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Nutrition, Growth, Brain Volume, and Neurodevelopment in Very Preterm Children

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Objective To explore the associations between nutrition in the first 28 days after birth with somatic growth from birth to term-equivalent age, brain volumes at term-equivalent age, and neurodevelopment at 24 months of corrected age.

Study design Prospective cohort study of 149 infants born from 2011 to 2014 at <30 weeks of gestation in a tertiary neonatal nursery in Australia. The following data were collected: average daily energy, protein, fat, and carbohydrate intakes from birth until 28 days, and the difference in weight and head circumference z scores between birth and term-equivalent. Total brain tissue volumes were calculated from brain magnetic resonance imaging at term-equivalent age. Children were assessed at 2 years of corrected age with the Bayley Scales of Infant and Toddler Development-Third Edition. Relationships of nutritional variables with growth, brain volumes, and cognitive, language, and motor development were explored using linear regression.

Results Complete nutritional data were available for 116 (78%) of the cohort. A 1 g/kg/day higher mean protein intake was associated with a mean increase in weight z score per week of 0.05 (95% CI 0.05, 0.10; $P = .04$). There was a lack of evidence for associations of any nutritional variables with head circumference growth, with brain volumes at term-equivalent age, or with 2-year neurodevelopment.

Conclusions Only higher protein intakes in the first 28 days after birth were associated with better weight growth between birth and term-equivalent age in very preterm infants. Nutrition in the first 28 days was otherwise not substantially related to brain size or to neurodevelopmental outcomes. *(J Pediatr 2019;215:50-5)*.

Infants born at <30 weeks of gestation are at high risk of postnatal growth failure because of medical morbidities that increase energy requirements and because the immature gastrointestinal tract impedes delivery of enteral nutrition.[1] The provision of adequate ex utero nutrition in preterm infants is challenging. Consequently, postnatal growth failure is common[2] and associated with poorer neurodevelopmental outcomes.[3-7]

Studies that have reported increased early protein intake and improved growth in weight and head circumference in preterm infants largely have focused on the effects of increased parenteral administration of protein, within varying periods of nutritional intervention during the first few weeks after birth.[3,5,8-11] There is growing evidence that increased early fat intake, particularly essential fatty acids, is associated with brain growth and functional neurodevelopment.[12-17] However, few studies have examined fat intake over the entire neonatal period (ie, 28 days after birth). Moreover, there is limited evidence for the role of carbohydrate in growth or brain development of preterm infants, except for 1 study that reported better growth velocity with the proportion of total energy from carbohydrate, but not that from fat and protein.[18]

We aimed to compare average daily energy, protein, fat, and carbohydrate intakes in the first 28 days after birth with recommended guidelines by the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[19] and to explore the associations of nutritional intake with weight and head circumference changes between birth and term-equivalent age, brain tissue volumes as measured using magnetic resonance imaging (MRI) at term-equivalent age, and neurodevelopment at 2 years of corrected age. We hypothesized that higher nutritional intakes would be associated with better growth, larger brains, and improved neurodevelopment.

Methods

The current study was nested within a larger prospective longitudinal cohort study of growth and development of infants born at <30 weeks of gestation.[20]

Bayley-III	Bayley Scales of Infant and Toddler Development-Third Edition
ESPGHAN	European Society of Pediatric Gastroenterology, Hepatology, and Nutrition
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis

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The study was approved by the Human Research Ethics Committee of the Royal Women's Hospital, Melbourne, Australia. Written informed consent was obtained from parents of all participants.

Infants born at <30 weeks of gestation admitted to the neonatal nurseries at the Royal Women's Hospital were recruited over a 3-year period from January 2011. Infants were excluded if they had congenital abnormalities known to affect neurodevelopment, or if they had non-English speaking parents, as there were English-based questionnaires used in the larger study.

Maternal and perinatal data were prospectively collected. The following data also were collected: weight and head circumference from birth until discharge or term-equivalent age (whichever came first) and daily volume totals for all nutritive fluids including parenteral nutrition solutions, enteral feedings, and oral sucrose given for pain relief (details available in the **Appendix** [available at www.jpeds.com]). Because of differences in gestational age and length of hospital stay, the duration of data collection varied for each participant. Once an infant began direct breastfeeding their daily intake became imprecise. Given these limitations, we focused on nutrition delivered in the first 28 days after birth when the data were more accurate and more complete and direct breast feeding was rare.

