gastric Emptying and Length of Parenteral Nutrition in Premature Neonates
Methods	Randomised controlled trial
Participants	Premature neonates
Interventions	Dietary supplement: glutamine (dipeptiven)
Outcomes	Primary outcome measure: gastric emptying Secondary outcome measures: intestinal transit time, age at total enteral nutrition, age at the end of hospitalisation, variation of cholecystokinin and gastrin postprandial concentration
Starting date	April 2002
Contact information	Contact: Anne Mercier, MD 02-32-88-80-97 ext 02-33-89-42-62 anne.mercier@ch-avranches-granville.fr
Notes	

NCT01263041

Trial name or title	Effect of L-arginine and Glutamine on Preterm (preterm)
Methods	Randomised controlled trial
Participants	Preterm infants
Interventions	Drug: enteral glutamine Drug: l-arginine Other: placebo
Outcomes	Primary outcome measures: necrotising enterocolitis incidence, sepsis incidence, severity and outcome Secondary outcome measures: incidence, severity and outcome of respiratory distress syndrome, pulmonary hypertension, intracranial haemorrhage
Starting date	December 2010
Contact information	Prof. Hesham Awad Ain Shams University
Notes	

DATA AND ANALYSES

Comparison 1. Glutamine supplementation versus no supplementation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	12	2877	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
1.1 Enteral supplementation	6	1095	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.49]
1.2 Parenteral supplementation	6	1782	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.79, 1.20]
2 Neurodevelopmental impairment	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.59, 1.92]
2.1 Enteral supplementation	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.59, 1.92]
2.2 Parenteral supplementation	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Invasive infection	11	2815	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.04]
3.1 Enteral supplementation	6	1095	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.64, 0.89]
3.2 Parenteral supplementation	5	1720	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.94, 1.20]
4 Necrotising enterocolitis	11	2849	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.66, 1.06]
4.1 Enteral supplementation	7	1172	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.49, 1.08]
4.2 Parenteral supplementation	4	1677	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.22]
5 Rate of weight gain (g/day)	3	100	Mean Difference (IV, Fixed, 95% CI)	0.59 [-1.42, 2.59]
5.1 Enteral supplementation	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Parenteral supplementation	3	100	Mean Difference (IV, Fixed, 95% CI)	0.59 [-1.42, 2.59]
6 Time to full enteral nutrition (days)	7	1594	Mean Difference (IV, Fixed, 95% CI)	-1.68 [-2.88, -0.48]
6.1 Enteral supplementation	2	171	Mean Difference (IV, Fixed, 95% CI)	-2.63 [-4.99, -0.27]
6.2 Parenteral supplementation	5	1423	Mean Difference (IV, Fixed, 95% CI)	-1.35 [-2.74, 0.05]
7 Duration of hospital stay (days)	8	2174	Mean Difference (IV, Random, 95% CI)	-0.85 [-3.39, 1.70]
7.1 Enteral supplementation	3	753	Mean Difference (IV, Random, 95% CI)	-1.32 [-5.55, 2.92]
7.2 Parenteral supplementation	5	1421	Mean Difference (IV, Random, 95% CI)	-0.58 [-3.77, 2.61]

Comparison 2. Trials in low- and middle-income countries

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death prior to hospital discharge	3	251	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.35, 1.90]
2 Invasive infection	2	223	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.45, 1.36]
3 Necrotising enterocolitis	2	223	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.21, 1.43]
4 Rate of weight gain (g/day)	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-7.57, 2.37]
5 Time to full enteral nutrition (days)	3	251	Mean Difference (IV, Fixed, 95% CI)	-1.44 [-3.20, 0.33]
6 Duration of hospital stay (days)	3	236	Mean Difference (IV, Fixed, 95% CI)	-1.85 [-5.77, 2.07]

Analysis 1.1. Comparison 1 Glutamine supplementation versus no supplementation, Outcome 1 Death prior to hospital discharge.

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 1 Glutamine supplementation versus no supplementation

Outcome: 1 Death prior to hospital discharge

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enteral supplementation					
Neu 1997	1/35	3/33		1.7 %	0.31 [0.03, 2.87]
Vaughn 2003	15/314	18/335		9.8 %	0.89 [0.46, 1.73]
van den Berg 2005	8/52	4/50		2.3 %	1.92 [0.62, 5.99]
Korkmaz 2007	3/36	2/33		1.2 %	1.38 [0.24, 7.72]
Sevastiadou 2011	3/51	4/50		2.3 %	0.74 [0.17, 3.12]
Pawlik 2012	1/50	3/56		1.6 %	0.37 [0.04, 3.47]
Subtotal (95% CI)	**538**	**557**		**18.9 %**	**0.93 [0.58, 1.49]**
Total events: 31 (Glutamine), 34 (Control)					
Heterogeneity: Chi² = 3.45, df = 5 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 0.30 (P = 0.76)					
2 Parenteral supplementation					
Lacey 1996	5/38	4/39		2.2 %	1.28 [0.37, 4.42]
Thompson 2003	5/17	2/18		1.1 %	2.65 [0.59, 11.86]
Poindexter 2004	124/721	127/712		71.8 %	0.96 [0.77, 1.21]
Bober-Olesi ska 2005	1/25	2/30		1.0 %	0.60 [0.06, 6.24]

0.05   0.2   1   5   20

Favours glutamine   Favours control

(*Continued* . . .)

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 2010	0/13	0/15			Not estimable
Mohamad Ikram 2011	6/76	9/78		5.0 %	0.68 [0.26, 1.83]
Subtotal (95% CI)	**890**	**892**		**81.1 %**	**0.97 [0.79, 1.20]**

Total events: 141 (Glutamine), 144 (Control)

Heterogeneity: Chi² = 2.57, df = 4 (P = 0.63); I² =0.0%

Test for overall effect: Z = 0.25 (P = 0.81)

Total (95% CI)	**1428**	**1449**		**100.0 %**	**0.97 [0.80, 1.17]**

Total events: 172 (Glutamine), 178 (Control)

Heterogeneity: Chi² = 6.03, df = 10 (P = 0.81); I² =0.0%

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² =0.0%

$$0.05 \quad 0.2 \quad 1 \quad 5 \quad 20$$

Favours glutamine   Favours control

Analysis 1.2. Comparison 1 Glutamine supplementation versus no supplementation, Outcome 2 Neurodevelopmental impairment.

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 1 Glutamine supplementation versus no supplementation

Outcome: 2 Neurodevelopmental impairment

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enteral supplementation					
van den Berg 2005	16/40	12/32		100.0 %	1.07 [0.59, 1.92]
Subtotal (95% CI)	**40**	**32**		**100.0 %**	**1.07 [0.59, 1.92]**
Total events: 16 (Glutamine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.83)					
2 Parenteral supplementation					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Glutamine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**40**	**32**		**100.0 %**	**1.07 [0.59, 1.92]**
Total events: 16 (Glutamine), 12 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.83)					
Test for subgroup differences: Not applicable					

0.5   0.7   1   1.5   2

Favours glutamine   Favours control

Analysis 1.3. Comparison 1 Glutamine supplementation versus no supplementation, Outcome 3 Invasive infection.

