NUTRITION AND NEURODEVELOPMENTAL OUTCOMES IN PRETERM INFANTS: A SYSTEMATIC REVIEW

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ABSTRACT

A systematic review with meta-analysis was carried out to investigate the effects of increased nutritional intake, via either macronutrient or multi-nutrient intervention, during the neonatal period on neurodevelopmental outcomes in infants born at <32 weeks of gestation or weighing <1501g at birth.

Conclusion: Although the relationship remains unclear, increased early nutrition may reduce neurodevelopmental impairment in this group of infants. Future research should focus on using standardised nutritional interventions and an agreed neurodevelopmental assessment battery.

Key notes

- Increased early enteral nutrition may reduce neurodevelopmental impairment in very preterm and/or very low birth weight infants, but the direct relationship between neurodevelopmental outcome and nutrition remains unclear

- There is a lack of recent adequately powered studies on this topic

- Additional research is required and should focus on using standardised nutritional interventions and an agreed neurodevelopmental assessment battery, as the lack of homogeneity was a major limitation in this review

Adverse neurodevelopmental outcome is common in very preterm (VP) and very low birth weight (VLBW) infants(1, 2). Postnatal growth failure is also common in these infants(3). Epidemiological studies(4, 5) have shown that infants born extremely preterm are often lighter and have a smaller head circumference compared with published population norms at expected delivery date, despite being born with average weight and head circumference for their gestation. Neurodevelopmental outcomes of preterm infants are subject to multiple influences and it is likely that nutrition plays a key part. Furthermore, nutrition can be measured and modified, and so offers a potential intervention to improve outcomes. At the same time, it should be acknowledged that altering early nutrition in preterm infants could potentially result in changes to body composition and in turn the risk of obesity and non-communicable disease in later life(6). Although there is evidence that in VLBW infants poor growth during the early postnatal period is associated with a higher incidence of neurodevelopmental impairment at toddler age(7), the findings of studies that have investigated the effect of early and/or increased nutrition in preterm infants have been inconsistent(8-10), and the evidence for nutritional interventions to improve neurodevelopmental outcome is unclear. We therefore carried out a systematic review to

examine the effects of increased early nutritional intake on neurodevelopmental outcomes in infants born VP and/or with VLBW assessed at toddler age or during childhood.

METHOD

Study design

Studies were considered if they were randomised controlled trials (RCT), non-randomised control trials (NRCT), or observational studies. There were no restrictions on publication status, language, or year of publication.

Inclusion criteria

Studies that specifically compared an intervention providing increased nutrient intakes during the neonatal period (defined as first 28 days after birth) in infants born VP, <32 weeks of gestational age (GA), or with birth weight (BW) <1501g, with a control group receiving a 'standard' amount of nutrition, were eligible for inclusion. The intervention had to include

higher quantity of nutrients over a defined period, such as consistently higher nutrient intakes in the intervention group compared to the control group, a difference in the increment of nutrient increase during the intervention period, or a difference in the length of intervention to provide a higher amount of nutrition overall. Nutritional interventions could be parenteral nutrition (PN), enteral nutrition (EN), or a combination of both. Studies were excluded if there was no documented protocol to increase nutrient intake, or if they focused on one single specific micronutrient.

Outcome measures

Outcome measures included neurodevelopmental outcome at 12-18 months, 24 months of corrected gestational age (CGA) (these ages of assessment hereafter referred to as toddler age) and/or at childhood as well as neurological status (presence or absence of Cerebral Palsy, CP). Since the Mental Developmental Index (MDI) and Psychomotor Developmental

Index (PDI) subscales of the Bayley Scales of Infant Development Second edition(11) (BSIDII) are widely used, meta-analyses were based on these subscales. Studies that reported cognitive, language and motor subscales of Bayley Scales of Infant and Toddler Development Third edition(12) (Bayley III), were converted into MDI and PDI using Moore et al's method(13) to allow meta-analyses.

Searches and information source

A search was carried out by using the search strategy detailed in table 1. The electronic databases MEDLINE, EMBASE and CINAHL were searched, with the last search carried out on 15th Jan 2015. Conference abstracts and other citations were identified using Web of Science. Reference searching was performed on articles that were selected for review.

Study selection

Studies were assessed for eligibility by two reviewers (SC and MJ) independently. Selection was on the basis of titles and abstracts where possible, with the full text obtained where necessary.

Data collection process

Data on study characteristics, nutritional interventions, nutritional intakes, and outcome measures (neurodevelopmental outcomes, morbidity and mortality) were collected using a study specific spreadsheet. Additional data were obtained from authors where required.

Risk of bias assessment

The quality of RCT and NRCT was assessed using the Cochrane Risk of Bias Assessment Tool(14), and observational studies were assessed using the Newcastle Ottawa Scale(15).

Synthesis of results

Parenteral nutrition and EN studies were analysed separately due to their relative timing of use during the neonatal period. Meta-analyses were performed where appropriate. Analysis was carried out using the software Review Manager v5.2(16). Heterogeneity was checked

using I^2 statistic. A random effects model was used for all continuous data analyses. Peto's

method was used to calculate a pooled odds ratio (OR) for binary outcome data(17). When

means and standard deviations (SD) were not provided, they were calculated using the

method described by Hozo et al(18). Meta-regression was carried out using Stata version

12.1 (StataCorp LP). All statistical analyses were conducted by authors SC and MJ.

RESULTS

Study selection

The review process is demonstrated in figure 1. Eighteen papers, published between 1982

and 2014 that reported 15 studies, were included (10 RCT, 1 NRCT, and 4 retrospective

observational studies). Three of the included studies reported follow-up findings from two

RCTs.

Study characteristics

Characteristics of included studies are summarised in table 2. There were no significant

differences in the mean±SD of GA (29.6±1.7 vs 29.6± 1.8 weeks, p= 0.80) or birth weight

(1226.8±321g vs 1234.7±322g, p= 0.60) between the intervention and the control groups.

Interventions varied between studies; five of the six PN trials investigated early delivery and

increased content of protein (19-23), the remaining PN trial investigated increases in both

micro- and macronutrients (24). Four of the seven EN studies investigated multi-nutrient

supplementation to either maternal or donor breast milk(8-10, 25-28), two studies

investigated protein supplementation to breast milk(29, 30), and one study compared protein

enriched formula to standard formula(31). In addition to supplementation, Lucas et al also

conducted trials that compared multi-nutrient enriched sole diet, containing preterm formula

only, to either only donor breast milk(9) or only term formula(10), these intervention hereafter

is referred to sole diet trials. In the two studies that investigated increasing both PN and EN,

Tan et al(32) investigated the effect of hyperalimentation, where the intervention group received parenteral or/and enteral nutrition that contained macronutrients above the recommended amount, whereas Rochow et al(22) investigated the implementation of a feeding program.

Quality assessment

Assessments of quality and risk of bias in the controlled trials and observational studies are summarised in table 3A and 3B respectively. The potential risk of bias in studies was taken into consideration during data interpretation. Observational studies were presented separately to RCTs and NRCTs in meta-analyses. Of the four observational studies, only two studies (21, 24) adjusted for morbidities in their analysis. This is also shown in table 3B.