Social risk was assessed using sociodemographic factors known to be related to outcomes in preterm infants, including family structure, education of the primary caregiver, employment status of the primary income earner, occupation of the primary income earner, language spoken at home, and maternal age at birth of child. Each variable was scored on a 3-point scale where 0 represented lowest risk, and 2 represented highest risk and summed to give a total score (range 0-12). Social risk was dichotomized to higher (total social risk score of ≥2) or lower (social risk score of <2) social risk.[21]

Nutritional and Growth Indices

The daily energy and macronutrient (protein, fat, and carbohydrate) intakes over the 28-day period were calculated by multiplying the volume (mL) of each nutritive fluid for each day by the kilocalorie content or grams of each macronutrient per mL (**Appendix**). These were sourced from nutritional information printed on parenteral and enteral nutrition products. Values for the composition of breast milk were taken from data published by the National Health and Medical Research Council of Australia for mature human milk.[22] The daily total for each nutrient was then divided by the infant's body weight on that day, with values expressed per kilogram of body weight for each day. The total intake for each nutrient in the first 28 days was averaged to give an average daily intake over the 28-day period. Infants with missing nutritional data during that time because of interhospital transfer or discharge from the hospital was excluded from the analysis.

Infants were weighed at birth and then approximately every third day. Weight and head circumference measurements at birth and at term-equivalent age were converted to z scores using LMS growth curves.[23] To assess growth in both weight and head circumference, we calculated the difference in z scores between birth and term-equivalent age, and divided that by the time (in weeks).

MRI and Neurodevelopmental Outcomes

MRI was performed between 38 and 44 weeks postmenstrual age using a 3T Siemens Magnetom Trio MRI system (Siemens, Erlangen, Germany). Quantitative image analysis was performed using structural T_2-weighted MR images. Measures of total brain tissue volume (excluding cerebrospinal fluid), cortical gray matter, white matter, deep nuclear gray matter, and cerebellum were derived using the morphologically adaptive neonate tissue segmentation toolbox.[24]

At 2 years of corrected age, the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III) were used to assess cognitive, language, and motor development. Each child was examined by a pediatrician for physical impairments (eg, cerebral palsy, blindness, deafness). Cerebral palsy was determined by abnormal tone and reflexes, and a loss of function. Vision was tested using a Snellen chart and blindness defined as having visual acuity <20/200 in the better eye. Hearing impairment was ascertained by history with deafness comprising a hearing impairment requiring amplification or a cochlear implant, or worse. Any neurosensory disability comprised any of cerebral palsy, blindness, deafness, or cognitive, language, or motor development (<-1SD compared with term controls).

Statistical Analyses

Data were analyzed using STATA v 14.0 (StataCorp, College Station, Texas). Participant characteristics of those with complete nutritional data were contrasted with those without complete nutritional data (**Table I**). In addition, participant characteristics of those with complete nutritional data and MRI were contrasted with those without complete data for both variables (**Table II**; available at www.jpeds.com).

Growth for both weight and head circumference was evaluated by calculating differences in z scores between birth and term-equivalent age. The relationships between nutritional indices and weight and head circumference growth were explored using linear regression fitted using generalized estimating equations with robust (sandwich) estimation of SEs to account for multiple births, with a separate model for each nutrition measure-outcome combination. The analyses were first unadjusted, then adjusted for sex, sepsis, or necrotizing enterocolitis (NEC), and the duration of ventilation (the latter 2 as surrogate measures of illness severity and potential confounders of growth).