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 1 Glutamine supplementation versus no supplementation

Outcome: 3 Invasive infection

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enteral supplementation					
Neu 1997	4/35	10/33		2.0 %	0.38 [0.13, 1.09]
Vaughn 2003	106/314	122/335		22.8 %	0.93 [0.75, 1.14]
van den Berg 2005	26/52	38/50		7.5 %	0.66 [0.48, 0.90]
Korkmaz 2007	4/36	7/33		1.4 %	0.52 [0.17, 1.63]
Sevastiadou 2011	11/51	26/50		5.1 %	0.41 [0.23, 0.75]
Pawlik 2012	1/50	4/56		0.7 %	0.28 [0.03, 2.42]
Subtotal (95% CI)	**538**	**557**		**39.4 %**	**0.76 [0.64, 0.89]**
Total events: 152 (Glutamine), 207 (Control)					
Heterogeneity: Chi² = 11.27, df = 5 (P = 0.05); I² =56%					
Test for overall effect: Z = 3.31 (P = 0.00092)					
2 Parenteral supplementation					
Lacey 1996	9/22	7/21		1.4 %	1.23 [0.56, 2.69]
Thompson 2003	5/17	7/18		1.3 %	0.76 [0.30, 1.93]
Poindexter 2004	301/721	273/712		52.9 %	1.09 [0.96, 1.24]
Bober-Olesińska 2005	7/25	11/30		1.9 %	0.76 [0.35, 1.67]
Mohamad Ikram 2011	14/76	16/78		3.0 %	0.90 [0.47, 1.71]
Subtotal (95% CI)	**861**	**859**		**60.6 %**	**1.06 [0.94, 1.20]**
Total events: 336 (Glutamine), 314 (Control)					
Heterogeneity: Chi² = 1.71, df = 4 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 1.02 (P = 0.31)					
Total (95% CI)	**1399**	**1416**		**100.0 %**	**0.94 [0.86, 1.04]**
Total events: 488 (Glutamine), 521 (Control)					
Heterogeneity: Chi² = 23.62, df = 10 (P = 0.01); I² =58%					
Test for overall effect: Z = 1.18 (P = 0.24)					
Test for subgroup differences: Chi² = 10.75, df = 1 (P = 0.00), I² =91%					

0.01   0.1   1   10   100

Favours glutamine   Favours control

Analysis 1.4. Comparison 1 Glutamine supplementation versus no supplementation, Outcome 4 Necrotising enterocolitis.

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 1 Glutamine supplementation versus no supplementation

Outcome: 4 Necrotising enterocolitis

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Enteral supplementation					
Lacey 1996	2/38	2/39		1.5 %	1.03 [0.15, 6.92]
Neu 1997	4/35	6/33		4.6 %	0.63 [0.19, 2.03]
Vaughn 2003	27/314	24/335		17.1 %	1.20 [0.71, 2.03]
van den Berg 2005	2/52	2/50		1.5 %	0.96 [0.14, 6.57]
Korkmaz 2007	1/36	2/33		1.5 %	0.46 [0.04, 4.82]
Sevastiadou 2011	1/51	14/50		10.4 %	0.07 [0.01, 0.51]
Pawlik 2012	1/50	4/56		2.8 %	0.28 [0.03, 2.42]
Subtotal (95% CI)	**576**	**596**		**39.3 %**	**0.73 [0.49, 1.08]**
Total events: 38 (Glutamine), 54 (Control)					
Heterogeneity: Chi² = 9.95, df = 6 (P = 0.13); I² =40%					
Test for overall effect: Z = 1.58 (P = 0.11)					
2 Parenteral supplementation					
Thompson 2003	0/17	0/18			Not estimable
Poindexter 2004	69/721	68/712		50.4 %	1.00 [0.73, 1.38]
Bober-Olesi ska 2005	0/25	5/30		3.7 %	0.11 [0.01, 1.87]
Mohamad Ikram 2011	5/76	9/78		6.5 %	0.57 [0.20, 1.62]
Subtotal (95% CI)	**839**	**838**		**60.7 %**	**0.90 [0.67, 1.22]**
Total events: 74 (Glutamine), 82 (Control)					
Heterogeneity: Chi² = 3.29, df = 2 (P = 0.19); I² =39%					
Test for overall effect: Z = 0.68 (P = 0.49)					
Total (95% CI)	**1415**	**1434**		**100.0 %**	**0.83 [0.66, 1.06]**
Total events: 112 (Glutamine), 136 (Control)					
Heterogeneity: Chi² = 13.08, df = 9 (P = 0.16); I² =31%					
Test for overall effect: Z = 1.51 (P = 0.13)					
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² =0.0%					

```
      0.01    0.1     1     10    100
     Favours glutamine    Favours control
```

Analysis 1.5.   Comparison 1 Glutamine supplementation versus no supplementation, Outcome 5 Rate of weight gain (g/day).

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 1 Glutamine supplementation versus no supplementation

Outcome: 5 Rate of weight gain (g/day)

Study or subgroup	Glutamine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 Enteral supplementation							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
2 Parenteral supplementation							
Lacey 1996	22	15 (5)	22	15 (5)		46.2 %	0.0 [-2.95, 2.95]
Thompson 2003	12	19.1 (2.9)	16	16.4 (5.8)		37.4 %	2.70 [-0.58, 5.98]
Wang 2010	13	13.4 (6.4)	15	16 (7)		16.4 %	-2.60 [-7.57, 2.37]
Subtotal (95% CI)	**47**		**53**			**100.0 %**	**0.59 [-1.42, 2.59]**
Heterogeneity: Chi² = 3.33, df = 2 (P = 0.19); I² =40%							
Test for overall effect: Z = 0.57 (P = 0.57)							
Total (95% CI)	**47**		**53**			**100.0 %**	**0.59 [-1.42, 2.59]**
Heterogeneity: Chi² = 3.33, df = 2 (P = 0.19); I² =40%							
Test for overall effect: Z = 0.57 (P = 0.57)							
Test for subgroup differences: Not applicable							

-4   -2   0   2   4

Favours control   Favours glutamine

Analysis 1.6. Comparison 1 Glutamine supplementation versus no supplementation, Outcome 6 Time to full enteral nutrition (days).

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 1 Glutamine supplementation versus no supplementation

Outcome: 6 Time to full enteral nutrition (days)

Study or subgroup	Glutamine		Control		Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	Mean(SD)	N	Mean(SD)			
1 Enteral supplementation							
Korkmaz 2007	36	12.3 (7.2)	33	14.5 (8.7)		10.1 %	-2.20 [-5.99, 1.59]
van den Berg 2005	52	13.1 (6.1)	50	16 (9.1)		15.9 %	-2.90 [-5.92, 0.12]
Subtotal (95% CI)	**88**		**83**			**25.9 %**	**-2.63 [-4.99, -0.27]**
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² =0.0%							
Test for overall effect: Z = 2.18 (P = 0.029)							
2 Parenteral supplementation							
Thompson 2003	12	15.7 (6.5)	16	26.3 (14.9)		2.2 %	-10.60 [-18.77, -2.43]
Wang 2010	13	20.2 (6.4)	15	21.3 (8.9)		4.5 %	-1.10 [-6.79, 4.59]
Lacey 1996	22	8.3 (5)	22	10.7 (7.4)		10.4 %	-2.40 [-6.13, 1.33]
Poindexter 2004	588	34.8 (20.4)	581	35.1 (21.2)		25.4 %	-0.30 [-2.69, 2.09]
Mohamad Ikram 2011	76	8.55 (6.06)	78	9.79 (7.41)		31.7 %	-1.24 [-3.38, 0.90]
Subtotal (95% CI)	**711**		**712**			**74.1 %**	**-1.35 [-2.74, 0.05]**
Heterogeneity: Chi² = 5.98, df = 4 (P = 0.20); I² =33%							
Test for overall effect: Z = 1.89 (P = 0.059)							
Total (95% CI)	**799**		**795**			**100.0 %**	**-1.68 [-2.88, -0.48]**
Heterogeneity: Chi² = 6.91, df = 6 (P = 0.33); I² =13%							
Test for overall effect: Z = 2.74 (P = 0.0062)							
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² =0.0%							

```
-20    -10    0    10    20
```

