**IMPACT OF EARLY NUTRITIONAL INTAKE ON PRETERM BRAIN: A MAGNETIC
RESONANCE IMAGING STUDY**

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ABBREVIATIONS

aOR: Adjusted Odds Ratio / BW: Birth Weight / BPD: Broncho-Pulmonary Dysplasia / CRIB: Critical Risk Index for Babies / DOL: Day of Life / HC: Head Circumference / GA: Gestational age / GM: Grey Matter / IQR: Interquartile Range / IVH: Intraventricular Hemorrhage / MRI: Magnetic Resonance Imaging / NEC: Necrotizing Enterocolitis / PDA: Patent Ductus Arteriosus / ROP: Retinopathy of Prematurity / SGA: Small for Gestational Age / TEA: Term Equivalent Age / WM: White Matter / 95% CI: 95 Percent Confidence Interval

ABSTRACT

Objectives To investigate the association between early nutritional intakes and brain development assessed by Magnetic Resonance Imaging.

Study design A cohort of neonates born at ≤ 30 weeks gestational age underwent magnetic resonance imaging at term equivalent age (TEA). Brain maturation and injury were scored according to Kidokoro. Two groups were defined by severity of the scores. The associations between macronutrients intake during the first two weeks of life, clinical factors and imaging scores were analyzed using logistic regression.

Results Magnetic resonance imaging scores from Group 1 patients (n=27) were normal to mildly abnormal (0-5). Group 2 (n=15) had more abnormal scores (6-12). The median gestational ages [Interquartile Range] were 27.4 [1.9] weeks in Group 1 and 27.0 [2.9] weeks in Group 2, with birth weights of 900 [318] g (Group 1) and 844 [293] g (Group 2). In Group 2, energy, lipid and carbohydrate intakes were significantly lower than in Group 1. Group 2 also showed higher rates of sepsis and clinical risk scores than Group 1. After adjustment in bivariable models, higher energy and lipid intakes remained significantly associated with improved scores on magnetic resonance imaging. This association was stronger for the grey matter component of the score.

Conclusion Higher energy and lipid intake during the first two weeks after birth was associated with a lower incidence of brain lesions and dysmaturation at TEA in preterm neonates.

Given the rise in rates of preterm birth and survival, it is important to attempt to decrease rates of neurological sequelae that may affect up to 40% of very preterm infants (1,2). Optimizing early nutritional support has been shown to improve neurodevelopment in preterm infants (3–6). During the first two of weeks after birth, preterm infants are vulnerable to nutritional deficits (3,4,7). Cumulative energy, protein and lipid intakes have been correlated positively with cognitive and motor outcomes, even if their relative impacts are not fully clarified (3–5). The effects of specific nutrients on brain lesions or morphological maturation itself are also poorly understood. Further investigations are required to unravel proposed neuroprotective effects of nutrition in preterm infants (8–10).

In the last decade, cerebral Magnetic Resonance Imaging (MRI) and particularly newly developed techniques of MRI have become powerful tools to assess preterm brain development (10–13). MRI studies reveal that the preterm brain, even without severe injuries, may show “dysmaturation” that can lead to neurological impairments later in life (14–16). However, only a few MRI studies have investigated the effects of nutritional factors on brain morphology (17–19). Isaacs et al first observed larger caudate volumes, related to higher verbal IQ, in 38 ex-preterm male adolescents, who had been randomized to receive a high nutrient diet (19). More recently, improved head growth and decreased regional white matter (WM) diffusivity at term equivalent age (TEA) were reported in 14 very low birth weight infants who received enhanced parenteral and enteral nutrition, suggesting nutritional improvements led to better WM maturation (18). In contrast, brain volumes were not related to macronutrients in two observational studies (17, 20). However, these studies focused on particular brain structures and did not assess early nutritional impact.

The aim of our study was to investigate the association between morphological brain development, assessed by MRI at TEA, and macronutrient and energy intake during the first two weeks after birth. We used a semi-quantitative MRI score, described by Kidokoro et al based on whole grey and white matter growth, maturation and lesion assessment (11).