For the relationships between nutritional indices and (1) brain volumes and (2) cognitive, language, and motor development, linear regression fitted using generalized estimating equations with robust (sandwich) estimation of SEs was used. For the MRI, adjustment occurred in 2 steps; first, adjusted for sex and postmenstrual age at MRI (as both variables affect brain size), and then for sepsis/NEC, and duration

Table I. Clinical characteristics of infants with and without nutritional data compared with those without

Characteristics	Infants with complete nutritional data; n = 116	Infants with incomplete out nutritional data; n = 33	*P* value
Multiple birth; n (%)	55 (47.4)	10 (30.3)	.02
Gestational age, wk; mean (SD)	27.5 (1.4)	28.1 (2.0)	.10
Birthweight, g; mean (SD)	995 (242)	1114 (304)	.02
Male; n (%)	57 (49.1)	17 (51.5)	.80
Birth weight z score; mean (SD)	−0.50 (1.1)	−0.29 (0.92)	.31
Intraventricular hemorrhage grade III-IV; n (%)	3 (2.6)	2 (6.1)	.33
Cystic periventricular leukomalacia; n (%)	0 (0)	1 (3)	.06
Sepsis*; n (%)	55 (47.4)	16 (48.5)	.63
Surgery in the newborn period; n (%)	4 (3.5)	7 (21.2)	.001
NEC; n (%)	9 (11.4)	8 (24.2)	.01
Retinopathy of prematurity (any); n (%)	26 (22.8)	6 (20.7)	.24
Oxygen at 36 wk; n (%)	38 (32.7)	8 (25.0)	.40
Postnatal corticosteroids; n (%)	14 (12.1)	4 (12.1)	.99
Higher social risk; n (%)	46 (44.6)	9 (36.0)	.43

*Diagnosis of sepsis both suspected and proven sepsis.

of ventilation. For the developmental outcomes, results are presented both unadjusted and adjusted for similar variables as for growth.

Results

Of the 149 participants enrolled in the study, 116 had complete nutritional and anthropometric data, of whom 81 had an MRI of sufficient quality to calculate brain tissue volumes. Compared with participants with incomplete nutritional data, infants with complete nutritional data were lighter at birth, had lower rates of NEC and surgery, and there were fewer singletons (**Table I**). Compared with participants with complete nutritional data and MRI, those with nutritional data only were lighter at birth, more likely to have retinopathy of prematurity and more likely to have received postnatal corticosteroids. They also showed a trend (P = .05) to higher rates of neonatal surgery and the need for supplemental oxygen at 36 weeks of postmenstrual age (**Table II**).

Although most participants met recommended requirements for energy, fat, and carbohydrate intake, few (3.4%) achieved protein intakes within recommended ranges (**Table III**; available at www.jpeds.com). In the first 28 days after birth, no infant was directly breast fed.

Higher protein intake was associated with a positive weight z score change between birth and term-equivalent, before and after adjustment for potential confounders. However, there was a lack of evidence for relationships between other nutritional variables and change in weight z scores from birth to term-equivalent age (**Table IV**).

Nutritional intakes were not associated with the change in head circumference z scores between birth and term-equivalent (**Table V**; available at www.jpeds.com), brain volumes at term-equivalent age (**Table VI**), any neurosensory disability (**Table VII**), or with Bayley-III cognitive, language, or motor outcomes at 2 years of corrected age (**Tables VIII-X**; available at www.jpeds.com).

Discussion

In our study of infants born at <30 weeks of gestation, higher protein intake in the first 28 days after birth was associated with better weight growth from birth to term-equivalent. However, we found no other associations between nutritional intakes in the first 28 days after birth and head circumference growth, brain volumes at term-equivalent age, or 2-year neurodevelopment. These findings need to be interpreted in the context of the range of nutritional intake and the time period studied.

In this study, all nutrient targets (as per ESPGHAN) were met in the first 28 days, except for protein. Very few (3.4%) of the infants met recommended intakes for protein. This can be explained by factors such as competing requirements by medications (antimicrobials, sedatives) that are not always compatible with the parenteral nutrition solutions. In addition, the parenteral solutions used at the time had kilocalorie intakes that were made up predominantly of parenteral dextrose and lipid. In the time since the current study was conducted, parenteral solutions with higher protein content have been introduced to address these barriers.