Favours glutamine   Favours control

Analysis 1.7. Comparison I Glutamine supplementation versus no supplementation, Outcome 7 Duration of hospital stay (days).
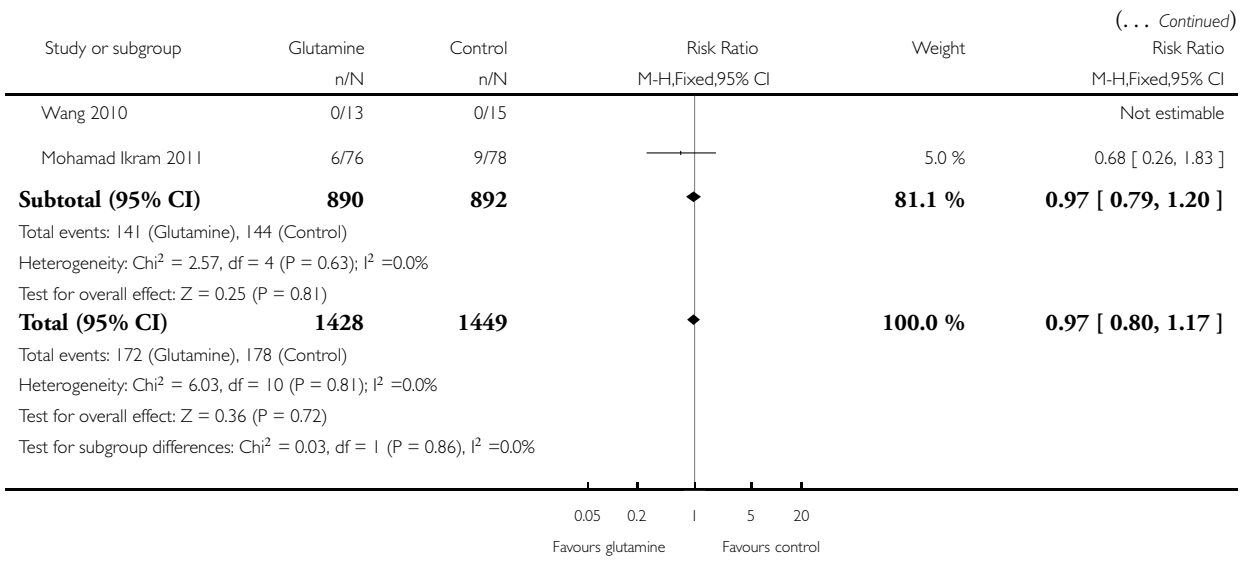
Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: I Glutamine supplementation versus no supplementation
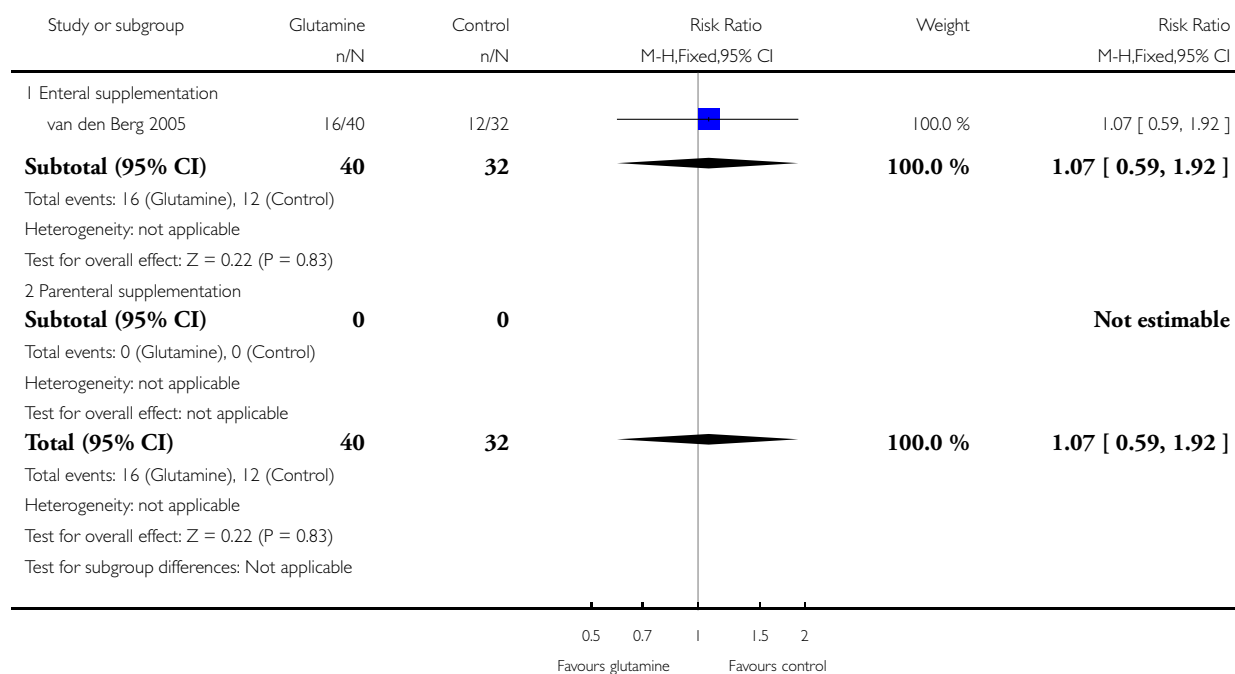
Outcome: 7 Duration of hospital stay (days)
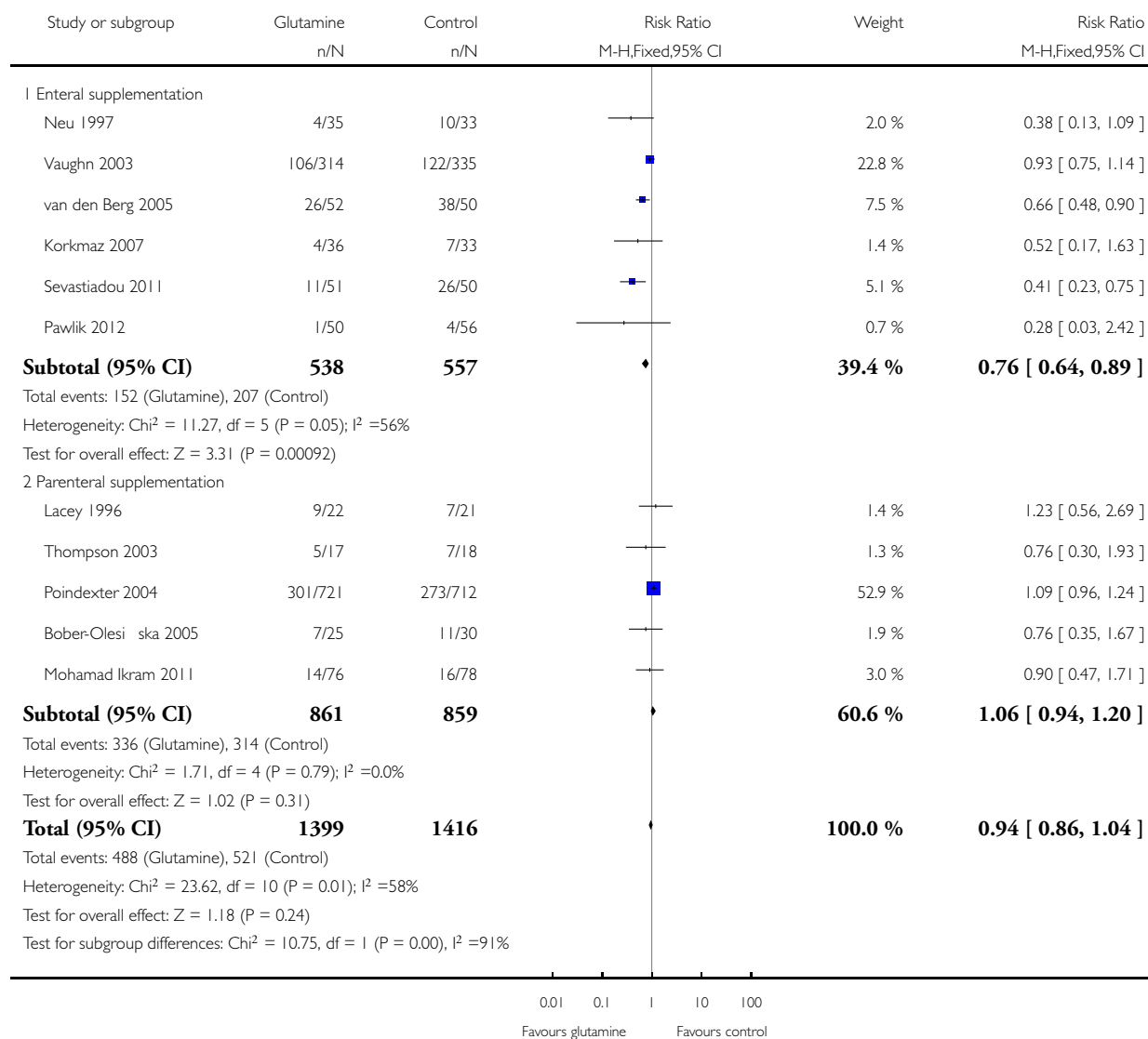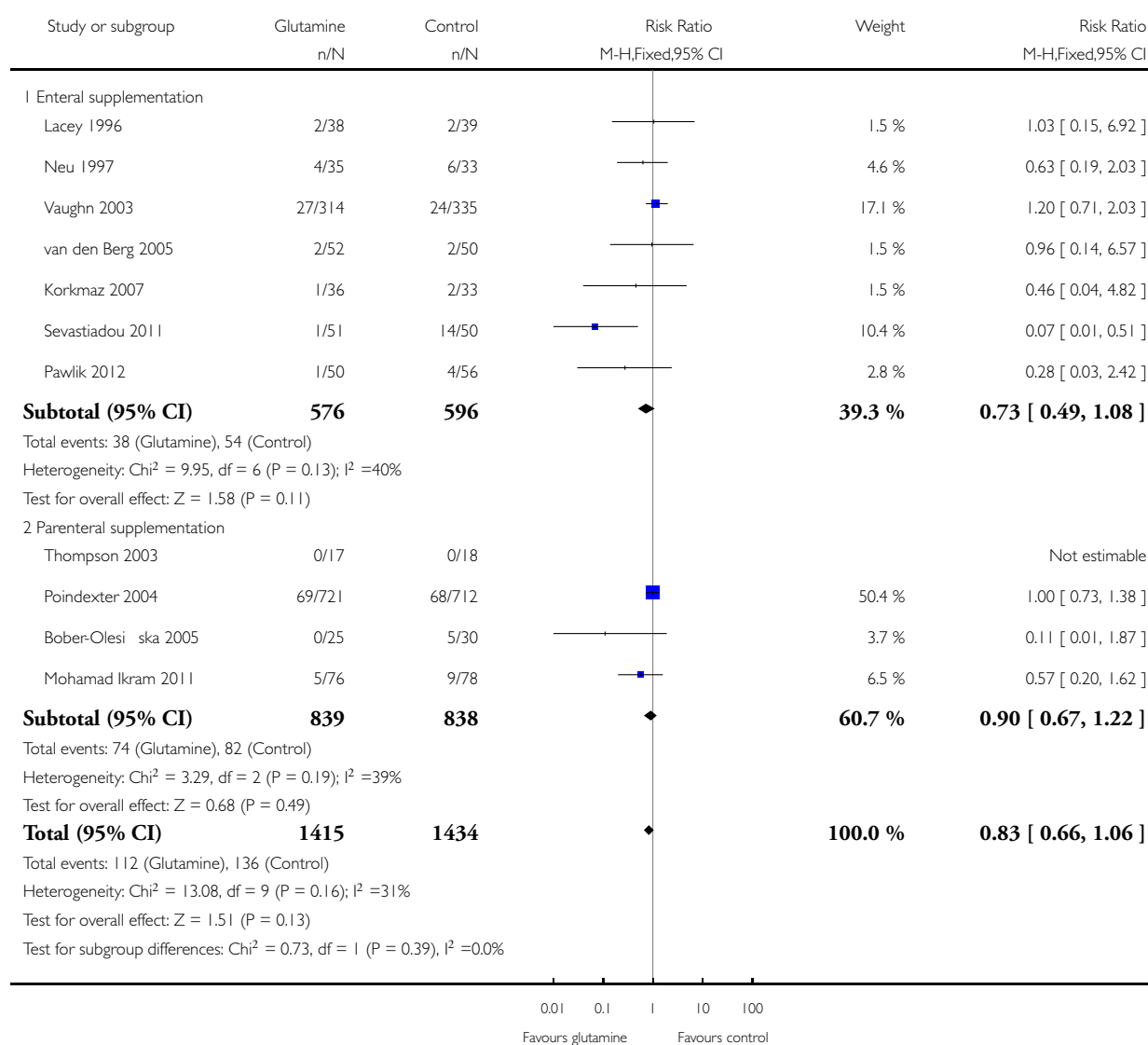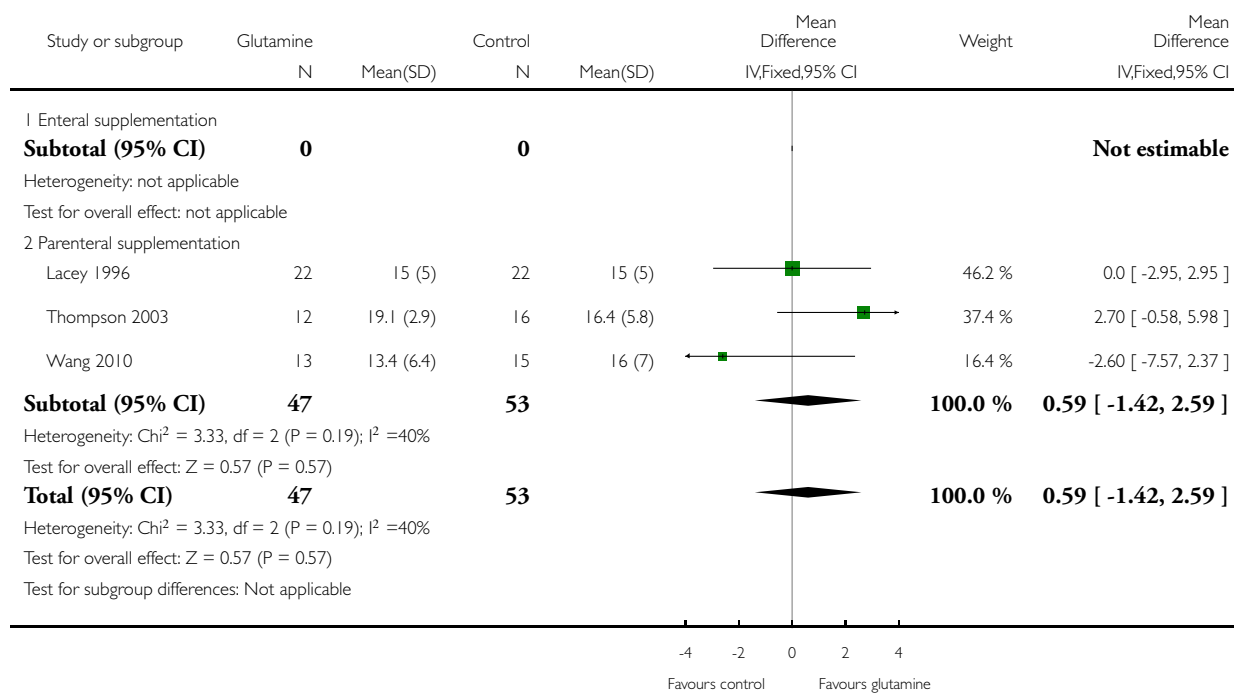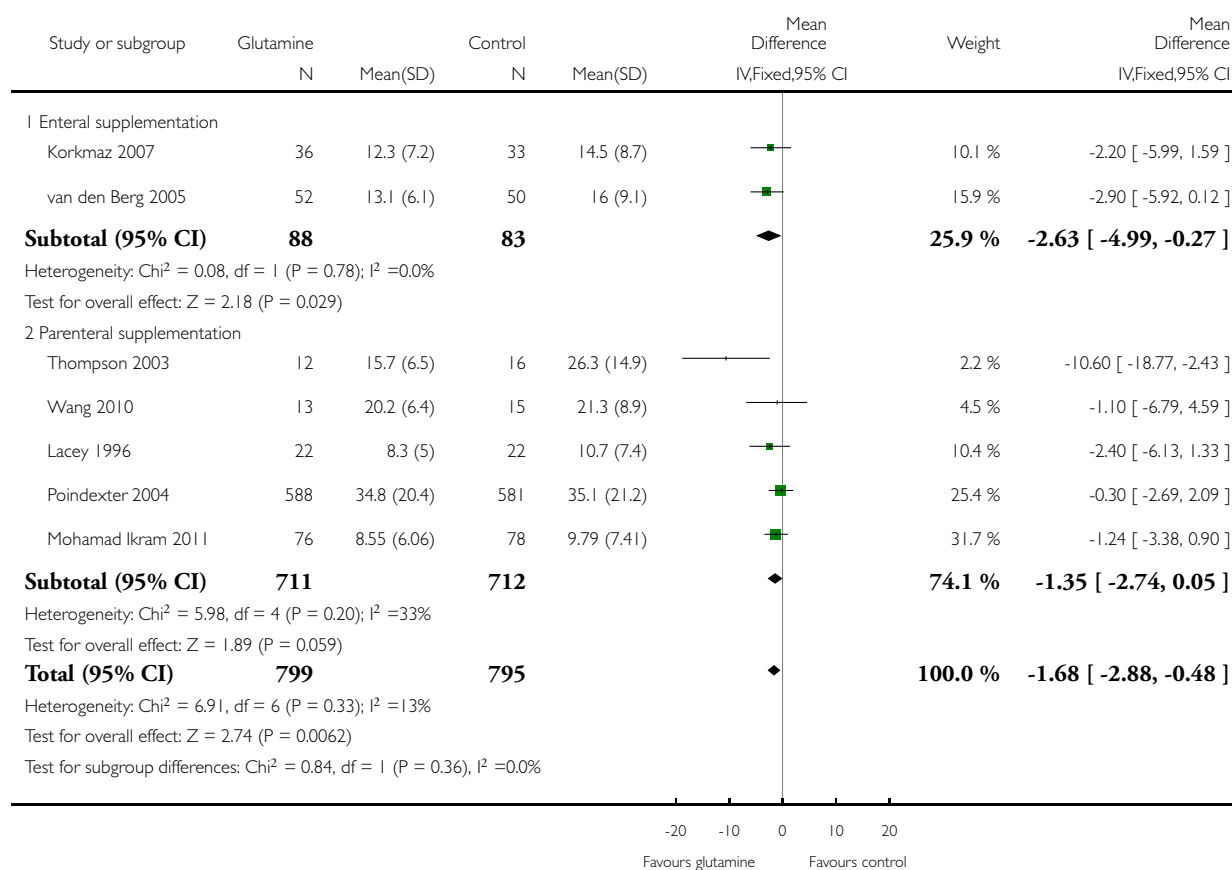
Study or subgroup	Glutamine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
I Enteral supplementation							
van den Berg 2005	45	57 (37.8)	46	65 (30.5)		3.2 %	-8.00 [-22.13, 6.13]
Korkmaz 2007	36	28.9 (23.9)	33	30.3 (21.1)		5.7 %	-1.40 [-12.02, 9.22]
Vaughn 2003	286	74.6 (30.8)	307	75.1 (29.8)		27.2 %	-0.50 [-5.38, 4.38]
Subtotal (95% CI)	**367**		**386**			**36.2 %**	**-1.32 [-5.55, 2.92]**
Heterogeneity: Tau² = 0.0; Chi² = 0.97, df = 2 (P = 0.62); I² =0.0%							