METHODS

The present study was nested in a prospective cohort that has been previously published (13). It included 51 neonates born at less than 30 weeks of gestational age (GA) between February 2011 and May 2013 in the level III Neonatal Intensive Care Unit of the University Hospital of Lausanne, Switzerland. Exclusion criteria were parental refusal, major congenital malformations, severe cardiorespiratory instability and/or intraventricular hemorrhage (IVH) grade >II diagnosed by cerebral ultrasound before day of life (DOL) 5. Patients with missing nutritional information and those who dropped out of the study before TEA were excluded from the final analysis (see flow chart online). The study protocol was approved by the local Ethical Committee and written parental informed consent was obtained.

MRI examination, analysis, and data

MRI was performed on a 3-Tesla MAGNETOM® Trio system (Siemens Healthcare, Erlangen, Germany), using a neonatal MR-compatible incubator (Nomag®, LMT, Luebeck, Germany) with integrated neonatal head coil. The MR-protocol included the following sequences (in-plane resolution, section thickness, repetition time, echo time, Field-of-View): (1) inversion recovery T1-weighted turbo-spin-echo axial (0.6 mm, 3 mm with 10% gap, 8000 ms, 17 ms, 160mm), (2) T2-weighted turbo-spin-echo axial (0.2 mm, 2.5 mm with 10% gap, 4520 ms, 143 ms, 160 mm), (3) T2-weighted turbo-spin-echo coronal (0.4 mm, 1.2 mm with 10% gap, 5410 ms, 159 ms, 200 mm), (4) T2* weighted gradient echo sequence (0.6 mm, 3 mm, 482 ms, 20 ms, 160 mm), (5) magnetization-prepared dual rapid acquisition of gradient echo (MP2RAGE) (0.7mm, 1.2 mm, 4000 ms, 3.17 ms, 190 mm, inversion time (TI) 1: 900 ms, TI 2: 2200ms).

Brain maturation and injuries were assessed using the Kidokoro score (11). This semi-

quantitative total score consists of 4 underscores (with a total of 13 scoring items, of which 6 are quantitative [brain metrics]): white matter (WM), cortex, deep grey matter (GM), and cerebellum. The last 3 underscores are summarized under GM score (7 items in total), whereas the WM abnormalities are summarized as WM score (6 items). The total score ranges from 0-40. The scores were assessed by 2 neonatologists trained in MRI reading (JS, AT), blinded for patient's information and supervised by a neuroradiologist (PH) in case of disagreement.

During the study, parenteral and enteral nutrients were individualized daily, according to our nutritional protocol, based on the ESPGHAN recommendations (21,22).

Carbohydrates and amino acids (Aminoven® Infant 10%, Fresenius-Kabi AG, Switzerland) were provided from birth at 5 mg/kg/min and 1.5 g/kg/d, respectively. A lipid emulsion of soybean (Lipovenös® 20%, Fresenius-Kabi AG, Switzerland) was added from DOL 3, at 0.5 g/kg/d until December 2011; from January 2012, a mixture of soybean and olive oil (Clinoleic®20%, Baxter AG, Switzerland) was introduced from DOL 2 at 1 g/kg/d. Daily progression was 1-2 mg/kg/min for glucose (max 12 mg/kg/min); 0.5 g/kg/d for amino acids (max 3.5 g/kg/d); and 0.5-1 g/kg/d for lipids, (max 3-3.5 g/kg/d). Parenteral nutrition was weaned when enteral intake reached 120±20 mL/kg/d.

Discontinuous milk feedings were initiated from DOL 1, at 15±5 mL/kg/d, and increased daily by 15±5 mL/kg/d according to the enteral tolerance until 160 mL/kg/d were reached. When available, mother's own milk (fresh or frozen) was preferred; a preterm formula was otherwise provided (BEBA Alprem® or BEBA Aliment pour Prématurés Etape 1®, Nestlé, Switzerland). Fortification (Aptamil FMS® 4%, Milupa SA, Switzerland) was introduced when 100 mL/kg/d of human milk was tolerated.