There are mixed reports concerning the relationship of higher nutritional intake with early growth in preterm infants. Cormack et al reported that higher nutritional intake in the first month, particularly protein intake, was associated with better postnatal growth.[11] In another study higher carbohydrate intake was associated with better growth in infants born at <33 weeks of gestation in a population where protein intake was adequate.[18] Some studies have reported improved growth with introduction of a more aggressive nutrition policy,[25,26] whereas others have not.[27] One of the few randomized controlled trials in preterm infants of low vs high amino acid intake in both enteral and parenteral form reported similar growth in hospital and at 2-year follow-up between the 2 groups.[28]

In contrast to the current study, Cormack et al reported better head circumference growth between birth and discharge in preterm infants randomized to receive high

Table IV. Relationships between nutritional intake in first 28 days and weight growth from birth to term-equivalent age

Nutritional intake	Unadjusted coefficient (95% CI)	Unadjusted *P* value	Adjusted* coefficient (95% CI)	Adjusted* *P* value
Growth in weight z score/wk from birth to term-equivalent age (n = 92)				
Energy	0.017 (−0.17, 0.17)	.87	−0.013 (−0.21, 0.17)	.89
Protein	0.05 (0.01, 0.10)	.04	0.05 (0.01, 0.10)	.05
Fat	−0.01 (−0.03, 0.02)	.84	−0.01 (−0.03, 0.02)	.59
Carbohydrate	−0.01 (−0.03, 0.02)	.55	−0.01 (−0.03, 0.01)	.44

Coefficients are z score changes per 100 kcal/kg/day increase for total energy, and per gram/kg/day increase for protein, fat, and carbohydrate intake.
*Adjusted for sex, sepsis or NEC, and days of ventilation.

(mean [SD] of 3.8 [0.3] g/kg/day) vs low (mean [SD] of 3.3 [0.4] g/kg/day) intake of protein.[11] This may in part be explained by the lower protein intakes (mean [SD] 2.9 [0.3] g/kg/day) in the current study than both groups in the study by Cormack et al. In a randomized-controlled trial of parenteral nutrition comparing a high energy and protein formulation with a control regime, Morgan et al reported that infants with gestational ages of <29 weeks in the high nutrient arm had a greater increase in head circumference in the first 28 days that was still evident at 36 weeks of corrected age, compared with infants in the control arm.[3] Similarly, the high nutrient arm group of the study received higher protein intakes (3.8 g/kg/day) than the majority of infants in the current study.

We found no associations between total brain tissue volume at term-equivalent and nutrition and energy intake during the first 28 days of life. In contrast, there are 2 studies that have reported associations between higher nutritional (energy and fat) intakes in the first 2 weeks and larger brain volumes on MRI at term-equivalent age.[14,15] Another study reported positive associations between cumulative fat and enteral intake in the first 4 weeks with cerebellar and basal ganglia and thalamic volumes at term-equivalent age.[16]

A key difference is lower nutritional intakes in those studies compared with ours. Thus, nutrition might be more influential on brain growth when caloric intake is suboptimal.

A randomized controlled trial[29] of a hyperalimented vs standard feeding regimen during the neonatal period found no benefit of increased nutrition on brain volume at term-equivalent age. The median energy and protein intakes of both the intervention and control groups were lower than the average nutritional intakes recorded in the current study, and comparable with those in the Beauport[14] and Schneider studies.[14,15] However, the difference between intervention and control groups was approximately 100 calories delivered over the course of 28 days. This is a very small difference and may not have been sufficient to show statistical significance.

We found no evidence of associations between nutritional outcomes and neurodevelopmental outcomes at 2 years of age. A systematic review published in 2016[17] reported that long chain polyunsaturated fatty acid supplementation of formula or breast milk during the "lactation" period in preterm infants was associated with significant improvement in neurodevelopment at toddler age. However, no studies to date have shown that increased total fat intake over the same time period confers the same benefit. Although Tan et al did not show increased brain size or improved neurodevelopmental scores with the hyperalimented nutrition regime, they did show that an energy deficit at the conclusion of the neonatal period (ie, not meeting the caloric targets set by ESPGHAN) was correlated with poorer neurodevelopmental outcome at 3-months' post term.[29] Interestingly, Coviello et al found that although total protein intake was not related to brain volume at term-equivalent age, it was the only nutritional variable positively associated with higher cognitive scores (on the Bayley-III) at 2 years of corrected age.[16] A recent systemic review of studies that examined the relationship between nutrition in the neonatal period and neurodevelopment at toddler age concluded that although early nutritional intervention was likely to help prevent neurological impairment in this population; a direct relationship between early nutrition and neurodevelopmental outcomes could not be established firmly.[6]