Primary outcomes

Neurodevelopmental outcome

Neurodevelopmental outcomes were reported in all included studies. Mental Developmental Index and PDI were reported in ten studies(8, 10, 19-21, 23, 26, 28, 30, 32). Knobloch et al's Developmental Inventory Quotients(33) were further reported in two studies(8, 9). Two studies reported subscales of Bayley III(24, 34). Cormack et al(24) reported scores on cognitive, language, and motor subscales which were also converted into MDI and PDI, and Burattini et al(34) reported Bayley III scores, but lack of details regarding individual subscales meant that MDI could not be calculated. Studies that reported MDI, PDI, or Bayley III subscales that allowed conversion to MDI at 12 to 18 months, were included in the meta-analysis. Other methods used to investigate neurodevelopment at toddler age included the Munich Functional Developmental Diagnostics(35) (MFED) test reported by Rochow et al(22), and the Griffiths Mental Development Scales(36) (GMDS) used by Biasini et al(29). Studies that investigated neurodevelopmental outcome in childhood and adolescence reported Verbal (VIQ) and Performance (PIQ) Intelligence Quotients, and Full Scale

Intelligence Quotient (FSIQ) using either Wechsler Intelligence Scale for Children (revised anglicised version: WISCR- UK)(37, 38), or Wechsler Intelligence Scale for Children-Third edition (WISC-III)(39) or Wechsler Adult Intelligence Scale- Revised(WAIS-R)(25, 40).

Neurodevelopmental outcome at age 12–18 months: Results of meta-analysis

Meta-analysis of EN trials (8, 10, 26, 28, 30), PN trials (19-21, 24) and two sole diet trials(10, 28) showed non-significant effects on MDI and PDI. A negative mean difference was observed in the meta-analysis of PN studies and MDI (figure 2), and although this was not statistically significant, this finding is consistent with meta-analysis at 24 months (figure 5). Significant heterogeneity was found in PDI in the meta-analysis of EN trials (I^2 = 95%, p<0.001) and sole diet trials (I^2 = 90%, p<0.001), demonstrated in figure 3 and figure 4, respectively.

Neurodevelopmental outcome at age 12-18 months: Results of meta-regression
The relationship between early increased nutrition and neurodevelopmental outcome was further explored using meta-regression. Energy and protein were considered separately. There were no significant linear relationships between energy or protein and MDI or PDI for studies using PN. For EN studies, there was no significant linear relationship between protein or energy content and MDI at 12-18 months (regression coefficients 1.62 and -0.09 respectively, p > 0.5 for both). While there was no significant linear relationship between increased EN protein and PDI (regression coefficient -30.20, p = 0.33) there was a positive linear correlation between energy and PDI that approached significance (regression coefficient 0.75, 95% CI: -0.05, 1.54, p = 0.06). Although not statistically significant, this suggests that for every extra calorie per kg per day of enteral energy intake, there may be a 0.75 point increase in PDI.

Neurodevelopmental outcome at age 24 months: Results of meta-analysis
Three PN studies(19, 23, 34) reported neurodevelopmental outcomes at 24 months; only two were appropriate for meta-analysis. The remaining study, Burattini et al(34), reported

only cognitive scales, and therefore MDI and PDI could not be calculated. Whilst Blanco et al(19) reported MDI and PDI at both 18 and 24 months, results were pooled into two different meta-analyses. The meta-analyses showed that increase in PN has a significant negative effect on MDI with a mean difference of -3.99 [(CI 95%, -7.69 to -0.29), p = 0.03], but with no significant effect on PDI at 24 months (figure 5A and B).

Neurodevelopmental outcome: Results not included in meta-analysis

Tan et al(32) and Rochow et al(22) investigated increasing both EN and PN, and neither study reported significant effects on neurodevelopment at 3 and 9 months, or at 24 months, respectively.

Similarly, Burattini et al(34) found no significant differences in Bayley III scores at 24 months between infants who received increased amino acid intake and those who received standard amount from birth to day four.

Two EN studies that investigated increasing protein showed contrasting results(29, 31), Svenningsen et al(31) reported no group differences in neurodevelopmental outcomes at two years of age, whereas Basini et al(29) found that infants receiving additional protein performed better in the items of the GMDS at three months CGA (95.5 vs 109.8, p = 0.04).

Long term cognitive outcomes were reported by two follow-up studies from the same original cohort. Lucas et al(27) reported no significant differences in the VIQ, PIQ and FSIQ at 7.5- 8 years of age between the intervention and control groups in both the sole diet trial and the supplementation trial. In contrast, Isaac et al(25) found that the mean±SD VIQ at the median age of 16 years was significantly higher in the intervention group compared to the control group from the same cohort (102±14 vs 94±11, p < 0.01).

Rate of survival without neurodevelopmental impairment:

Meta-analyses of the rate of survival without neurodevelopmental impairment were carried out on four EN(9, 10, 26, 34, 41) and four PN(20, 21, 23, 34) studies. Meta-analyses revealed that infants who received increased EN were approximately twice as likely to survive without neurodevelopmental impairment compared to the infants who received a standard amount of nutrition, OR 1.89 (1.24, 2.73; p= 0.003). No difference was found on meta-analysis of PN studies, OR 1.04 (0.74, 1.46; p= 0.82), as demonstrated in figure 6. Of note, one RCT(10) reported the incidence of MDI < 70 and PDI < 70 seperately, rather than the number of infants with neurodevelopmental impairment (defined as either MDI or PDI being less than 70). Therefore, in order to be included in the meta-analysis, the total number of infants with either MDI < 70 and PDI < 70 were combined to give a total number of infants with impairment, though the actual number of infants with neurodevelopmental impairment may be overestimated in comparison to the other included studies, as some infants with both a MDI < 70 and PDI < 70 will have been double counted.

Secondary outcomes

Neurological outcome

Four RCTs and two observational studies reported the rate of CP. Meta-analyses of two EN trials(27, 28), four PN trials(19-21, 23), and two sole diet trials(12,28) showed no significant difference in incidence of CP, with OR of 0.84 (0.44, 1.6; p = 0.59),1.06 (0.68, 1.63; p = 0.66) and 1.6 (0.56, 4.55), respectively.

Rate of neurodevelopmental impairment at toddler age: Results of meta-analysis

Definitions of neurodevelopmental impairment differed across studies. Meta-analysis of three PN trials(20, 21, 23) (which defined impairment as at least one of the following: MDI or PDI <70, presence of CP, hearing loss or blindness) showed no significant differences in the

rates of neurodevelopmental impairment at 18-24 months with an OR of 1.10 (0.78, 1.56; p= 0.58).

Rate of neurodevelopmental impairment: Results not included in meta-analysis

Of the remaining studies that reported neurodevelopmental impairment(9, 10, 26, 27, 29), only one RCT, Lucas et al 1990(10), and its follow-up(27), reported a significantly higher incidence in the group that received standard nutrition, with a significantly lower incidence of psychomotor impairment (defined as PDI < 86) in the group that received increased nutrition at 18 months. The follow-up study also reported a significantly lower rate of cognitive impairment (VIQ < 85) at 7.5-8 years in a combined cohort of infants that received either increased EN via sole diet or supplementation. This remained statistically significant after adjusting for CP(27).