Test for overall effect: Z = 0.61 (P = 0.54)							
2 Parenteral supplementation							
Thompson 2003	12	92.6 (47.1)	16	85.4 (33.2)		0.7 %	7.20 [-24.02, 38.42]
Lacey 1996	22	88 (21)	22	92 (25)		3.5 %	-4.00 [-17.64, 9.64]
Wang 2010	13	48.7 (11.4)	15	48.3 (13.8)		7.4 %	0.40 [-8.94, 9.74]
Poindexter 2004	597	99.9 (48.7)	585	98.1 (43.7)		23.3 %	1.80 [-3.47, 7.07]
Mohamad Ikram 2011	70	13.88 (12.48)	69	16.4 (15.78)		28.9 %	-2.52 [-7.25, 2.21]
Subtotal (95% CI)	**714**		**707**			**63.8 %**	**-0.58 [-3.77, 2.61]**
Heterogeneity: Tau² = 0.0; Chi² = 1.95, df = 4 (P = 0.74); I² =0.0%							
Test for overall effect: Z = 0.36 (P = 0.72)							
Total (95% CI)	**1081**		**1093**			**100.0 %**	**-0.85 [-3.39, 1.70]**
Heterogeneity: Tau² = 0.0; Chi² = 2.99, df = 7 (P = 0.89); I² =0.0%							
Test for overall effect: Z = 0.65 (P = 0.51)							
Test for subgroup differences: Chi² = 0.07, df = I (P = 0.79), I² =0.0%							

```
        -20   -10    0    10    20
      Favours glutamine   Favours control
```