Though there is some evidence to suggest that increased protein and lipid administration in early life improves

Table VI. Relationships between nutritional intake in first 28 days and brain tissue volumes at term-equivalent age

	Brain tissue volumes at term-equivalent age (n = 82)				
Nutritional intake	Total brain volume Coefficient (95% CI), *P* value	Cortical gray matter Coefficient (95% CI), *P* value	White matter Coefficient (95% CI), *P* value	Deep nuclear gray matter Coefficient (95% CI), *P* value	Cerebellum Coefficient (95% CI), *P* value
Energy	8.79 (−89.1, 106.7), *P* = .86	3.35 (−42.6, 49.0), *P* = .89	0.13 (−39.7, 40.2), *P* = .99	1.67 (−4.6, 7.5), *P* = .62	3.35 (−5.9, 12.1), *P* = .49
Protein	27.2 (−11.5, 66.0), *P* = .17	12.0 (−5.9, 29.9), *P* = .19	10.6 (−4.8, 25.9), *P* = .18	0.9 (−1.3, 3.1), *P* = .43	3.1 (−0.7, 6.8), *P* = .11
Fat	−2.4 (−17.7, 13.0), *P* = .76	−0.8 (−8.0, 6.3), *P* = .82	−1.5 (−7.8, 4.7), *P* = .63	0.1 (−0.8, 1.1), *P* = .76	−0.1 (−1.5, 1.3), *P* = .85
Carbohydrate	4.4 (−5.2, 14.0), *P* = .37	2.2 (−2.5, 6.9), *P* = .36	1.1 (−2.5, 4.8), *P* = .55	0.3 (−0.3, 0.9), *P* = .34	0.7 (−0.2, 1.6), *P* = .11

Coefficients are changes in brain volume (cc) per 100 kcal/kg/day increase for total energy, and per gram/kg/day increase for protein, fat, and carbohydrate intake. All coefficients are adjusted for sex, postmenstrual age at MRI, sepsis or NEC, and days of ventilation.

Table VII. Relationships between nutritional intake in first 28 days and any disability (n = 116) at 2 years of corrected age

Nutritional intake	Unadjusted OR (95% CI)	Unadjusted *P* value	aOR* (95% CI)	Adjusted* *P* value
Energy	1.0 (0.9, 1.0)	.83	1.0 (0.9, 1.0)	.94
Protein	0.7 (0.2, 2.4)	.56	0.9 (0.2, 3.8)	.85
Fat	0.9 (0.5, 1.6)	.74	1.0 (0.5, 1.9)	.94
Carbohydrate	1.0 (0.7, 1.5)	.89	1.1 (0.7, 1.7)	.66

ORs and coefficients per 100 kcal/kg/day increase for total energy, and per gram/kg/day increase for protein, fat, and carbohydrate intake.
Disability defined as cerebral palsy or developmental delay in any of cognitive, language, or motor development (<-1SD below the mean compared with term controls).
*Adjusted for sex, sepsis or NECs, and days of ventilation.

brain growth and development in preterm infants, many studies only evaluated nutrition in the first two weeks. It has been acknowledged that delivery of nutrition to preterm infants is particularly challenging in the first weeks after birth and barriers to nutrition are multifactorial. An important confounder in these studies is that infants who have higher nutritional intakes in the early days of life are likely to be less unwell, have fewer medical parenteral requirements (allowing a higher rate of parenteral nutrition delivery) and tolerate a more rapid increase in enteral feeds. Although statistical methods adjust for surrogate measures of "unwellness" (eg, sepsis, NEC, time spent on mechanical ventilation, lower birthweight); there is no universal measure to describe the clinical status of each infant.