Nutritional data collection and calculation: Actual parenteral and enteral intake were recorded in the electronic medical charts (Metavision®), allowing an exact record of enteral and parenteral intake. Daily intakes were summed from DOL 1 to 14 into a cumulative intake. Total intake was

obtained adding enteral and parenteral contributions. Caloric intake calculations assumed that protein and carbohydrates provide 4 Kcal per gram and lipids provide 9 Kcal per gram. Nutrient composition of human milk was calculated according to the American Academy of Pediatrics (23), and the composition of formulas was calculated according to the manufacturer's declarations.

Clinical data were prospectively collected. Respiratory distress syndrome was defined as requiring exogenous surfactant; bronchopulmonary dysplasia (BPD) as ventilatory or supplementary oxygen requirement at the age of 36 weeks post-menstrual age; necrotizing enterocolitis as Bell stage ≥ 2 ; sepsis as clinical signs of infection with positive blood culture and/or inflammatory syndrome. IVH was graded according to Papile (24). A birth weight small for GA (SGA) was determined by a weight more than 2 standard deviations below the mean on the Fenton growth chart (25). Weight gain (in g/kg/day) calculation was: $[1000 * (\text{weight at TEA MRI} - \text{BW}) / ((\text{weight at TEA MRI} + \text{BW}) / 2)] / \text{number of days}$ (26,27).

Statistical analyses

Continuous variables were summarized by their median and inter-quartile range (IQR), and categorical variables were summarized by their frequency. Using the Kidokoro score on the TEA MRI, the study patients were divided into 2 groups: Group 1, consisting of the patients with total Kidokoro scores <75 percentile (the reference group), and Group 2, consisting of the patients with total scores ≥ 75 th percentile (more severe abnormalities). Logistic regression analyses assessed associations between the two groups, nutritional intakes, GA, BW, sepsis, sex, SGA status, and co-morbidities. The association between each nutrient and the outcome was adjusted on the co-variable with a $p < 0.05$ in univariable analysis or other potential confounders. Statistical analysis was performed using Stata 14 software (StataCorp. 2015. Stata Statistical Software: TX: StataCorp LP).

RESULTS

Of the 51 preterm infants included in the initial cohort (13), 9 were excluded from the final analysis (1 withdrawal, 2 death before TEA, 2 missing nutritional data, and 4 non interpretable MRIs) (Figure x; [available](#) at www.jpeds.com). The median (IQR) GA of the population was 27.4 (2.0) weeks and BW was 890 (283) g. Clinical, growth and nutritional characteristics of the study population are presented in Table I.

MRI outcomes and groups

The median (IQR) postmenstrual age for the TEA MRI scan was 41.1 (39.6-41.5) weeks. The total Kidokoro scores ranged from 0 to 12 (median: 4, IQR: 2-6), with a median (IQR) WM score of 3 (2-4) and a median (IQR) GM score of 2 (0-3).

Compared with the study of Kidokoro, the infants in this study had lower severity scores with the distribution shifted to the left. The maximum score was 12 (which corresponds to the lower cut off for "severe scoring" in the Kidokoro classification). Thus, this cohort appeared to be at lower cerebral risk, and it was not possible to perform the statistical analysis using the original Kidokoro classification. The quartile distribution of the group was used instead: Group 1 included infants with scores in quartiles 1-3 (<75th percentile) and Group 2 included infants in the 4th (most abnormal) quartile (≥75th percentile). Group 1 (n=27) had total scores between 0 and 5, corresponding to normal or mildly abnormal MRI. Group 2 (n=15) had total scores between 6 and 12, corresponding to more abnormal MRI findings. Because of the less severe distribution in this cohort, the grading differed from Kidokoro (11).

Univariable analysis

Factors that were found to be significantly associated ($p < 0.05$) with the risk of having a more severe MRI (score ≥ 6) in our population were: sepsis, Critical Risk Index for Babies (CRIB) scores, DOL 1-14 cumulative intake of total energy, fat and carbohydrates. Odds ratios (with Group 1 as reference group) and corresponding p-values are presented in Table I.