DISCUSSION

This review found that increased PN, particularly increased amino acid intake in the early period after birth, may result in sub-optimal neurodevelopmental outcomes at 24 months CGA. However, only two studies could be pooled in the meta-analysis (figure 5) due to the variation in outcomes measures and data reporting, therefore this finding requires confirmation through further research. On the other hand, importantly, the review also suggests that increased enteral nutrition may result in increased numbers of very preterm and/or very low birthweight infants surviving without neurodevelopmental impairment. A speculative explanation for such findings is that the omission of infants who did not survive for neurodevelopmental assessment and were thus omitted from the meta-analyses, may have confounded the results. By including survival in the outcome as 'survival without

neurodevelopmental impairment', we were able to adjust for this possible confounding effect,

and have shown that higher PN intake does not increase the likelihood of

neurodevelopmental impairment in preterm infants. With regard to the negative outcome

from early increased amino acid intake seen in Blanco et al's study, it is important to consider that this could be related to the specific composition of the amino acid solution, rather than to overall intake of protein. Therefore, findings from this study may not be generalisable to other studies with early increased amino acid interventions. Additionally, this study has a high attrition rate with the fewest participants (n = 16) in the meta-analysis at 24 months. Overall, our review showed no significant effects from increased nutrition on the rates of CP.

Meta-regression did not provide additional information on the relationship between nutritional intake and neurodevelopment, but individual studies from this review have demonstrated significant associations. In a retrospective observational study which investigated increased parenteral nutrition via multi-nutrient intervention, Cormack et al(24), found that mean enteral protein intake during the first two postnatal weeks had a positive association with cognitive (r^2= 0.13, p = 0.03) and motor subscales (r^2= 0.27, p = 0.001) of Bayley III at 18 months CGA. Similarly, Stephens et al(42) reported a positive association between average energy and protein intake in the first week after birth and MDI at 18 months CGA. In addition, nutritional deficits at 28 days after birth were found to be negatively associated with neurodevelopment at 3 months. Tan et al (32) calculated energy and protein deficit at 28 days after birth by subtracting actual daily intakes from recommended intakes of 120 kcal/kg/day of energy and 3 g/kg/day of protein. Energy and protein deficit significantly correlated with MDI (R = -20.25, p = 0.03 and R= -20.32, p = 0.004, respectively), and PDI (R= -20.29, p = 0.01 and R= -20.3, p = 0.006, respectively)

Longer term outcome was reported in two studies of the same RCT cohort, but with inconclusive findings(25, 27). Lucas et al(27) reported a small, but non-significant, advantage in VIQ and PIQ at 7.5-8 years of age in the multi-nutrient supplementation trial, and Isaacs et al(25) also reported significantly higher VIQ at 16 years of age in the higher

nutrient group. However, the reported confidence interval was contradictory to the p-value (CI: -14, 12; p < 0.01), thus the significance is unclear.

Although our review has not specifically explored the effects of gender, several studies have suggested that early increased nutrition may have greater beneficial effects on premature boys than girls. Van den Akker et al demonstrated that preterm male infants are six times more likely to have normal outcomes with parenteral nutritional intervention compared to preterm female infants [adjusted odds ratio = 6.17, 95% CI (1.01 – 38.46)]. This was similar to the studies by Lucas et al, who observed greater impact of increased early enteral nutrition on neurodevelopment in male than female preterm infants throughout their series of RCTs and follow-up studies. Substantial effects from enteral supplementation on mental and motor development in males compared to females were found particularly at the 18 month CGA follow-up. Brain development is different between male and female, and it has been suggested that this may influence the periods of maximal sensitivity to environmental factors such as nutrition.

Significant heterogeneity was found across the meta-analyses. The meta-analysis for PN trials and MDI at 12-18 months showed significant heterogeneity (I^2 = 75.9%) between the study designs. The only RCT that was pooled into this meta-analysis demonstrated significant negative findings within the subgroup analysis, however, this study included the smallest sample size and when combined with observational studies, the mean difference became statistically non-significant. Similarly, meta-analysis of EN studies and PDI at 12-18 months CGA showed I^2 = 95%, where significant benefits were described by two of the five studies, with Lucas et al(10) reporting the greatest effect. Although this study (10) was assessed to contain low risk of bias, it was conducted more than two decades ago, and further studies in a more contemporary sample may strengthen the evidence for the conclusion made in this study. Likewise, the reviewed literature is dominated by research published over a decade ago, and there is a lack of recent adequately powered studies on

this topic. Recent trials that were included were predominately single centered. Results of larger multi-centered studies investigating neurodevelopmental outcome as a primary or secondary outcome are not currently available.

A considerable amount of variation in the type of interventions, outcomes, and age at assessment was found across the studies, particularly in the EN trials. The components of nutritional interventions differed markedly between studies. The proportion of mother's

breast milk and supplementation used in individual trials was also not controlled except in one of the supplement trials(9). Consequently, the actual effect of increased nutrition might not be fully reflected in these studies. Another major limitation in the data is that not all the studies reported whether the actual nutritional intervention was achieved, and for the 11 studies that have reported this, only 4 studies achieved the intended nutrient intakes.

While this review supports the concept that early nutrition is important for optimal neuro-development, it provides no clarity on which specific nutrients or clusters of nutrients might be beneficial – or potentially harmful. Furthermore, the recommended nutritional intakes for

preterm infants have changed over the last two decades, and this is demonstrated by the significant variations between the nutrition interventions in studies published at different times over the past 20 years or so (see table S1). The older studies appear to provide smaller amounts of nutrition in their control groups compared to more recent studies. When the standard nutrition is below optimal, providing more nutrition may be beneficial; however, providing nutrition above the optimal level may not be beneficial and may even be harmful.

Nutrition is complex and it is likely that there is a pattern of optimal intake of multiple nutrients, including energy, amino acids and micro-nutrients, which must be balanced with metabolic capacity. Including neurodevelopment as an outcome measure to identify these intakes is vitally important. In addition to nutrition, other contributing factors such as

intrauterine toxins and infections, maternal co-morbidities, genetic factors and many other variables could not be considered in this review.

CONCLUSION

This study provides a comprehensive review of the published evidence for the effects of increased early nutrition, either via increased macronutrients or multi-nutritional intervention, on neurodevelopmental outcome in VP and/or VLBW infants at toddler age and in childhood. The review has shown that increased early nutrition may increase the likelihood of survival without neurodevelopmental impairment in VP and/or VLBW infants, but the direct relationship between neurodevelopmental outcome and nutrition after birth remains unclear. Whilst early nutritional interventions may be beneficial for neurodevelopment, optimal nutritional regimens are still not defined, and as such there is a need for additional research in this field. Further research should follow the Core Outcome Measures in Effectiveness Trials initiative(43) to develop a core set of agreed standardised outcomes. This will facilitate data synthesis for future systematic reviews, as the lack of homogeneity was a major limitation in this review.

Abbreviations:

Bayley III- Bayley Scales of Infant and Toddler Development - Third edition

BSID II- Bayley Scales of Infant Development - Second edition

BW- birth weight

CGA- corrected gestational age

CLD- chronic lung disease

CP- cerebral palsy

ELBW- extremely low birth weight

EN- enteral nutrition

FSIQ- Full Scale Intelligence Quotient

GA- gestational age

GMDS- Griffiths Mental Development Scales

IVH- intraventricular haemorrhage

MDI- Mental Developmental Index

MFED- Munich Functional Developmental Diagnostic test

NEC- necrotising enterocolitis

NRCT- non randomised controlled trial

OR- odds ratio

PDI- Psychomotor Developmental Index

PIQ- Performance Intelligence Quotient

PN- parenteral nutrition

RCT- randomised controlled trial

SD- standard deviation

VIQ- Verbal Intelligence Quotient

VLBW- very low birth weight

VP- very preterm

WAIS-R- Wechsler Adult Intelligence Scale-Revised

WISC-III- Wechsler Intelligence Scale for Children - Third edition

WISC-R- Wechsler Intelligence Scale for Children - Revised

References:

1.   Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371:261-9.
2.   Delobel-Ayoub M, Arnaud C, White-Koning M, Casper C, Pierrat V, Garel M *et al.* Behavioral problems and cognitive performance at 5 years of age after very preterm birth: the EPIPAGE Study. *Pediatrics* 2009;123:1485-92.
3.   Ehrenkranz RA. Early nutritional support and outcomes in ELBW infants. *Early Hum Dev* 2010;86 Suppl 1:21-5.