Analysis 2.1.   Comparison 2 Trials in low- and middle-income countries, Outcome 1 Death prior to hospital discharge.
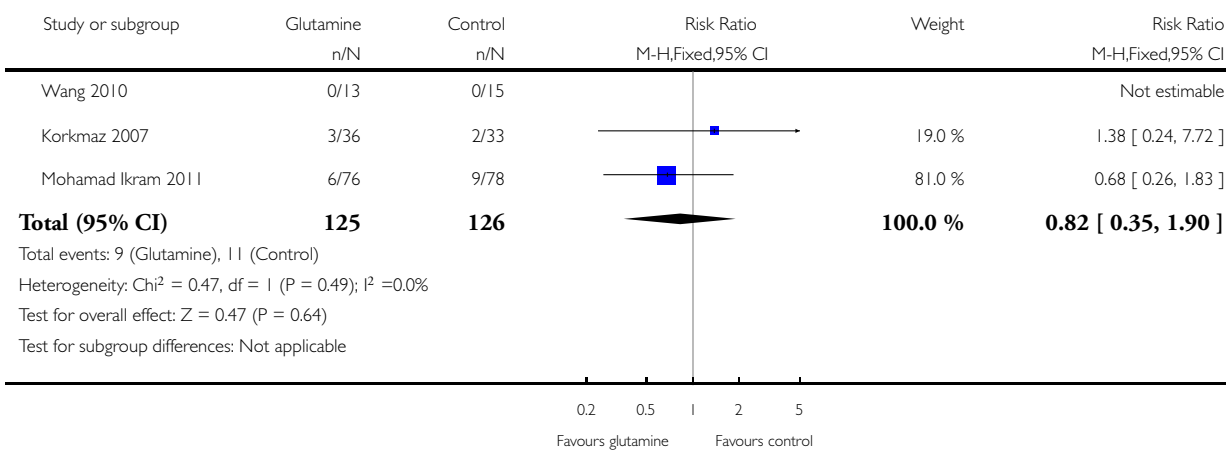
Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 2 Trials in low- and middle-income countries

Outcome: 1 Death prior to hospital discharge

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 2010	0/13	0/15			Not estimable
Korkmaz 2007	3/36	2/33		19.0 %	1.38 [0.24, 7.72]
Mohamad Ikram 2011	6/76	9/78		81.0 %	0.68 [0.26, 1.83]
Total (95% CI)	**125**	**126**		**100.0 %**	**0.82 [0.35, 1.90]**

Total events: 9 (Glutamine), 11 (Control)

Heterogeneity: Chi^2 = 0.47, df = 1 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 0.47 (P = 0.64)

Test for subgroup differences: Not applicable

```
0.2    0.5     1      2      5
Favours glutamine      Favours control
```
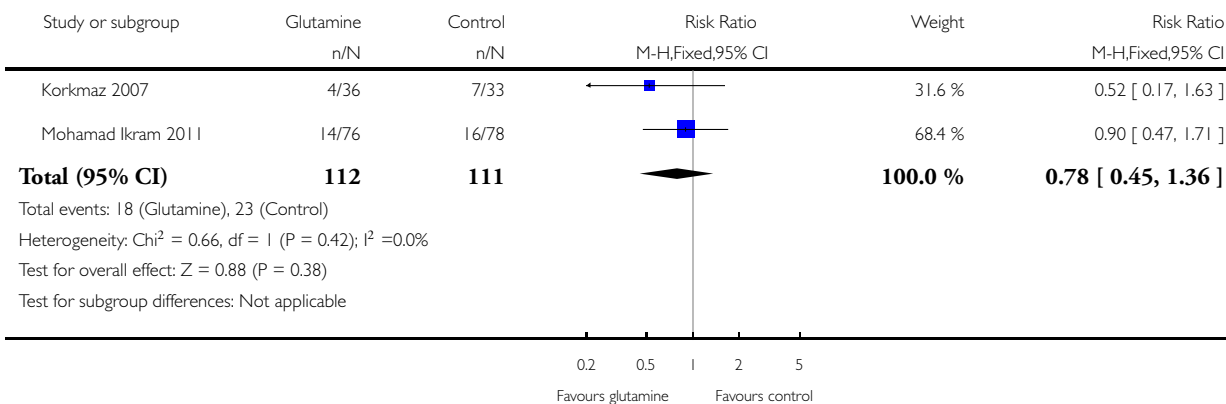
Analysis 2.2.   Comparison 2 Trials in low- and middle-income countries, Outcome 2 Invasive infection.