Adjusted analysis

Bivariable models adjusting for DOL 1-14 cumulative nutritional intake and relevant clinical variables are presented in Table II. Clinical variables retained in the bivariable models were selected either from the univariable analysis ($p < 0.05$; CRIB, sepsis), or as main potential other confounders from the existing literature (GA, postnatal corticoids, BPD). In these models, the association between total energy and fat intake remained significant after adjustments. The construction of multivariable models adjusting for all these nutritional and clinical variables was not possible, due to the limited number of patients in the study groups (28).

Figure 1 illustrates how the adjusted models for sepsis allow us to estimate the probability of having a more severe MRI at TEA (score ≥ 6) according to nutritional intake. For example, an increase of 140 Kcal/kg during the first two weeks of life would reduce the risk of having a more severe TEA MRI by 68%, and an increase of 10 g/kg (0.7 g/kg/d) in lipids would reduce this risk by 64%, respectively.

Finally, considering the two components of the total score separately, we found a significant association of total energy, fat, carbohydrate and protein intake with the GM score (cortical, deep grey matter, cerebellum) component, but no significant association was found with the WM score.

DISCUSSION

This study showed an association between early nutrition and morphological brain development in very preterm neonates. We found a significant strong and consistent negative association between the amounts of energy and fat intake during the first two weeks of life and the severity of brain lesions and dysmaturation at TEA, assessed by a global MRI score. These results were independent of sepsis, clinical risk index, gestational age, bronchopulmonary dysplasia and postnatal steroids in bivariable models. Adjusted models estimated that a 10 Kcal/kg/d increase in energy or a 0.7 g/kg/d increase in lipids intake would reduce the risk of having more severely abnormal MRI at TEA by >60%.

These results support the importance of early nutrition for brain development in an early window of time, the first two postnatal weeks. Our study suggests that insufficient nutritional support may be harmful for brain maturation. Despite the existing guidelines, actual nutritional intakes are often lower than recommended for preterm neonates, as noted in our population (30–33). This corresponds to a daily reality in clinical care, where several factors, including enteral or metabolic intolerances, fluid restriction, venous access, or protocol observance may influence nutritional intake. Our study highlights that such daily routine variations might impact on brain maturation.

The association between early nutrients and TEA MRI scores was stronger for the GM component of the score (cortex, deep GM, and cerebellum) than the WM score component. This preferential GM association was also reported in preterm neonates suffering from intra-uterine growth restriction (34). Compared with MRI studies on early postnatal nutrition, similar positive effects were observed on cortical (35) and subcortical GM (19), although MR methods and the age at assessment differed between studies. One reason for this finding could be the high metabolic demand of the GM at this developmental stage, and therefore a higher sensitivity to variations in

nutrient intakes. GM involvement in addition to that of WM in premature brain injury is a relatively new concept that was well described by Volpe in the encephalopathy of prematurity (14,15). Regarding the WM involvement, we were not able to show an association, contrary to Strommen et al who found a correlation between nutrient supply and maturation of the WM using diffusion MRI (18). This could be due to a lack of power in our small and low-risk population. Furthermore, the WM assessment on conventional images may not be as precise and sensitive as diffusion-weighted imaging, especially in a low-risk population. Vinall et al, using diffusion tensor imaging, demonstrated a correlation between postnatal growth and cortical structural development (36). Interestingly, we did not observe a similar correlation between growth and MRI outcome in our study. This difference could be due to the distinctive MR methods used, or to later nutritional support, that was not assessed. Alternatively, it could also suggest direct benefits of early nutrition on brain development that are not necessarily growth-mediated. It is worth noting that our growth velocities were slower than the recommended goals to mimic fetal growth at the same age (15-20 g/kg/d). Recently, Horbar et al found similar weight gain rates in a large multicenter study showing continued lower growth rates in preterm infants despite some improvement over the past decades (30). Likewise, weight growth rate velocity from Martin et al (37), from birth to DOL 28 was 10-11 g/kg/d. This underscores the difficulties in clinical reality in preventing postnatal growth failure, and it also reinforces the importance in further improving early nutritional support.