4.   Wood N, Costeloe K, Gibson A, Hennessy E, Marlow N, Wilkinson A. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F492-F500.

5.   Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *Bmj* 2012;345:e7976.

6.   Johnson MJ, Wootton SA, Leaf AA, Jackson AA. Preterm birth and body composition at term equivalent age: a systematic review and meta-analysis. *Pediatrics* 2012;130:e640-9.

7.   Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics* 2006;117:1253-61.

8.   Lucas A, Fewtrell MS, Morley R, Lucas PJ, Baker BA, Lister G *et al.* Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. *Am J Clin Nutr* 1996;64:142-51.

9.   Lucas A, Morley R, Cole TJ, Gore SM, Davis JA, Bamford MF *et al.* Early diet in preterm babies and developmental status in infancy. *Arch Dis Child* 1989;64:1570-8.

10.   Lucas A, Morley R, Cole TJ, Gore SM, Lucas PJ, Crowle P *et al.* Early diet in preterm babies and developmental status at 18 months. *Lancet* 1990;335:1477-81.

11.   Bayley N. Bayley Scales of Infant Development. *Psychological Corporation*. 2nd ed. San Antonio, TX. 1993.

12.   Bayley N. Bayley Scales of Infant and Toddler Development. *Harcourt Assessment* 3rd ed. San Antonio, TX. 2006.

13.   Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. *J Pediatr* 2012;160:553-8.

14.   Higgins J, Green, S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2011]. *The Cochrane Collaboration* 2011.

15.   Wells GA, Shea B, O' Connell D, Peterson J, Welch V, Losos M *et al.* The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Ottawa (ON). *Ottawa Health Research Institute* 1999.

16.   Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre: *The Cochrane Collaboration*; 2008.

17.   Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53-77.

18.   Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;5:13.

19.   Blanco CL, Gong AK, Schoolfield J, Green BK, Daniels W, Liechty EA *et al.* Impact of early and high amino acid supplementation on ELBW infants at 2 years. *J Pediatr Gastroenterol Nutr* 2012;54:601-7.

20.   Karakus F, Türker G, Gökalp AS. The effect of early parenteral amino acids, on growth and neurodevelopment of very low birth weight infants [Turkish]. *Turkish Pediatrics Archive* 2010;45:111-8.

21.   Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA. Early provision of parenteral amino acids in extremely low birth weight infants: Relation to growth and neurodevelopmental outcome. *J Pediatr* 2006;148:300-.e7.

22.   Rochow N, Fusch G, Muhlinghaus A, Niesytto C, Straube S, Utzig N *et al.* A nutritional program to improve outcome of very low birth weight infants. *Clin Nutr* 2012;31:124-31.

23.   van den Akker CH, te Braake FW, Weisglas-Kuperus N, van Goudoever JB. Observational outcome results following a randomized controlled trial of early amino acid administration in preterm infants. *J Pediatr Gastroenterol Nutr* 2014;59:714-9.

24.   Cormack BE, Bloomfield FH, Dezoete A, Kuschel CA. Does more protein in the first week of life change outcomes for very low birthweight babies? *J Paediatr Child Health* 2011;47:898-903.

25.   Isaacs EB, Gadian DG, Sabatini S, Chong WK, Quinn BT, Fischl BR *et al.* The effect of early human diet on caudate volumes and IQ. *Pediatr Res* 2008;63:308-14.

26.   Kocourkova I, Sobotkova D, Pilarova M, Dittrichova J, Vondracek J, Stranak Z. [Effect of early nutrition on growth parameters and psychomotor development of children of very low birth weight]. *Ceska Gynekol* 2004;69 Suppl 1:108-13.

27.   Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *Bmj* 1998;317:1481-7.

28.   Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1994;70:F141-6.

29.   Biasini A, Marvulli L, Neri E, China M, Stella M, Monti F. Growth and neurological outcome in ELBW preterms fed with human milk and extra-protein supplementation as routine practice: Do we need further evidence. *Journal of Maternal-Fetal and Neonatal Medicine* 2012;25:64-6.

30.   Ergenekon E, Hirfanoglu I, Soysal S, Gucuyener K, Bas V, Turan O *et al.* Short and longterm effects of individualized enteral protein supplementation in preterm newborns. *Journal of Maternal-Fetal and Neonatal Medicine* 2012;25:135.

31.   Svenningsen NW, Lindroth M, Lindquist B. A comparative study of varying protein intake in low birthweight infant feeding. *Acta Paediatr Scand Suppl* 1982;296:28-31.

32.   Tan M, Abernethy L, Cooke R. Improving head growth in preterm infants--a randomised controlled trial II: MRI and developmental outcomes in the first year. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F342-6.

33.   Knobloch H, Pasamanick B, Sherard ES. A developmental screening inventory for infants *Pediatrics* 1966;38:viii-1.

34.   Burattini I, Bellagamba MP, Spagnoli C, D'Ascenzo R, Mazzoni N, Peretti A *et al.* Targeting 2.5 versus 4 g/kg/day of amino acids for extremely low birth weight infants: a randomized clinical trial. *J Pediatr* 2013;163:1278-82.e1.

35.   Hellbrügge T. Munich functional developmental diagnosis for the first, second, and third year of life. *Theodor Hellbruegge International Institute for Developmental Rehabilitation*. Kerala. 1995.

36.   Griffith R. The Griffiths mental developmental scales from birth to two years, manual, the 1996 version. *Association for Research in infant and Child Development*. Henley, Test Agency.1996.

37.   Psychological Corporation. Wechsler intelligence scale for children, Anglicised. Rev ed. Sidcup. *Rev ed. Sidcup: Psychological Corporation* 1974.

38.   Lucas A. Programming by early nutrition: an experimental approach. *J Nutr* 1998;128:401S-6S.

39.   Wechsler Intelligence Scale for Children. 3rd ed. Sidcup, Kent: *The Psychological Corporation*; 1992.

40.   Wechsler D. Wechsler Adult Intelligence Scale. 3rd ed. London: The Psychological Corporation; 1997.

41.   Biasini A, Neri C, China MC, Monti F, Di Nicola P, Bertino E. Higher protein intake strategies in human milk fortification for preterms infants feeding. Auxological and neurodevelopmental outcome. *J Biol Regul Homeost Agents* 2012;26:43-7.

42.   Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M *et al.* First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics* 2009;123:1337-43.

43.   Williamson P, Altman D, Blazeby J, Clarke M, Devane D, Gargon E *et al.* Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012;13:132.

	Search terms
1	exp Infant, Very Low Birth Weight/ or exp Infant, Newborn/ or exp Infant, Premature/ or exp Infant, Extremely Low Birth Weight/
2	preterm*.mp.
3	prematur*.mp.
4	neonat*.mp.
5	1 or 2 or 3 or 4
6	exp Nutrition Therapy/ or exp Enteral Nutrition/ or exp Parenteral Nutrition, Total/ or nutrition*.mp. or exp Parenteral Nutrition/
7	exp Child Development/
8	exp Neurologic Examination/
9	(cerebral adj palsy).mp.
10	exp Cerebral Palsy/
11	disabilit*.mp.
12	neurodevelopment*.mp.
13	bayley.mp.
14	(mental adj development).mp.
15	(psychomotor adj development).mp.
16	(motor adj scales).mp
17	(language adj scales).mp.
18	(cognitive adj scales).mp
19	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20	5 and 6 and 19
21	limit 20 to Humans

Table 1: Search terms and strategy used for electronic searches[1]
[1]Performed by using OvidSp (Wolters Kluwer Health; http://www.ovid.com). adj, adjacent to; exp, exploded Medical Subject Headings term; .mp.,multipurpose search across the fields title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, and drug manufacturer.