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 2 Trials in low- and middle-income countries

Outcome: 2 Invasive infection

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Korkmaz 2007	4/36	7/33		31.6 %	0.52 [0.17, 1.63]
Mohamad Ikram 2011	14/76	16/78		68.4 %	0.90 [0.47, 1.71]
Total (95% CI)	**112**	**111**		**100.0 %**	**0.78 [0.45, 1.36]**

Total events: 18 (Glutamine), 23 (Control)

Heterogeneity: Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%

Test for overall effect: Z = 0.88 (P = 0.38)

Test for subgroup differences: Not applicable

```
0.2    0.5     1      2      5
Favours glutamine      Favours control
```
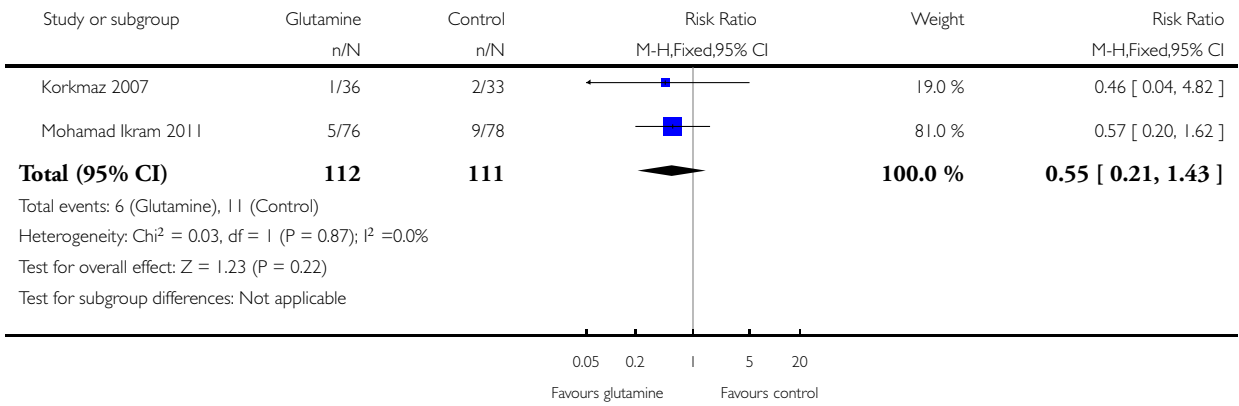
Analysis 2.3. Comparison 2 Trials in low- and middle-income countries, Outcome 3 Necrotising enterocolitis.

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 2 Trials in low- and middle-income countries

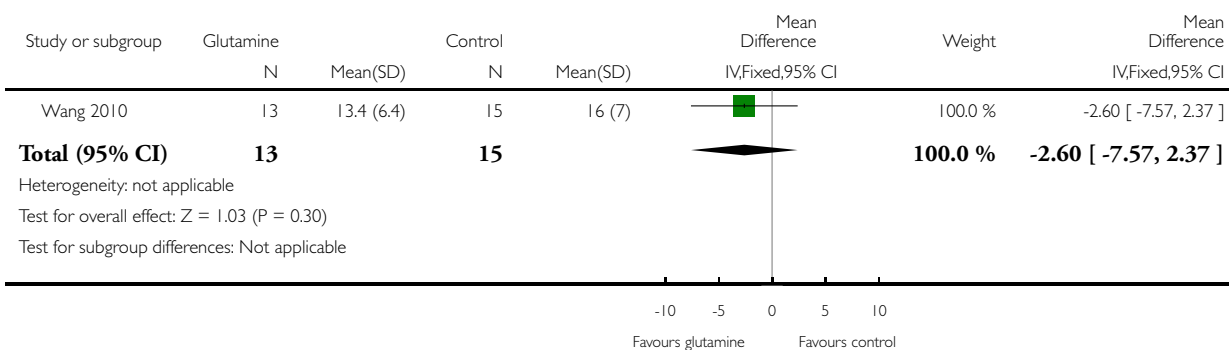Outcome: 3 Necrotising enterocolitis

Study or subgroup	Glutamine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Korkmaz 2007	1/36	2/33		19.0 %	0.46 [0.04, 4.82]
Mohamad Ikram 2011	5/76	9/78		81.0 %	0.57 [0.20, 1.62]
Total (95% CI)	**112**	**111**		**100.0 %**	**0.55 [0.21, 1.43]**

Total events: 6 (Glutamine), 11 (Control)

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² =0.0%

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

0.05　0.2　1　5　20

Favours glutamine　　　Favours control

Analysis 2.4. Comparison 2 Trials in low- and middle-income countries, Outcome 4 Rate of weight gain (g/day).

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 2 Trials in low- and middle-income countries
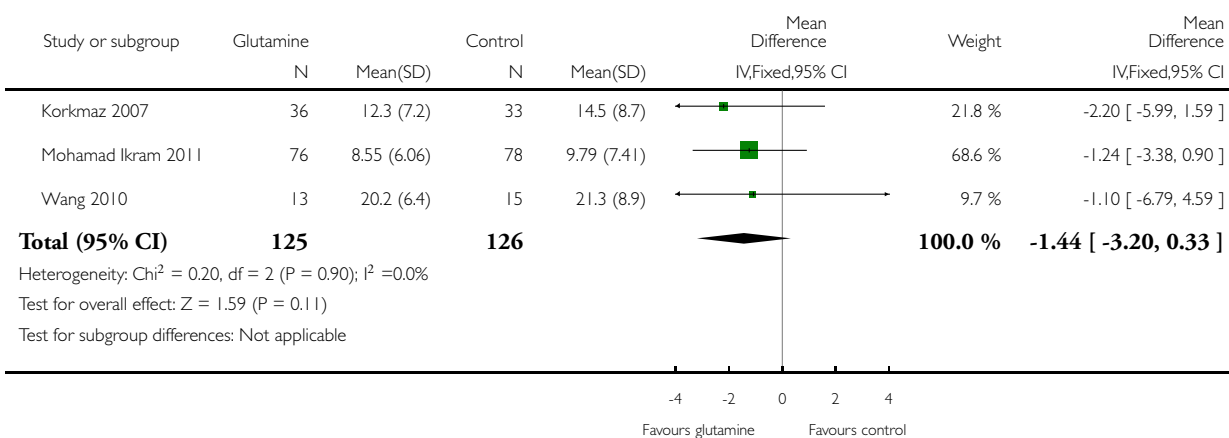
Outcome: 4 Rate of weight gain (g/day)

Study or subgroup	Glutamine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Wang 2010	13	13.4 (6.4)	15	16 (7)		100.0 %	-2.60 [-7.57, 2.37]
Total (95% CI)	**13**		**15**			**100.0 %**	**-2.60 [-7.57, 2.37]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable

```
        -10   -5    0    5    10
     Favours glutamine    Favours control
```

Analysis 2.5. Comparison 2 Trials in low- and middle-income countries, Outcome 5 Time to full enteral nutrition (days).

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 2 Trials in low- and middle-income countries

Outcome: 5 Time to full enteral nutrition (days)

Study or subgroup	Glutamine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Korkmaz 2007	36	12.3 (7.2)	33	14.5 (8.7)		21.8 %	-2.20 [-5.99, 1.59]
Mohamad Ikram 2011	76	8.55 (6.06)	78	9.79 (7.41)		68.6 %	-1.24 [-3.38, 0.90]
Wang 2010	13	20.2 (6.4)	15	21.3 (8.9)		9.7 %	-1.10 [-6.79, 4.59]
Total (95% CI)	**125**		**126**			**100.0 %**	**-1.44 [-3.20, 0.33]**

Heterogeneity: Chi² = 0.20, df = 2 (P = 0.90); I² =0.0%

Test for overall effect: Z = 1.59 (P = 0.11)