Further, studies where nutritional intake is documented over a longer time period[6,29] including the current study, show less convincing relationships between nutritional intake and brain growth and neurodevelopment. The discrepancy in results could suggest that there is confounding due to early and limited periods of observation. Alternatively, it could also suggest that there is a window of time for enhanced nutrition delivery in preterm infants that is most influential on brain volume at term-equivalent age and neurodevelopment.

The strengths of the current study are that it was a prospective longitudinal cohort study with detailed nutritional data, brain MRI available, and neurodevelopmental outcome at 2 years of age. We acknowledge a potential bias of not including sicker infants with surgical problems (eg, NEC) as they would have been transferred to another center for surgery. In our sample, infants with complete nutritional data were lighter at birth and had lower rates of singleton births than infants without complete nutritional data. This may have limited our ability to find associations between nutritional intake and the various outcomes. Caloric content of breast milk is variable, and we used estimates of nutrition of breast milk from mature breast milk, which are more widely reported. We acknowledge that there are some data of a higher caloric, protein, and fat content in milk from lactating mothers of preterm infants but this data is less robust.[30]

The focus of the current study was nutrition in the neonatal period (28 days). It is important to acknowledge the effect of the infants' nutrition and environmental exposures after 28 days. A key difficulty with studies of infant nutrition is that accurate data collection in some cases is nearly impossible (ie, when babies begin to breast feed, when they are discharged home, or with late complications which impede nutrition delivery). These factors would no doubt influence growth and brain development but were not measured in the current study.

There were many factors in early life potentially affecting growth and brain development for this cohort. Many of these were treated as confounders and adjusted for in the analysis. However, their cumulative impact on a very preterm infant may ultimately influence growth and developmental outcomes more than nutrition, particularly as the average energy, carbohydrate, and fat intakes were mostly sufficient (according to ESPHGAN guidelines). The lack of variability (or lack of babies deficient in these nutrients) meant that a statistical difference was not observed. If the study had been interventional and included a group of infants with a fortified diet, the results may have been different. There were many infants deficient in protein intakes and the results showed increased protein intake was associated with better growth in weight at term-equivalent age. This supports the existing body of evidence that suggests protein intake in early life is particularly important for growth in weight.

Our study adds to the pool of divergent results with regard to the role of early nutrition in somatic growth, brain volumes, and neurodevelopment in very preterm infants. What is needed is an adequately powered randomized-controlled trial to enable this most pressing question to be addressed. ■

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Table II. Clinical characteristics of infants with nutritional and MRI data vs those with nutritional data only

Characteristics	Infants with nutritional and MRI data; n = 82	Infants with nutritional data only; n = 34	*P* value
Multiple birth; n (%)	39 (48.1)	16 (45.7)	.29
Gestational age, wk; mean (SD)	27.8 (1.3)	27.3 (1.5)	.07
Birthweight, g; mean (SD)	1032 (244)	908 (219)	.01
Male; n (%)	43 (53.1)	14 (40.0)	.20
Birth weight z score; mean (SD)	−0.41 (1.1)	−0.71 (0.96)	.16
Intraventricular hemorrhage grade III-IV; n (%)	1 (2.9)	2 (2.5)	.90
Cystic periventricular leukomalacia; n (%)	0 (0)	0 (0)	NA
Sepsis*; n (%)	34 (42.0)	21 (60.0)	.20
Surgery in the newborn period; n (%)	1 (1.2)	3 (8.6)	.05
NEC; n (%)	5 (6.2)	4 (11.4)	.33
Retinopathy of prematurity (any); n (%)	12 (15.2)	14 (40.0)	.003
Oxygen at 36 wk; n (%)	22 (27.2)	16 (45.7)	.05
Postnatal corticosteroids; n (%)	4 (4.9)	10 (28.6)	<.001
Higher social risk; n (%)	31 (41.9)	15 (51.7)	.37

*Diagnosis of sepsis both suspected and proven sepsis.