Author, year	Study type	PN or EN	N Inter-vention	N Control	Gestational age (weeks)	Birth weight (g)	Nutrition content Intervention	Nutrition content Control	Start of intervention	Duration of intervention
Lucas1996(8)	RCT	EN	137	138	29.8	1285	Multinutrient supplement to MBM*	Control supplement to MBM*	48-72 hrs	39d
Lucas 1989a(9)	RCT	EN	76	83	31.2	1378	PTF sole diet*	DBM sole diet*	<48 hrs	30d
Lucas 1989b(9)	RCT	EN	173	170	30.8	1386	PTF supplement to MBM*	DBM supplement to MBM*	<48 hrs	30d
Lucas 1994a(28)	FU	EN	76	83	31.3	1400	PTF sole diet*	DBM sole diet*	<48 hrs	30d
Lucas 1994b(28)	FU	EN	173	170	31.1	1388	PTF supplement to MBM*	DBM supplement to MBM*	<48 hrs	30d
Lucas 1990a(10)	RCT	EN	81	79	30.8	1372	PTF sole diet*	Term formula sole diet*	<48 hrs	28d
Lucas 1990b(10)	RCT	EN	132	132	31.2	1427	PTF supplement to MBM*	Term formula supplement to MBM*	<48 hrs	28d
Lucas 1998a(27)	FU	EN	67	68	30.8	1379	PTF sole diet*	Term formula sole diet*	<48 hrs	28d
Lucas 1998b(27)	FU	EN	112	113	31.3	1425	PTF supplement to MBM*	Term formula supplement to MBM*	<48 hrs	28d
Isaacs 2008(25)	FU	EN	38	38	28.7	1216	PTF supplement to MBM*	Term formula supplement to MBM*	<48 hrs	28d
Tan 2008(32)	RCT	Both	68	74	26.1	913	Hyperalimentated diet*	Control diet*	<7d	7d
Biasini 2012(29)	RCT	EN	19	13	28.1	976	Protein enriched supplement to MBM*	Control supplement to MBM*	At full EN	34d
Blanco 2012(19)	RCT	PN	30	31	26.4	813	2g/1g until 4g Protein in PN	0.5g/0.5g until 3g Protein in PN	24-36 hours	7d
Ergenekon 2012(30)	RCT	EN	33	32	30.3	1361	Protein supplement to fortified MBM/PTF*	Control supplement to fortified MBM/PTF*	At full EN	Unknown
Svenningsen 1982(31)	RCT	EN	16	18	30.6	1348	Protein enriched formula*	Control formula*	Soon After birth	28d
Kocourkova 2004(26)	NRCT	EN	22	17	30.8	1307	Fortified DBM*	MBM*	<7d	56d
Cormack 2011(24)	Obs	PN	49	40	27	920	Reformulated nutrient enriched PN*	Previous PN*	Soon After birth	7d
Poindexter 2006(21)	Obs	PN	182	836	26.1	798	>3.5g/kg/d Protein PN	<3.5g/kg/d Protein PN	After birth	5d
Karakus 2010(20)	Obs	PN	31	45	29.2	1146	1g/1g until 3.5-4g Protein in PN	0.5g/0.5g until 3.5g Protein in PN	Day 2	5d
Rochow 2012(22)	Obs	Both	123	115	28.9	1070	After feeding implementation*	Before feeding implementation*	From birth	Approx. 7 wks (intervention until 36 wk PMA)
Burattini 2013(34)	RCT	PN	56	58	28.7	984	2.5g/kg/d at d1 to 4g/kg/d at d4	1.5g/kg/d at d1 to 2.5g/kg/d at d4	<24 hours	10d

Study	Type	Route	EN n	PN n	GA (wk)	BW (g)	Intervention group	Control group	Start	Duration
van den Akker 2014(23)	RCT	PN	66	69	28.4	1014	Glucose + 2.4g/kg/d (from 2 hours to d3	Glucose + 1.2g/kg/d increased to 2.4g/kg/d 24 hours later until d 3	From 2 hours	3d

Table 2. Characteristics of included studies; EN: enteral nutrition, PN: parenteral nutrition, RCT: randomised controlled trial, FU: Follow Up study, NRCT: non randomised controlled trial, Obs: Observational Study, MBM: maternal breast milk, DBM: donor breast milk, PTF: preterm formula, d: day; PMA: Post Menstrual Age
*See supplementation table

Study	Sequence generation[1]	Allocation concealment[2]	Blinding-personnel[3]	Blinding-outcomes[4]	Incomplete outcome data[5]	Selective outcome reporting[6]
Lucas 1996(8)	low	low	low	low	low	low
Lucas 1989(9)	low	low	**high**	low	low	low
Lucas 1994(28)	low	low	**high**	low	low	moderate
Lucas 1990(10)	low	low	low	low	low	low
Lucas 1998(27)	low	low	low	low	low	low
Isaacs et al 2008(25)	unclear	low	low	low	low	low
Tan 2008(32)	low	low	**high**	**high**	low	low
Biasini 2012(29)	unclear	unclear	unclear	unclear	unclear	low
Blanco 2012(19)	low	low	unclear	low	low	low
Ergenekon 2012(30)	unclear	unclear	unclear	unclear	unclear	unclear
Svenningsen 1982(31)	unclear	low	unclear	unclear	unclear	unclear
Kocourkova 2004(26)	low	**high**	**high**	unclear	unclear	Low
Burattini 2013(34)	low	low	**high**	low	low	Low
Van Den Akker(23)	unclear	unclear	**low**	unclear	low	low

Table 3A. The level of apparent bias in included RCTs as assessed using the Cochrane risk of bias assessment tool
1. *Selection bias due to inadequate generation of a randomised sequence.*
2. *Selection bias due to inadequate concealment of allocation prior to assignment.*
3. *Performance bias due to knowledge of the allocated interventions by personnel during the study.*
4. *Detection bias due to knowledge of the allocated interventions by outcome assessors.*
5. *Attrition bias due to the amount, nature or handling of incomplete data.*
6. *Reporting bias due to selective outcome reporting.*

Study	Representa-tiveness of exposed cohort[1]	Selection of the non-exposed cohort[2]	Ascertain-ment of exposed cohort[3]	Outcome not present at start of study[4]	Compara-bility of cohorts[5]	Assess-ment of outcome[6]	Follow-up long enough for outcome to occur	Adequacy of follow up[7]
Cormack 2011(24)	+	+	+	+	+	-	+	+
Poindexter 2006(21)	+	+	+	-	+	+	+	+
Karakus 2010 (20)	+	+	+	+	-	-	+	+
Rochow 2012 (22)	+	+	+	+	-	-	+	-

Table 3B. Quality assessment of observational studies using Newcastle Ottawa Scale.
1. *Truly or somewhat representative (+) Selected group of user or no description (-)*
2. *Drawn from same community as the exposed (+) Drawn from different source or no description(-)*
3. *Secure record or structured interview(+) written self report or no description (-)*
4. *Yes (+) No (-)*
5. *Controls for baseline weight (+) controls for any factors (+) Does not control for any factor (-)*
6. *Independent blind assessment or record linkage (+) self report or no description (-)*
7. *Complete follow up all subject accounted for or minimal lost unlikely to introduce bias (+) No description or statement (-)*

Records identified through database searching (n = 4300)

Additional records identified through other sources (n = 4)

Records after duplicates removed (n = 3245)

Records screened (n = 3245)

Full-text articles assessed for eligibility (n = 60)

Studies included in qualitative synthesis (n = 15)

Studies included in quantitative synthesis (meta-analysis) (n = 10)

Full-text articles excluded, with reasons (n= 42)

Study reported in another definitive paper (n= 1)

Review articles (n= 13)

Specific nutrient intervention (n= 22)

No increase nutritional intervention (n= 4)

No appropriate data (n= 1)

Intervention outside neonatal period (n= 1)

Figure 1. Flow chart of review process

Figure 2: Forest plots for meta-analyses of differences in (a) MDI and (b) PDI scores at 12-18 months between VP and/ or VLBW infants received increased or standard parental nutrition.