In this setting, the choice of a simple semi-quantitative MRI score to quantify the global cerebral maturation and injury provided several advantages. The quantitative measures in different regions and structures (brain metrics) might be more discriminative in a relatively low-risk population. This is important as major brain injuries, or “lesion patterns”, observed in the last decades, are shifting to subtler injuries and dysmaturational patterns (14,15). This latter “developmental pattern” is more difficult to identify, even on MRI, due to the lack of sensitive tools. Compared with new techniques, such as segmentation or diffusion tensor imaging, the semi-quantitative score allows a global appreciation of the GM and WM maturation, constitutes an

easy technique that is rapidly performed, feasible on conventional sequences, and potentially more accessible for the clinician. Moreover, the Kidokoro score adapted from Woodward et al (38), has been, at least partially, correlated with clinical and neurological later outcome (16).

Regarding the previously reported associations of macronutrients with neurodevelopment, our results are coherent with those of di Trolle et al who showed a positive correlation between early lipid intake and neurological outcome (7). The role of lipids for the developing brain may be direct, by providing essential fatty acids and docosahexaenoic acid that are necessary for the developing cell membranes of the brain and the retina, or indirect, mediated by caloric intake. Previous studies (35,39) showed that lower intakes of calories and lipids were significantly associated with an increased risk of retinopathy of the prematurity. However, our study was not adequately powered to assess this issue, as only 2 patients (one in each group) developed retinopathy of prematurity. The importance of energy supply was also stressed by Stephens et al, who reported that an increase of 10 Kcal/kg per day during the first week was associated with a 4.6-point increase in the Bayley Mental Development Index (4). On the other hand, our study failed to demonstrate a statistically significant association between protein intake and the MRI score, although a trend was observed. This could be due to relatively small variations observed for amino acid intakes in our population, or to insufficient power in our cohort size. Two other recent studies also did not find either such an association between protein and neurodevelopment (7,40).

There are several limitations of this study. First, it is an observational study carrying a risk of bias; a confounding bias, in particular, cannot be ruled out. The lower nutritional intakes in the two first weeks of life could be the reflection of more sick babies (41), and causality cannot be established. This rather homogeneous population did not show other significant clinical differences between the groups, except for sepsis and CRIB scores, which were controlled in bivariable models. Adjusting for other additional possible confounders, as gestational age or BPD, did not modify the association between lipid or energy intake and MRI outcome. However, the limited

sample size did not allow the construction of a multivariable model adjusting for all nutritional and clinical variables together (28). The relatively low number of patients constitutes another limitation, despite the fact that it exceeds those of several previous MR studies (18,20). As already noted, our cohort was at low-risk, limiting its general applicability. Finally, despite reported associations between TEA MRI and neurodevelopment (16,36,42), correlation to long-term outcome in our population will be needed. Neurodevelopmental follow-up of this cohort through 5 years is ongoing.

In conclusion, the results of this study showed a consistent and clinically relevant association between early nutritional intakes and morphological brain development evaluated by TEA MRI in very premature infants. Increased calorie or lipid intakes during the first 2 weeks of life were associated with an increased likelihood of normal MRI scores at term. This association increased after adjustment for sepsis. Consequently, reduced lipid and energy intakes may increase the risk of poorer brain maturation. Optimizing nutritional intakes may be an effective and feasible way to improve preterm brain development and to potentially alleviate the effect of early stressors such as inflammation and infection. The impact on long-term neurodevelopmental outcome must be confirmed, especially in more vulnerable populations. Finally, larger interventional trials are needed to further investigate and develop effective neuroprotective nutritional strategies.

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Figure legends:

Figure 1.

Probability of having a more severe MRI at TEA (score ≥ 6) according to the cumulative total intakes of energy (a), fat (b), carbohydrates (c) and proteins (d) during the 2 first weeks of life (DOL1-14), after adjustments on sepsis.

Footnote: DOL: Day of Life

Figure 2.

Predicted MRI grey matter scores according to the cumulative total intakes of energy (a), fat (b), carbohydrates (c) and proteins (d) during the 2 first weeks of life (DOL1-14), after adjustments on sepsis.