Table III. Average nutritional intakes for the first 28 days after birth (n = 116)

Average intake	Mean (SD)	Range	Recommended ranges*	Percent meeting who met guidelines (%)
Energy (kcal/kg/d)	114.2 (10.3)	70.9-131.7	110-135	71.8
Protein (g/kg/d)	2.9 (0.3)	1.7-3.9	3.5-4.4	3.4
Fat (g/kg/d)	5.4 (0.3)	1.9-6.5	4.4-6.6	90.6
Carbohydrate (g/kg/d)	13.9 (0.3)	10.3-15.8	11.6-13.2	96.6

*Based on Guidelines from the ESPGHAN.

Table V. Relationships between nutritional intakes in first 28 days and head circumference growth from birth to term-equivalent age

	Growth in head circumference z score/wk between birth and term-equivalent age (n = 87)			
Nutritional intake	**Unadjusted coefficient (95% CI)**	**Unadjusted *P* value**	**Adjusted* coefficient (95% CI)**	**Adjusted* *P* value**
Energy	0.083 (−0.13, 0.25)	.45	0.017 (−0.21, 0.25)	.89
Protein	0.02 (−0.03, 0.07)	.39	0.01 (−0.05, 0.07)	.84
Fat	0.01 (−0.02, 0.04)	.48	0.01 (−0.03, 0.03)	.87
Carbohydrate	0.01 (−0.02, 0.03)	.64	0.01 (−0.02, 0.02)	.89

Coefficients are z score changes per 100 kcal/kg/day increase for total energy, and per gram/kg/day increase for protein, fat, and carbohydrate intake.
*Adjusted for sex, sepsis or NEC, and days of ventilation.

Table VIII. Relationships between nutritional intake in first 28 days and Bayley-III cognitive development composite score on Bayley-III (n = 107) at 2 years of corrected age

Nutritional intake	Unadjusted coefficient (95% CI)	Unadjusted *P* value	Adjusted* coefficient (95% CI)	Adjusted* *P* value
Energy	5.02 (−18.0, 28.0)	.67	−1.70 (−28.4, 25.5)	.91
Protein	3.4 (−5.7, 12.6)	.46	0.4 (−10.1, 10.9)	.94
Fat	0.6 (−2.7, 3.9)	.72	−0.3 (−4.0, 3.5)	.89
Carbohydrate	0.3 (−2.4, 3.0)	.82	−0.2 (−3.2, 2.7)	.88

ORs and coefficients per 100 kcal/kg/day increase for total energy, and per gram/kg/day increase for protein, fat, and carbohydrate intake.
*Adjusted for sex, sepsis or NEC, and days of ventilation.

Table IX. Relationships between nutritional intake in first 28 days and language development score on Bayley-III (n = 106) at 2 years of corrected age

Nutritional intake	Unadjusted coefficient (95% CI)	Unadjusted *P* value	Adjusted* coefficient (95% CI)	Adjusted* *P* value
Energy	14.64 (−18.0, 46.4)	.38	9.2 (−27.6, 45.6)	.63
Protein	5.4 (−5.0, 15.9)	.31	1.5 (−10.5, 13.5)	.80
Fat	1.9 (−3.1, 6.9)	.46	1.2 (−4.3, 6.6)	.67
Carbohydrate	0.7 (−2.8, 4.1)	.71	0.03 (−3.6, 3.7)	.99

ORs and coefficients per 100 kcal/kg/day increase for total energy, and per gram/kg/day increase for protein, fat, and carbohydrate intake.
*Adjusted for sex, sepsis or NEC, and days of ventilation.

Table X. Relationships between nutritional intake in first 28 days and Bayley-III motor development composite score on Bayley-III (n = 106) at 2 years of corrected age

Nutritional intake	Unadjusted coefficient (95% CI)	Unadjusted *P* value	Adjusted* coefficient (95% CI)	Adjusted* *P* value
Energy	23.8 (−7.11, 55.2)	.13	22.6 (−13.0, 58.6)	.21
Protein	3.5 (−7.4, 14.4)	.53	−0.3 (−12.3, 11.7)	.96
Fat	3.2 (−1.4, 7.8)	.17	3.0 (−2.1, 8.0)	.25
Carbohydrate	2.0 (−1.2, 5.3)	.22	1.7 (−1.7, 5.2)	.33

*Adjusted for sex, sepsis or NEC, and days of ventilation.