Fig. 3A

Study or Subgroup	Increased nutrition Mean	SD	Total	Standard nutrition Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.10.1 RCT									
Ergenekon 2012	94.5	13	18	89.3	11.3	20	11.3%	5.20 [-2.58, 12.98]	
Lucas 1990	104.4	19.5	95	103.3	19	101	23.4%	1.10 [-4.30, 6.50]	
Lucas 1994	103.8	20	139	102.2	20.8	134	29.1%	1.60 [-3.24, 6.44]	
Lucas 1996	106	22.4	125	103.8	21.9	138	23.7%	2.20 [-3.16, 7.56]	
Subtotal (95% CI)			377			393	87.5%	2.09 [-0.70, 4.88]	

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)

1.10.2 NRCT									
Kococourkova 2004	101	13.3	22	98.2	10.2	17	12.5%	2.80 [-4.58, 10.18]	
Subtotal (95% CI)			22			17	12.5%	2.80 [-4.58, 10.18]	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)

Total (95% CI)			399			410	100.0%	2.18 [-0.43, 4.79]	

Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%

-50   -25   0   25   50
Favours standard   Favours increase

Fig. 3B

Study or Subgroup	Increased nutrition Mean	SD	Total	Standard nutrition Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
1.11.1 RCT									
Ergenekon 2012	94.8	15.8	18	96.8	8.3	20	18.8%	-2.00 [-10.16, 6.16]	
Lucas 1990	114.9	14.6	95	92.5	17.1	101	20.7%	22.40 [17.96, 26.84]	
Lucas 1994	94.5	16.5	139	95.5	15	134	21.0%	-1.00 [-4.74, 2.74]	
Lucas 1996	92.3	17.9	125	89.9	16.4	120	20.8%	2.40 [-1.90, 6.70]	
Subtotal (95% CI)			377			375	81.2%	5.58 [-6.06, 17.23]	

Heterogeneity: Tau² = 133.67; Chi² = 72.20, df = 3 (P < 0.00001); I² = 96%
Test for overall effect: Z = 0.94 (P = 0.35)

1.11.2 NRCT									
Kococourkova 2004	94.3	12.5	22	84.4	14.6	20	18.8%	9.90 [1.64, 18.16]	
Subtotal (95% CI)			22			20	18.8%	9.90 [1.64, 18.16]	

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)

Total (95% CI)			399			395	100.0%	6.41 [-3.48, 16.29]	

Heterogeneity: Tau² = 117.79; Chi² = 72.96, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%

-100   -50   0   50   100
Favours standard   Favours increase

Figure 3: Forest plots for meta-analyses of differences in (a) MDI and (b) PDI scores at 12-18 months between VP and/ or VLBW infants received increased or standard enteral nutrition.

Fig. 4A

Study or Subgroup	Increased nutrition			Standard nutrition			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Lucas 1990	98.6	18.4	59	92.6	17.2	55	51.0%	6.00 [-0.54, 12.54]
Lucas 1994	95.3	19.5	52	94.8	16.5	62	49.0%	0.50 [-6.21, 7.21]
Total (95% CI)			**111**			**117**	**100.0%**	**3.30 [-2.09, 8.69]**

Heterogeneity: Tau² = 3.71; Chi² = 1.33, df = 1 (P = 0.25); I² = 25%
Test for overall effect: Z = 1.20 (P = 0.23)

Fig. 4B

Study or Subgroup	Increased nutrition			Standard nutrition			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Lucas 1990	98.9	16.9	59	84.2	15.6	55	49.7%	14.70 [8.73, 20.67]
Lucas 1994	94.2	15.9	52	93	14.2	62	50.3%	1.20 [-4.38, 6.78]
Total (95% CI)			**111**			**117**	**100.0%**	**7.91 [-5.32, 21.14]**