Test for subgroup differences: Not applicable

```
        -4    -2    0    2    4
     Favours glutamine    Favours control
```
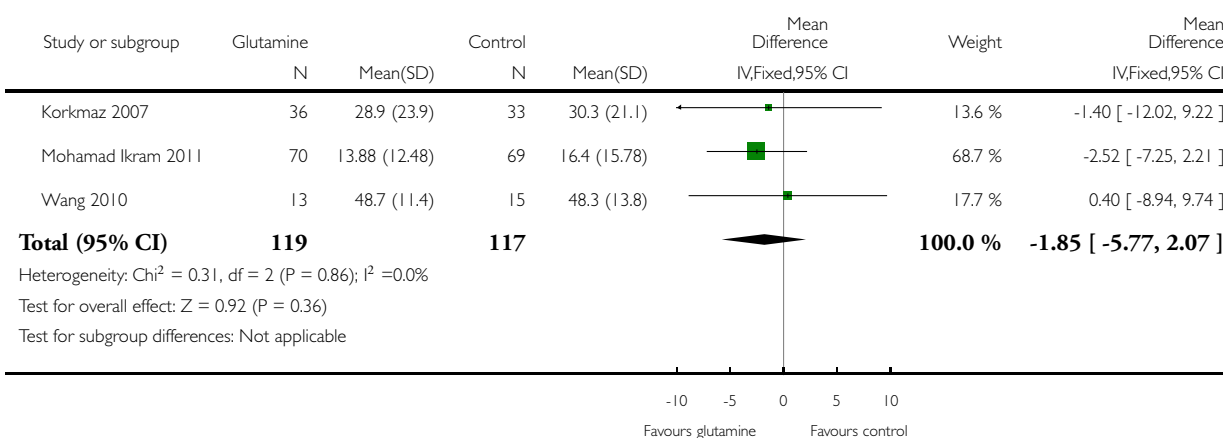
Analysis 2.6.   Comparison 2 Trials in low- and middle-income countries, Outcome 6 Duration of hospital stay (days).

Review: Glutamine supplementation to prevent morbidity and mortality in preterm infants

Comparison: 2 Trials in low- and middle-income countries

Outcome: 6 Duration of hospital stay (days)

Study or subgroup	Glutamine		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Korkmaz 2007	36	28.9 (23.9)	33	30.3 (21.1)		13.6 %	-1.40 [-12.02, 9.22]
Mohamad Ikram 2011	70	13.88 (12.48)	69	16.4 (15.78)		68.7 %	-2.52 [-7.25, 2.21]
Wang 2010	13	48.7 (11.4)	15	48.3 (13.8)		17.7 %	0.40 [-8.94, 9.74]
Total (95% CI)	**119**		**117**			**100.0 %**	**-1.85 [-5.77, 2.07]**

Heterogeneity: Chi^2 = 0.31, df = 2 (P = 0.86); I^2 =0.0%

Test for overall effect: Z = 0.92 (P = 0.36)

Test for subgroup differences: Not applicable

```
        -10   -5    0    5    10
    Favours glutamine      Favours control
```

APPENDICES

Appendix 1. Electronic search strategy

Database searches

Cochrane Central Register of Controlled Trials (CENTRAL)

Wiley http://onlinelibrary.wiley.com/

#1 MeSH descriptor: [Infant, Newborn] explode all trees

#2 MeSH descriptor: [Premature Birth] this term only

#3 (neonat* or neo next nat*):ti,ab,kw

#4 (newborn* or new next born* or newly next born*):ti,ab,kw

#5 (preterm or preterms or pre next term or pre next terms):ti,ab,kw

#6 (preemie* or premie or premies):ti,ab,kw

#7 (prematur* near/3 (birth* or born or deliver*)):ti,ab,kw

#8 (low near/3 (birthweight* or birth next weight*)):ti,ab,kw

#9 (lbw or vlbw or elbw):ti,ab,kw

#10 infan*:ti,ab,kw

#11 (baby or babies):ti,ab,kw

#12 MeSH descriptor: [Enterocolitis, Necrotizing] this term only

#13 enterocolitis:ti,ab,kw

#14 NEC:ti,ab,kw

#15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 MeSH descriptor: [Glutamine] this term only

#17 glutam*:ti,ab,kw

#18 levoglutam*:ti,ab,kw

#19 #16 or #17 or #18

#20 #15 and #19

#21 #15 and #19 in Trials

#22 #15 and #19 Publication Year from 2007 to 2015, in Trials

Key

MeSH descriptor = indexing term (MeSH heading)

* = truncation

:ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

EMBASE

OvidSP http://ovidsp.ovid.com/

A search strategy developed by Lefebvre 2008 to identify randomised trials in EMBASE was used to limit retrieval to clinical trials (lines 22-36).

1 exp infant/

2 prematurity/

3 premature labor/

4 exp low birth weight/

5 (neonat$ or neo nat$).ti,ab.

6 (newborn$ or new born$ or newly born$).ti,ab.

7 (preterm or preterms or pre term or pre terms).ti,ab.

8 (preemie$ or premie or premies).ti,ab.

9 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.

10 (low adj3 (birthweight$ or birth weight$)).ti,ab.

11 (lbw or vlbw or elbw).ti,ab.

12 infan$.ti,ab.

13 (baby or babies).ti,ab.

14 necrotizing enterocolitis/

15 enterocolitis.ti,ab.

16 NEC.ti,ab.

17 or/1-16

18 glutamine/

19 glutam$.ti,ab.

20 levoglutam$.ti,ab.

21 18 or 19 or 20

22 random$.ti,ab.

23 factorial$.ti,ab.

24 crossover$.ti,ab.

25 cross-over$.ti,ab.

26 placebo$.ti,ab.

27 (doubl$ adj blind$).ti,ab.

28 (singl$ adj blind$).ti,ab.

29 assign$.ti,ab.

30 allocat$.ti,ab.
31 volunteer$.ti,ab.
32 Crossover Procedure/
33 double blind procedure/
34 Randomized Controlled Trial/
35 single blind procedure/
36 or/22-35
37 17 and 21 and 36
38 animal/
39 exp animal experiment/
40 Nonhuman/
41 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
42 38 or 39 or 40 or 41
43 exp human/
44 human experiment/
45 43 or 44
46 42 not (42 and 45)
47 37 not 46
48 limit 47 to em

Key:
/ = indexing term (EMTREE heading)
$ = truncation
.ti,ab. = terms in either title or abstract fields
adj3 = terms within three words of each other (any order)
.sh.= subject heading field
.em. = entry date - date added to database

Maternity and Infant Care
OvidSP http://ovidsp.ovid.com/
1 Infant.de.
2 Infant - newborn.de.
3 Infant - premature.de.
4 infant - very premature.de.
5 Infant - low birth weight.de.
6 Infant - very low birth weight.de.
7 Premature birth.de.
8 Infant - small for gestational age.de.
9 (neonat$ or neo nat$).ti,ab.
10 (newborn$ or new born$ or newly born$).ti,ab.
11 (preterm or preterms or pre term or pre terms).ti,ab.
12 (preemie$ or premie or premies).ti,ab.
13 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.
14 (low adj3 (birthweight$ or birth weight$)).ti,ab.
15 (lbw or vlbw or elbw).ti,ab.
16 infan$.ti,ab.
17 (baby or babies).ti,ab.
18 Enterocolitis.de.
19 enterocolitis.ti,ab.
20 NEC.ti,ab.
21 or/1-20
22 Glutamine.de.
23 glutam$.ti,ab.
24 levoglutam$.ti,ab.
25 22 or 23 or 24

26 21 and 25

27 limit 26 to yr="2007 -Current"

Key

.de. = indexing term

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

yr = year published

MEDLINE

OvidSP http://ovidsp.ovid.com/

The Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE (sensitivity-maximizing version) was used to limit retrieval to clinical trials (lines 21-31) (Lefebvre 2011).

1 exp Infant, Newborn/

2 Premature Birth/

3 (neonat$ or neo nat$).ti,ab.

4 (newborn$ or new born$ or newly born$).ti,ab.

5 (preterm or preterms or pre term or pre terms).ti,ab.

6 (preemie$ or premie or premies).ti,ab.

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.

8 (low adj3 (birthweight$ or birth weight$)).ti,ab.

9 (lbw or vlbw or elbw).ti,ab.

10 infan$.ti,ab.

11 (baby or babies).ti,ab.

12 Enterocolitis, Necrotizing/

13 enterocolitis.ti,ab.

14 NEC.ti,ab.

15 or/1-14

16 Glutamine/

17 glutam$.ti,ab.

18 levoglutam$.ti,ab.

19 16 or 17 or 18

20 15 and 19

21 randomized controlled trial.pt.

22 controlled clinical trial.pt.

23 randomized.ab.

24 placebo.ab.

25 drug therapy.fs.

26 randomly.ab.