Footnote: DOL: Day of Life

Figure x. Online figure : flow chart

Table 1. Clinical and nutritional characteristics of the study population and group comparisons

	Total n=42	Group 1 n = 27	Group 2 n= 15	OR (95%CI)	P- value
<u>Baseline clinical data</u>					
Gestational age (weeks)	27.4 (26.4-28.4)	27.4 (26.6-28.4)	27.0 (25.5-28.4)	0.95 (0.88-1.02)	0.17
Birth weight (g)	890 (763-1045)	900 (775-1093)	844 (738-1030)	1.00 (1.00-1.00)	0.47
SGA	0	0	0	-	-
Female sex	23 (54.8)	14 (51.9)	9(60.0)	1.39 (0.39-5.01)	0.61
Chorioamnionitis	16 (38.1)	10 (37.0)	6 (40.0)	1.03 (0.26-4.07)	0.97
Antenatal steroids	37 (88.1)	25 (92.6)	12 (80.0)	0.32 (0.05-2.18)	0.24
<u>Postnatal clinical data</u>					
CRIB score	4 (1-6.8)	2 (1-5)	6 (4-9)	1.42 (1.10-1.82)	0.006*
Postnatal steroids	6 (14.3)	2 (7.4)	4 (26.7)	4.55 (0.72-28.61)	0.11
BPD (moderate to severe)	12 (29.3)	5 (19.2)	7 (46.7)	3.68 (0.90-15.01)	0.07
Treated PDA	17 (40.5)	10 (37.0)	7 (46.7)	1.6 (0.43-5.94)	0.48
Sepsis	19 (45.2)	9 (33.3)	10 (66.7)	4.0 (1.05-15.26)	0.04*
NEC	0	0	0	-	-
IVH ≥2	2 (4.8)	1 (3.7)	1 (6.7)	1.86 (0.11-32.00)	0.67
ROP ≥2	2 (4.8)	1 (3.7)	1 (6.7)	1.86 (0.11-32.00)	0.67
<u>Growth (birth to TEA MRI)</u>					
Weight gain (g/kg/d)	11.8 (11.2-12.4)	11.95 (11.3-12.8)	11.7 (11.0-12.4)	0.74 (0.40-1.37)	0.35
	0.99 (0.87-1.1)	0.97 (0.86-1.09)	1.0 (0.91-1.09)	2.25 (0.16-305.62)	0.75
HC growth (cm/week)	0.78 (0.74-0.83)	0.79 (0.74-0.81)	0.78 (0.76-0.85)	3.54 (0.0-7577.1)	0.75
<u>Cumulative nutritional intake (DOL 1-14)</u>					
Energy (Kcal/kg)					
-Parenteral	587 (476-776)	555 (418-764)	643 (552-762)	1.00 (1.0-1.0)	0.48
-Total	1227 (1109-1305)	1286 (1195-1334)	1077 (1035-1227)	0.99 (0.99-0.99)	0.01*
Fat (g/kg)					
- Parenteral	16.5 (12.9-23.7)	15.1 (13.0-24.8)	17.6 (13.3-23.4)	1.01 (0.94-1.08)	0.85
- Total	53.6 (43.9-59.7)	56.1 (52.5-61.5)	42.3 (36.6-50.1)	0.89 (0.83-0.97)	0.01*
Carbohydrates (g/kg)					
- Parenteral	86.8 (62.0-114.8)	85.0 (60.5-104.2)	102.3 (70.6-118.0)	1.01 (0.99-1.03)	0.40
- Total	149.2 (141.7-158.8)	150.1 (146.9-164.0)	145.7 (128.6-154.2)	0.95 (0.91-0.99)	0.04*
Proteins (g/kg)					
-Parenteral	25.5 (20.7-33.6)	23.5 (17.8-32.3)	30.1 (24.4-34.6)	1.04 (0.97-1.12)	0.27
-Total	44.5 (40.2-48.9)	44.9 (42.1-49.7)	44.3 (38.4-45.0)	0.93 (0.84-1.04)	0.19

*p<0.05. ;Quantitative variables are indicated in median (Q1,Q3) and qualitative variables in n (%);

OR: Odds ratio; 95% CI: 95% confidence interval; BPD: Broncho-Pulmonary Dysplasia /CRIB: **Critical Risk Index for Babies**/ DOL:

Day of Life / HC: Head Circumference / IVH: Intraventricular Hemorrhage / MRI: Magnetic Resonance Imaging / NEC:

Necrotizing Enterocolitis / PDA: Patent Ductus Arteriosus / ROP: Retinopathy of Prematurity / SGA: Small for Gestational Age /

TEA: Term Equivalent Age

Table 2. Unadjusted and adjusted Odds ratio (OR and aOR) and 95% confidence intervals (95%CI) for more abnormal MRI at TEA (score ≥ 6) according to cumulative total nutritional intake (day 1-14) and: 1. sepsis, 2. gestational age, 3. BPD, 4. CRIB score, 5. post-natal steroids (*bivariable models*)

	<u>Unadjusted</u>		<u>Model 1: Sepsis and nutritional intake</u>		<u>Model 2: GA and nutritional intake</u>		<u>Model 3: BPD and nutritional intake</u>		<u>Model 4: CRIB score and nutritional intake</u>		<u>Model 5: PN corticoids and nutritional intake</u>	
	OR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Cumulative total energy intake												
by + 140kcal/kg (+10Kcal/kg/d)	0.29 (0.12-0.70)	0.01*	0.32 (0.13-0.76)	0.01*	0.31 (0.13-0.74)	0.008*	0.32 (0.13-0.78)	0.01*	0.37 (0.15-0.94)	0.036*	0.31 (0.12-0.79)	0.015*
sepsis/GA/BPD/CRIB/ PNcorticoids	<i>Cf. Table 1</i>		3.36 (0.74-15.18)	0.11	0.97 (0.89-1.06)	0.50	1.81 (0.36-9.23)	0.47	1.29 (0.99-1.69)	0.06	1.36 (0.16-11.2)	0.78
Cumulative total fat intake												
by + 10g/kg (+0.7g/kg/d)	0.33 (0.15-0.71)	0.01*	0.36 (0.16-0.80)	0.01*	0.35 (0.16-0.76)	0.008*	0.37 (0.17-0.82)	0.015	0.41 (0.19-0.92)	0.03*	0.36 (0.16-0.80)	0.012*
sepsis/GA/BPD/CRIB/ PN corticoids	<i>Cf. Table 1</i>		2.86 (0.65-12.66)	0.17	0.97 (0.89-1.06)	0.48	2.00 (0.40-9.92)	0.40	1.32 (1.00-1.74)	0.05	1.81 (0.24-13.5)	0.56
Cumulative total carbohydrate intake												
by + 10 g/kg (+0.7g/kg/d)	0.61 (0.38-0.97)	0.04*	0.62 (0.38-1.00)	0.05	0.62 (0.38-1.01)	0.05	0.60 (0.35-1.01)	0.05	0.64 (0.37-1.11)	0.11	0.65 (0.40-1.05)	0.08
sepsis/GA/BPD/CRIB/ PN corticoids	<i>Cf. Table 1</i>		3.9 (0.94-16.18)	0.06	0.96 (0.89-1.04)	0.33	2.91 (0.64-13.1)	0.17	1.36 (1.06-1.75)	0.02	2.68 (0.38-18.8)	0.32
Cumulative total protein intake												
by + 10 g/kg (+0.7g/kg/d)	0.49 (0.17-1.42)	0.19	0.41 (0.13-1.30)	0.13	0.54 (0.19-1.56)	0.26	0.66 (0.21-2.09)	0.48	0.83 (0.25-2.72)	0.76	0.62 (0.20-1.92)	0.41
sepsis/GA/BPD/CRIB/ PN corticoids	<i>Cf. Table 1</i>		4.74 (1.15-19.64)	0.03*	0.95 (0.89-1.03)	0.23	2.92 (0.63-13.5)	0.17	1.40 (1.08-1.82)	0.01*	3.48 (0.50-24.2)	0.21

*p<0.05; GA: gestational age; BPD: bronchopulmonary dysplasia; CRIB: Critical Risk Index for Babies; PN: postnatal;

Figure x.