Heterogeneity: Tau² = 82.44; Chi² = 10.49, df = 1 (P = 0.001); I² = 90%
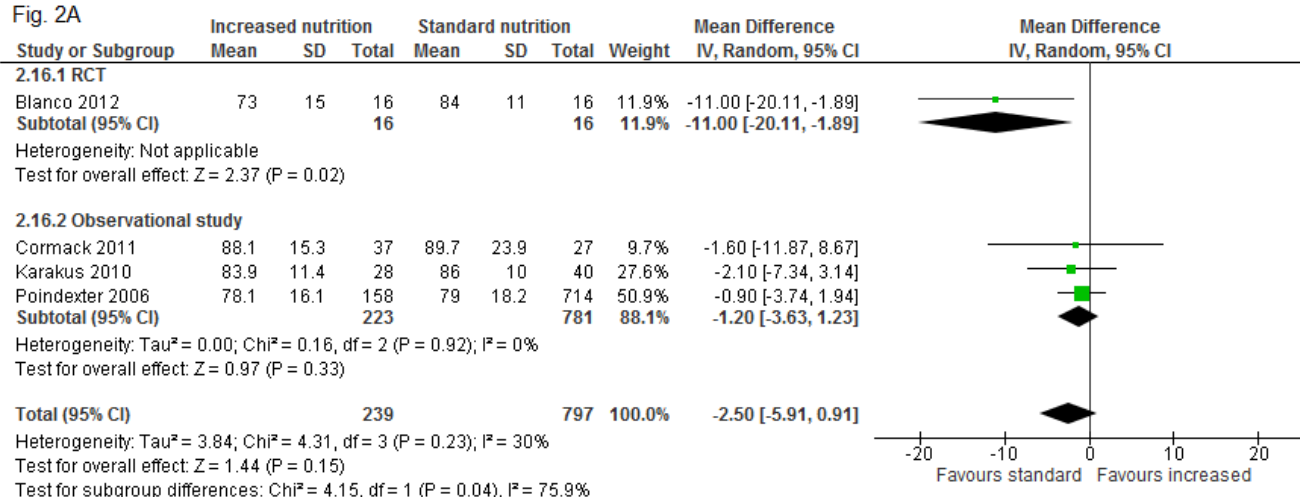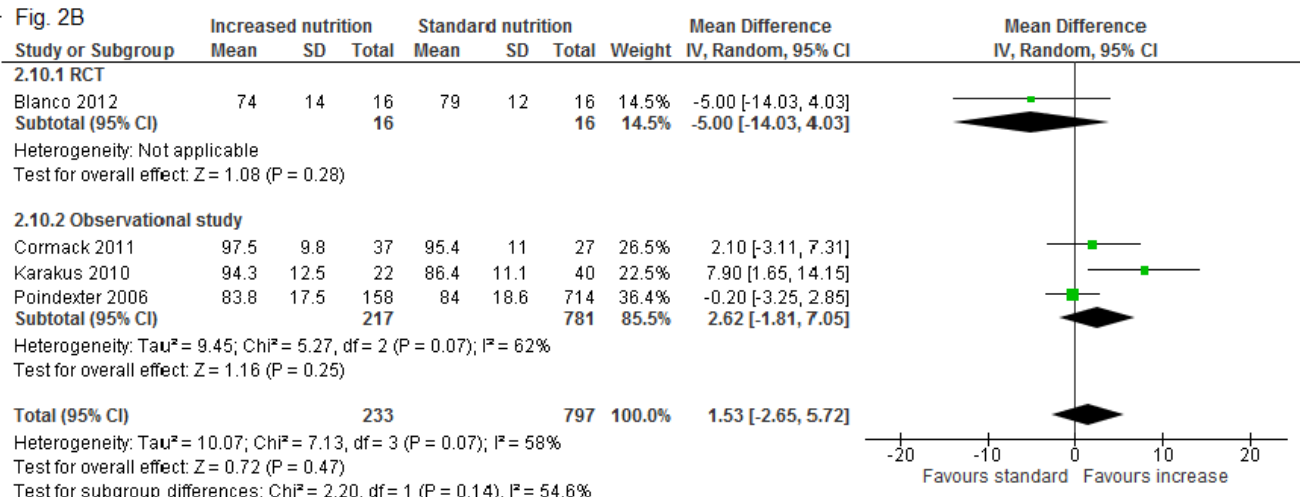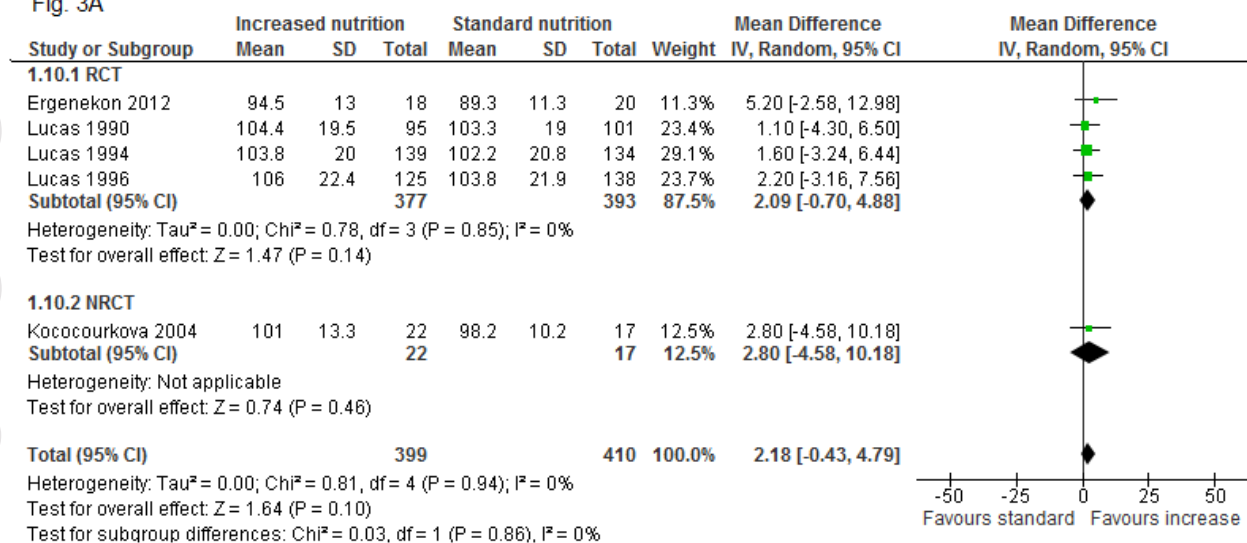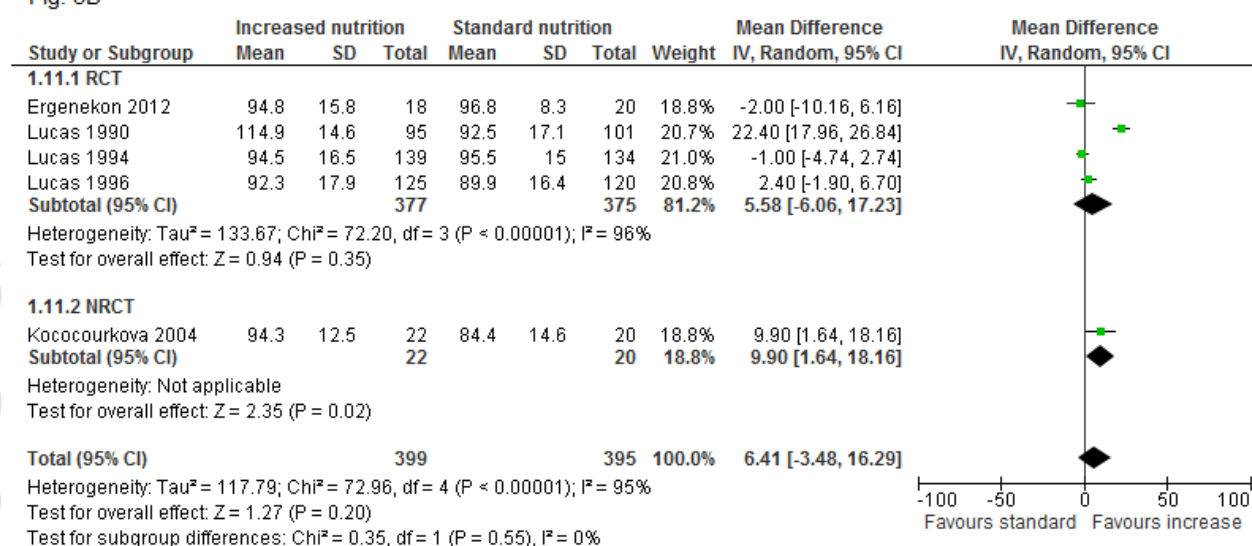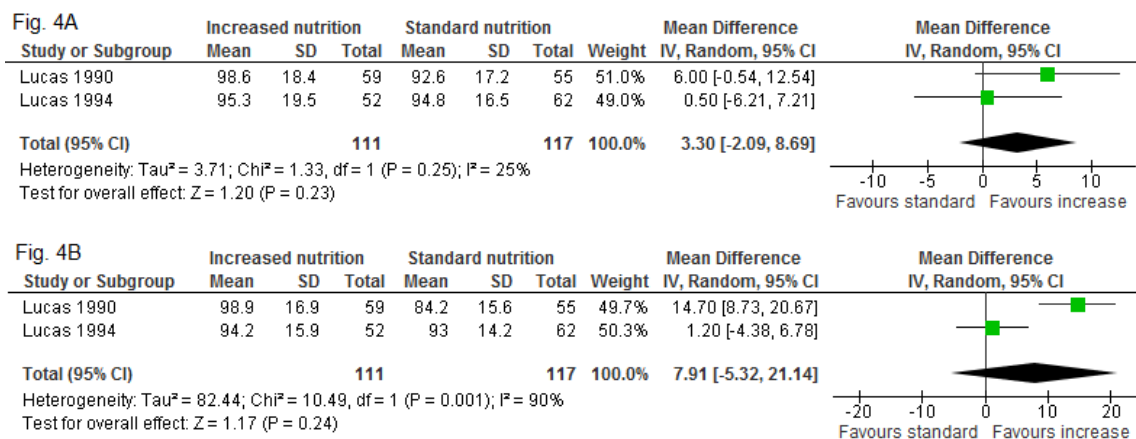Test for overall effect: Z = 1.17 (P = 0.24)

Figure 4: Forest plots for meta-analyses of differences in (a) MDI and (b) PDI scores at 12-18 months between VP and/ or VLBW infants received increased or standard sole diet. Both studies are RCTs.

Fig. 5A

Study or Subgroup	Increased Nutrition			Standard Nutrition			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Blanco 2012	57	11	16	63	13	16	19.7%	-6.00 [-14.34, 2.34]
Van Den Akker 2014	93.1	9.8	54	96.6	12.3	57	80.3%	-3.50 [-7.63, 0.63]
Total (95% CI)			**70**			**73**	**100.0%**	**-3.99 [-7.69, -0.29]**

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.11 (P = 0.03)

Fig 5B

Study or Subgroup	Increased Nutrition			Standard Nutrition			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Blanco 2012	67	15	16	64	12	16	30.1%	3.00 [-6.41, 12.41]
Van Den Akker 2014	89.3	15.3	54	92.2	16.7	57	69.9%	-2.90 [-8.85, 3.05]
Total (95% CI)			**70**			**73**	**100.0%**	**-1.12 [-6.43, 4.18]**

Heterogeneity: Tau² = 1.26; Chi² = 1.08, df = 1 (P = 0.30); I² = 7%
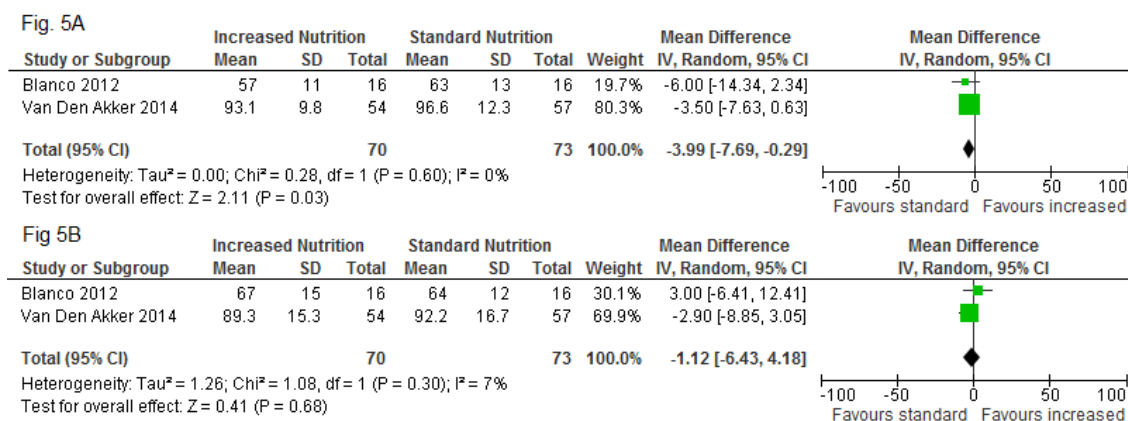Test for overall effect: Z = 0.41 (P = 0.68)

Figure 5: Forest plots for meta-analyses of differences in (a) MDI and (b) PDI scores at 24 months between VP and/ or VLBW infants received increased or standard parenteral nutrition. Both studies are RCTs.
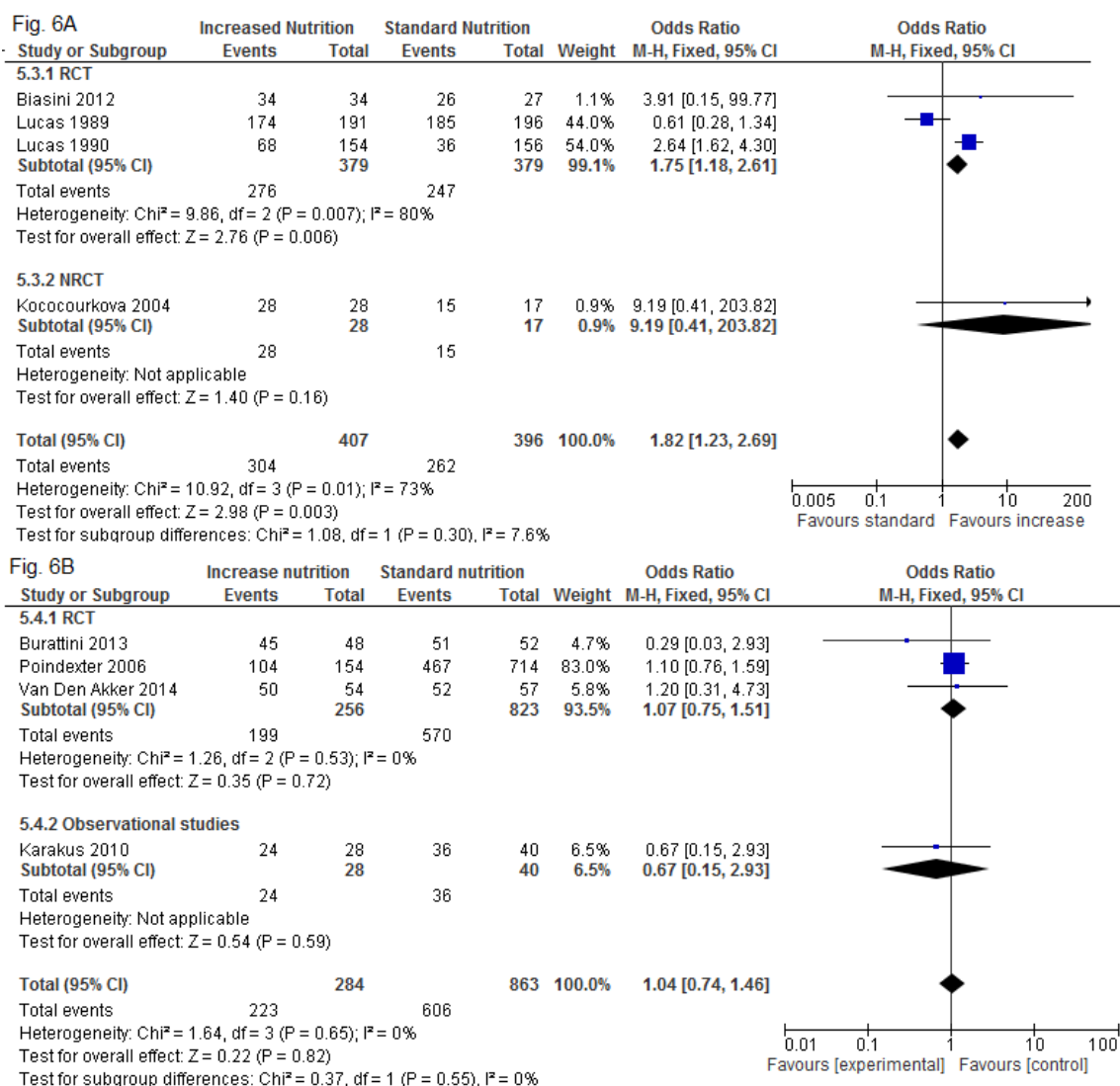
Figure 6: Forest plots for meta-analyses of differences in the survived infants without neurodevelopmental impairment in (a) enteral nutrition studies and (b) parenteral nutrition studies