27 trial.ab.

28 groups.ab.

29 or/21-28

30 exp animals/ not humans.sh.

31 29 not 30

32 15 and 19 and 31

33 limit 32 to ed=20111101-20140911

Key

/ = indexing term (MeSH heading)

exp = exploded MeSH heading

$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

.pt. = publication type

.fs. = floating subheading

.sh.= subject heading
.ed. = entry date - date added to the database
MEDLINE In-Process & Other Non-Indexed Citations
OvidSP http://ovidsp.ovid.com/
1 exp Infant, Newborn/
2 Premature Birth/
3 (neonat$ or neo nat$).ti,ab.
4 (newborn$ or new born$ or newly born$).ti,ab.
5 (preterm or preterms or pre term or pre terms).ti,ab.
6 (preemie$ or premie or premies).ti,ab.
7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab.
8 (low adj3 (birthweight$ or birth weight$)).ti,ab.
9 (lbw or vlbw or elbw).ti,ab.
10 infan$.ti,ab.
11 (baby or babies).ti,ab.
12 Enterocolitis, Necrotizing/
13 enterocolitis.ti,ab.
14 NEC.ti,ab.
15 or/1-14
16 Glutamine/
17 glutam$.ti,ab.
18 levoglutam$.ti,ab.
19 16 or 17 or 18
20 15 and 19
21 limit 20 to ed=20111101-20140918
Key
/ = indexing term (MeSH heading)
exp = exploded MeSH heading
$ = truncation
.ti,ab. = terms in either title or abstract fields
adj3 = terms within three words of each other (any order)
ed = entry date - date added to the database
PubMed
http://www.ncbi.nlm.nih.gov/pubmed/
The Cochrane highly sensitive search strategy for identifying randomized trials in PubMed (sensitivity-maximizing version) was used to limit retrieval to clinical trials (Lefebvre 2011).
Search (((((((((((((((((((((("Infant, Newborn"[Mesh])) OR ("Premature Birth"[Mesh])) OR (((neonat*[Title/Abstract]) OR neo nat*[Title/Abstract]) OR neo-nat*[Title/Abstract])) OR (((((newborn*[Title/Abstract]) OR new born*[Title/Abstract]) OR newborn*[Title/Abstract]) OR newly born*[Title/Abstract]) OR newly-born*[Title/Abstract])) OR ((((((preterm[Title/Abstract]) OR preterms[Title/Abstract]) OR pre term[Title/Abstract]) OR pre-term[Title/Abstract]) OR pre terms[Title/Abstract]) OR pre-terms[Title/Abstract])) OR (((preemie*[Title/Abstract]) OR premie[Title/Abstract]) OR premies[Title/Abstract])) OR ((prematur*[Title/Abstract]) AND birth*[Title/Abstract])) OR ((prematur*[Title/Abstract]) AND born[Title/Abstract])) OR ((prematur*[Title/Abstract]) AND deliver*[Title/Abstract])) OR ((low[Title/Abstract]) AND birthweight*[Title/Abstract])) OR ((low[Title/Abstract]) AND birth weight*[Title/Abstract])) OR ((low[Title/Abstract]) AND birth-weight*[Title/Abstract])) OR (((lbw[Title/Abstract]) OR vlbw[Title/Abstract]) OR elbw[Title/Abstract])) OR (infan*[Title/Abstract])) OR ((baby[Title/Abstract]) OR babies[Title/Abstract])) OR ("Enterocolitis, Necrotizing"[Mesh:noexp]) OR (enterocolitis[Title/Abstract]) OR (NEC[Title/Abstract]))) AND (((levoglutam*[Title/Abstract]) OR glutam*[Title/Abstract]) OR "Glutamine"[Mesh:noexp]))) AND (((((((((((randomized controlled trial[Publication Type])) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract]))) NOT (animals[mh] NOT humans[mh])))) AND ("2011/11/01"[Date - Entrez] : "3000"[Date - Entrez])
Key
[Mesh] = exploded Medical Subject heading (MeSH)
[mh] = exploded MeSH

[Mesh:noexp] = MeSH not exploded

* = truncation

[Title/Abstract] = terms in either title or abstract fields

[Date - Entrez] = entry date - date added to the database

Trial register searches

Clinical Trials.gov

http://clinicaltrials.gov/

Glutamine AND (infant OR infants OR newborn OR newborns OR premature OR prematurity OR neonate OR neonates OR neonatal OR preterm OR preterms OR preemie OR preemies OR premie OR premies OR birthweight OR baby OR babies) | received on or after 11/01/2011 | updated on or after 11/01/2011

1 study found for: Glutamine AND (NEC OR enterocolitis) | received on or after 11/01/2011 | updated on or after 11/01/2011

12 studies found for: "Glutamine" | Child | received on or after 11/01/2011 | updated on or after 11/01/2011

metaRegister of Controlled Trials (mRCT)

http://www.controlled-trials.com/mrct/searchform

(Glutamine AND (infant OR infants OR newborn OR newborns OR premature OR prematurity OR neonate OR neonates or neonatal OR preterm OR preterms OR preemie OR preemies OR premie OR premies OR birthweight OR baby OR babies OR enterocolitis or NEC))

WHO International Clinical Trials Registry Platform

http://apps.who.int/trialsearch/AdvSearch.aspx

1. glutam* in title, clinical trials in children

2. glutam* in intervention field, clinical trials in children

F E E D B A C K

Hans Van Rostenberghe Feedback and Review Author Response, 11 September 2007

Summary

Glutamine has been shown to be a very useful additive to parenteral nutrition in adults. For neonates, it may be useful to consider the potential differences between developed and developing nations. Differences in nutritional status of the mothers may result in less available glutamine for the neonate. Furthermore infection rates tend to be a lot higher in settings of developing nations. Large trials in a developing nation may be still very useful to perform.

Reply

Thank you for highlighting that the findings of studies undertaken in high-income countries may not be wholly applicable to infants in low-and middle-income countries. We have pre-specified subgroup analyses of studies undertaken in low- and middle-income countries in the 2011 update of this review.

Contributors

Thirimon Moe Byrne, Jennifer VE Wagner, William McGuire.

W H A T ' S   N E W

Last assessed as up-to-date: 18 December 2015.

Date	Event	Description
18 April 2016	Amended	Minor edit
7 January 2016	New citation required but conclusions have not changed	Inclusion of a new trial and new follow-up data did not change the conclusion
18 December 2015	New search has been performed	This updates the review "Glutamine supplementation to prevent morbidity and mortality in preterm infants" published in the Cochrane Database of Systematic Reviews (Moe-Byrne 2012). Updated search identified one new trial and one publication of follow-up data for inclusion in this review

H I S T O R Y

Protocol first published: Issue 2, 1999

Review first published: Issue 2, 1999

Date	Event	Description
30 November 2011	New citation required and conclusions have changed	Further evaluation of routine parenteral glutamine supplementation in preterm infants is unlikely to be considered a research priority, but the inclusion of new trial data in this update provides some support for further trials of enteral glutamine supplementation to be undertaken New authorship.
30 November 2011	New search has been performed	This updates the review "Glutamine supplementation to prevent morbidity and mortality in preterm infants" published in the Cochrane Database of Systematic Reviews (Tubman 2008). Updated search identified four new trials for inclusion in this review
30 November 2011	Feedback has been incorporated	Feedback on 2008 version of review by Hans Von Rostenberghe (Feedback 1) incorporated by adding an additional subgroup analysis.
8 May 2008	Amended	Converted to new review format.

(Continued)

8 May 2008	Feedback has been incorporated	Feedback incorporated
13 November 2007	New search has been performed	This updates the existing review of "Glutamine supplementation to prevent morbidity and mortality in preterm infants" published in The Cochrane Library, Issue 1, 2005 (Tubman 2005). One new trial was identified for this update (Bober-Olesinska 2005). Inclusion of data from this trial did not change the main findings or conclusions of this review

CONTRIBUTIONS OF AUTHORS

JVEW, WM and TMB searched and screened the studies for inclusion, assessed the methodological quality of the trials and extracted and entered the relevant information and data from each included study independently. WM and JVEW completed the final review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Infant Mortality; *Infant Nutritional Physiological Phenomena; *Infant, Premature; Glutamine [*administration & dosage]; Infant, Very Low Birth Weight; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn