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Early caloric deprivation in preterm infants affects Bayley-III scales performance at 18–24 months of corrected age

Maria Lithoxopoulou[a], Dimitrios Rallis[a,*], Helen Christou[b], Evanthia Goutsiou[a], Agoritsa Varaklioti[c], Paraskevi Karagianni[a], Christos Tsakalidis[a], Philip Domeyer[c], Georgia Kuriakeli[a], Vasiliki Soubasi[a]

[a] 2nd Department of Neonatology, Papageorgiou Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece
[b] Brigham and Women's Hospital and Boston Children's Hospital, Harvard Medical School, Boston, MA, United States
[c] Faculty of Social Sciences, Department of Health Management, Hellenic Open University, Patras, Greece

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ABSTRACT

Background: Adequate nutrition is essential for optimal neurodevelopment to preterm infants. Our aim was to evaluate the impact of caloric deprivation on Bayley-III scales performance at 18–24 months of corrected age, in a cohort of preterm infants.

Methods: We prospectively enrolled infants with gestational age < 30 weeks and birth weight < 1500 g. Apart from a whole cohort analysis, we performed a subgroup analysis between infants received inadequate calories (< 85 Kcal/kg/day) during the first two weeks of age, compared to a standard nutrition group. All infants underwent a Bayley-III assessment at 18–24 months of corrected age.

Results: From the 63 preterm infants analysed, 25% had caloric deprivation compared to 75% with adequate nutrition. Caloric deprived infants were of lower gestational age and birth weight, and received a lower amount of enteral feeding during the first 14 days of age. There were no differences between the two groups regarding the common neonatal co-morbidities. Caloric deprived infants had significantly lower composite index scores at 18–24 months of corrected age. Caloric deprivation, late onset sepsis, necrotizing enterocolitis, and bronchopulmonary dysplasia were significant risk factors of neurodevelopmental impairment.

Conclusions: Several neonatal factors affect the neurodevelopmental outcome of preterm infants, and nutrition may pose an important role.

What this paper adds?

Providing adequate energy is essential for the neurodevelopment of extremely preterm infants, although it's not always feasible in the clinical settings. The current study suggests that the caloric deprivation during the first two weeks of age in combination to the development of specific neonatal co-morbidities have a significant role in the neurodevelopment of preterm infants.

Abbreviations: IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; CA, corrected age; GA, gestational age; BSID-III, Bayley-III Scales for Infant and Toddler Development

* Corresponding author at: 2nd Department of Neonatology, Papageorgiou Hospital, Ring Road, Pavlos Melas, 56429, Thessaloniki, Greece.
E-mail address: drallis@uoi.gr (D. Rallis).

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1. Introduction

The nutritional management of preterm infants includes specific challenges, primary due to difficulties in meeting their enhanced requirements during this period of rapid growth (Agostoni et al., 2010). Furthermore, the rapid growth of the developing brain during the early post-natal life makes it particularly vulnerable to nutritional deficits. Current evidence has shown that inadequate nutrition in addition to certain clinical co-morbidities such as prolonged mechanical ventilation, intraventricular haemorrhage (IVH), sepsis, necrotizing enterocolitis (NEC) or bronchopulmonary dysplasia (BPD) may have a potential impact on the neurodevelopmental outcomes (Alshaikh et al., 2014; Tsai et al., 2014; Wadhawan et al., 2014). Moreover, the administration of ideal nutrition which is essential for an optimal development is particularly important in very low birth weight infants, who appear to be at increased risk for cognitive delays and disturbances, even in the absence of specific cerebral pathology (Neubauer, Voss, & Kattner, 2008).

The affected developmental domains of preterm infants include mainly impaired language skills, memory, and executive functions as well as motor and behavior deficits, that often persist and even become more apparent during childhood (Nosarti, Murray, & Hack, 2010). There is evidence that prematurity *per se* is a significant risk factor, and in fact, very preterm infants less than 30 weeks' gestation are at increased risk for cognitive dysfunction and diminished levels of attention and memory (Marlow, Wolke, Bracewell, Samara, & Group, 2005; Pickler et al., 2010; Tich et al., 2011). Furthermore, an increased risk of a less favorable pre-verbal development and a delayed language development at 12 months of age has been recorded in preterm compared to term infants (De Schuymer, De Groote, Beyers, Striano, & Roeyers, 2011; Rechia, Oliveira, Crestani, Biaggio, & Souza, 2016). Prematurity, irrespective of other factors, has been also related to poor motor performance, in particular to visual-motor integration (Goyen, Lui, & Hummell, 2011; Rademaker et al., 2007) and to fine/gross motor development (Goyen & Lui, 2009). Early intervention is significant for reducing the risk of such disturbances and among others, one potential approach may be through adequate nutrition (Schneider & Garcia-Rodenas, 2017). In the setting of clinical practice, however, is not always feasible to provide the desirable nutrition to the preterm infants and nevertheless, the evidence regarding the potential correlation of nutrition administration and the neurological development remain scarce.

The aim of the current study was to evaluate the impact of the inadequate, as opposed to the standard, nutritional intake during the first two weeks of age in a cohort of preterm infants, on the neurodevelopmental outcome at 18–24 months of corrected age (CA). Furthermore, we sought to address other possible neonatal risk factors for neurodevelopmental impairment.

2. Materials and methods

2.1. Study design

A prospective non-interventional study was conducted from January 2014 to December 2015 in the 2nd Neonatal Unit of Aristotle University of Thessaloniki, Greece. This is a tertiary, 22-bed neonatal unit with an average number of 550 admissions per year. The ethical committee of the institution and the Aristotle University of Thessaloniki approved the study, and a written consent was obtained from the parents of each infant prior to the enrollment.

All infants with gestational age (GA) < 30 weeks and birth weight $\leq$1500 g, who were admitted in our NICU during the study period were enrolled. According to our institutional guidelines, nutrition was initiated at a range of 30–60 Kcal/kg/day provided parenterally and/or enterally. Nutrition was increased in daily increments as allowed by the infants' clinical status, aiming to the establishment of an adequate caloric intake of 130–150 Kcal/kg/day by two weeks of age. Caloric deprivation was defined by the administration of $\leq$85 Kcal/kg/day (Stephens & Vohr, 2014). We performed a descriptive evaluation of the whole study population, and furthermore, we performed a subgroup analysis based on the administration of the calories during the first 14 days of life; infants who due the severity of their clinical condition could not tolerate a proper advance of their nutritional intake and received $\leq$85 Kcal/kg/day during the above period constituted the caloric deprivation group, while those infants that received > 85 Kcal/kg/day constituted the standard group. Every participant underwent a neurodevelopmental evaluation at 18–24 months of CA with the Bayley-III Scales for Infant and Toddler Development (BSID-III). Infants with congenital malformations of the central nervous system, those who did not survive at 18–24 months of CA, or those that did not attend the follow-up appointment were excluded from the study.

The nutritional data, including caloric intake, protein and lipid administration, enteral feeding ratio and body weight were recorded on a daily basis during the study period. We also recorded the perinatal characteristics, such as GA, preeclampsia, chorioamnionitis, intrapartum steroids administration, intrauterine growth restriction and neonatal characteristics, including mechanical ventilation and oxygen administration duration, the need for blood transfusion, and the development of BPD based on the National Institute for Child Health and Development criteria (Ehrenkranz et al., 2005), patent ductus arteriosus, late onset sepsis (sepsis after 72 h of age), NEC grade II-III according to the modified Bell criteria (Walsh & Kliegman, 1986), IVH III-IV according to the Papile classification (Papile, Burstein, Burstein, & Koffler, 1978), retinopathy of prematurity according to the International Committee criteria (International Committee for the Classification of Retinopathy of, P., 2005) and the overall hospitalization duration.

2.2. Bayley-III Scale of Infant and Toddler Development

The evaluation of the neurological development of the study population was performed at 18–24 months of CA with BSID-III. This assessment can be used as early as 15 days of age up to 42 months of CA, providing information about distinct domains including

cognitive, language (expressive and receptive), motor (fine and gross), social/emotional and adaptive behavior. Each scale is estimated with composite and subscale score, in addition to normal centiles. The normal reference index that has been established for the composited score is 100 ± 15, while values below 85 indicate neurodevelopment impairment (Vohr et al., 2012). In the present study, all infants had a comprehensive neurodevelopmental assessment at 18–24 months of CA by a licensed Pediatric neuropsychologist, including the evaluation of the cognitive, language and motor domain. Since no standardized normative values to Greek population were available, translated versions of the necessary manuals, questionnaires and administration sheets were utilized.

2.3. Statistical analysis

Descriptive statistics were calculated for perinatal and neonatal characteristics, nutritional data and developmental outcome. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate. The normality of the distributions of continuous variables was assessed by the *Kolmogorov-Smirnoff test*. Comparisons of continuous variables were performed utilizing *student's unpaired t*-test or the non-parametric *Mann-Whitney test*. Categorical variables were expressed as n (%) and compared with *Pearson's chi-square (x^2) test* or *Fisher's exact test*.

The primary outcome of the study was the association of the caloric deprivation during the first 14 days of life with the neurodevelopmental outcome at 18–24 months of CA, based on the BSID-III index scores in the cognitive, language and motor domain. The secondary outcome was the evaluation of any association of significant risk factors with the cognitive, language and motor composite scores and the with neurodevelopmental delay, utilizing linear and logistic regression analysis, respectively. Only risk factors that were significantly related with the above outcomes in the univariate analysis was utilized in the multivariate regression model.

All performed tests were two-sided and a p-value less than 0.05 was considered statistically significant (alpha 0.05). The power analysis revealed that the study was powered to detect differences ≥40% in the neurodevelopmental outcome (dichotomous score) between the two groups with a power 0.8 and type-I error 0.05. The data were analyzed using SPSS Statistics Version 20.0 (IBM, Chicago, Illinois, USA).

3. Results

During the study period, 88 infants were enrolled; of those, 25 infants were excluded (2 due to congenital malformation, 11 died and 12 did not attend the follow-up appointment), leaving 63 infants for final analysis.

The mean GA of the study population was 27 + 2 ± 1.3 weeks and the mean birth weight 975 ± 228 g. Half of the infants (49%) were male, while intrauterine growth restriction had been diagnosed in 9 (14%) of them. The mean caloric intake in two weeks of life was 102 ± 19 Kcal/kg/day, provided by protein of 3.3 ± 0.5 g/kg/day and lipids of 4.1 ± 1.5 g/kg/day. The proportion of the enteral feeding on day 14 was 67% of the total feeding regime, while the median day of reaching full enteral feeding was day 17 (13–23) (Table 1). The incidence of common neonatal morbidities is presented in Table 2; severe IVH (grade III-IV) was identified in 1.6%, late onset sepsis in 60%, NEC stage II-III in 14% and BPD in 75% of the total cohort. Finally, regarding the neurodevelopmental

Table 1
Perinatal and nutritional characteristics of the study population and subgroup analysis between caloric deprived and standard calories intake groups.

	Total cohort (n = 63)	Caloric deprivation (n = 16)	Standard calories (n = 47)	p
Gestational age, weeks	27 + 2 ± 1.3	26 + 5 ± 1.4	27 + 2 ± 1.2	0.076
Birth weight, g	975 ± 228	891 ± 172	1003 ± 239	0.088
Birth weight < 1000 g	39 (62)	14 (88)	25 (53)	0.018
Head circumference at birth, cm	25.5 ± 2	24.8 ± 1.9	25.7 ± 2.1	0.158
Length at birth, cm	36.1 ± 3.1	35.2 ± 2.9	36.4 ± 3.2	0.220
Monolingual family	62 (98)	16 (100)	46 (98)	1.000
Preeclampsia	9 (14)	2 (13)	7 (15)	1.000
Chorioamnionitis	11 (18)	3 (19)	8 (17)	1.000
Intrauterine growth restriction	9 (14)	3 (19)	6 (13)	0.683
Antenatal steroids	57 (91)	15 (94)	42 (89)	1.000
Gender, male	31 (49)	8 (50)	23 (49)	1.000
Calories day 14, kcal/kg/day	102 ± 19	78 ± 8	109 ± 14	< 0.001
Protein day 14, g/kg/day	3.3 ± 0.5	3.2 ± 0.5	3.4 ± 0.5	0.232
Lipids day 14, g/kg/day	4.1 ± 1.5	2.7 ± 1.2	4.6 ± 1.3	< 0.001
Enteral feeding day 14 (%)	67 (22-100)	33 (9-72)	69 (29-100)	0.033
Full enteral feeding, day	17 (13-23)	19 (16-24)	16 (12-23)	0.091
Discharge weight, g	2390 ± 535	2369 ± 502	2397 ± 550	0.859
Discharge head circumference, cm	32 ± 1.8	32 ± 2.2	32 + 1 ± 1.6	0.805
Discharge length, cm	46.1 ± 2.8	45.5 ± 2.5	46.3 ± 2.9	0.352

Continuous variables expressed as mean ± standard deviation or median (interquartile range). *P* of student's *t*-test or Mann – Witney test. Categorical variables expressed as n (%). *P* of Pearson's chi square test or Fisher's exact test.

Table 2
Common neonatal morbidities of the study population and subgroup analysis between caloric deprived and standard calories intake groups.

	Total cohort (n = 63)	Caloric deprivation (n = 16)	Standard calories (n = 47)	p
Patent Ductus Arteriosus	21 (33)	5 (31)	16 (34)	1.000
Blood transfusion	27 (43)	6 (38)	21 (46)	0.771
Intraventricular haemorrhage III-IV	1 (1.6)	1 (6)	–	0.254
Late onset sepsis	38 (60)	11 (69)	27 (57)	0.558
Bronchopulmonary dysplasia	47 (75)	12 (75)	35 (75)	1.000
Necrotizing enterocolitis II-III	9 (14)	3 (19)	6 (13)	0.681
Retinopathy of prematurity	8 (13)	3 (19)	5 (11)	0.407
Mechanical ventilation, days	4 (1-11)	4 (1-8)	5 (1–14)	0.937
Oxygen administration, days	34 (22–56)	33 (26–53)	34 (22–57)	0.782
Overall hospitalization, days	69 (53–85)	67 (57–88)	71 (52–85)	0.676

Continuous variables expressed as mean ± standard deviation or median (interquartile range). *P* of student's *t*-test or Mann – Witney test. Categorical variables expressed as n (%). *P* of Pearson's chi square test or Fisher's exact test.

outcome of the study population, the mean cognitive index score was 96 ± 12, the mean language score was 99 ± 13 and the mean motor score was 98 ± 14. Of note, all but one infants were raised in a monolingual family. Almost one fifth of the cohort was assessed with suboptimal (< 85) score in cognitive, language or motor domain indicating a moderate neurodevelopmental delay (Table 3).

With regards to the subgroup analysis, 16 (25%) infants received suboptimal calories (≤85 Kcal/kg/day) during the first 14 days of age, compared to 43 (75%) of infants that had an adequate caloric intake (> 85 Kcal/kg/day) during the same period. The mean GA and birth weight of the caloric deprived group was lower compared to the standard calories group, *albeit* statistically insignificant (26 + 5 ± 1.4 weeks compared to 27 + 2 ± 1.2 weeks, and 891 ± 172 g compared to 1003 ± 239 g, respectively). However, 88% of the caloric deprived infants were born with birth weight < 1000 g compared to 53% of the standard calories group (p = 0.018). There were no other differences in perinatal characteristics between the two groups (Table 1). As expected, caloric intake at two weeks of age was significant lower in the caloric deprived group compared to the standard calories group (78 ± 8 Kcal/kg/day compared to 109 ± 14 Kcal/kg/day, p < 0.001), partially due to significant lower lipids administration (2.7 ± 1.2 g/kg/day compared to 4.6 ± 1.3 g/kg/day, p < 0.001), as those infants could not tolerate advance in their nutritional intake, especially lipids. The enteral feeding represented 33% of the total intake on day 14 in the caloric deprived group, in contrast to 69% of the standard caloric group (p = 0.033). There were no differences between the two groups regarding the common neonatal morbidities as shown in Table 2.

Infants of the caloric deprivation group had significant lower BSID-III index scores in language and motor domain (89 ± 9 and 92 ± 10) compared to the infants of the standard caloric intake group (103 ± 12 and 100 ± 14, respectively). In addition, a significantly higher proportion of infants of the caloric deprivation group had a suboptimal cognitive and language composite score and thus an indication of neurodevelopmental impairment at their assessment at 18–24 months CA (Table 3).

Finally, birth weight less than 1000 g, caloric deprivation, NEC II-III, late onset sepsis and BPD were related with suboptimal composite index scores in the univariate analysis (data not shown). Of those, in the multivariate analysis, caloric deprivation and late onset sepsis were significantly associated with suboptimal composite index scores in the cognitive domain, while caloric deprivation, NEC II-III and BPD with suboptimal index scores in the language domain (Table 4). Furthermore, the same risk factors were correlated with lower cognitive and language composite score; in particular, caloric deprivation and late onset sepsis were correlated with lower cognitive composite score, while caloric deprivation, NEC II-III and BPD with lower language composite score (Table 5).

4. Discussion

The current study suggests that in a cohort of infants with birth weight ≤1500 g, the caloric deprivation within the first two

Table 3
Neurodevelopmental outcome of the study population and subgroup analysis between caloric deprived and standard calories intake groups.

	Total cohort (n = 63)	Caloric deprivation (n = 16)	Standard calories (n = 47)	p
Index scores continuous				
Cognitive composite score	96 ± 12	92 ± 13	98 ± 11	0.065
Language composite score	99 ± 13	89 ± 9	103 ± 12	< 0.001
Motor composite score	98 ± 14	92 ± 10	100 ± 14	0.028
Index scores dichotomous				
Cognitive suboptimal (< 85) score	11 (18)	7 (44)	4 (9)	0.004
Language suboptimal (< 85) score	11 (18)	8 (50)	3 (6)	< 0.001
Motor suboptimal (< 85) score	12 (19)	6 (38)	6 (13)	0.059

Continuous variables expressed as mean ± standard deviation. *P* of student's *t*-test. Categorical variables expressed as n (%). *P* of Pearson's chi square test or Fisher's exact test.

Table 4
Logistic regression analysis of the risk factor for suboptimal (< 85) composite index scores in the cohort.

	Cognitive domain		Language domain		Motor domain	
	p	95% CI	p	95% CI	p	95% CI
Birth weight < 1000 g	0.638	0.107–3.930	0.921	0.102–12.476	0.970	0.196–4.804
Caloric deprivation	0.014	1.570–6.989	0.003	3.462–8.122	0.139	0.687–4.824
Necrotizing enterocolitis II-III	0.429	0.336–13.008	0.039	1.233–8.566	0.793	0.242–6.388
Late onset sepsis	0.043	0.108–3.230	0.344	0.309–8.873	0.757	0.175–3.550
Bronchopulmonary dysplasia	0.097	0.699–5.681	0.031	1.472–9.898	0.160	0.559–4.216

Table 5
Linear regression analysis of the risk factor for composite index scores in the cohort.

	Cognitive domain			Language domain			Motor domain		
	b	p	95% CI	b	p	95% CI	b	p	95% CI
Birth weight < 1000 g	3.554	0.254	0.371-10.299	0.345	0.913	0.165-2.333	1.345	0.752	0.506-8.226
Caloric deprivation	13.427	0.005	7.633-17.818	13.219	0.001	7.326-18.785	8.674	0.061	0.983-14.967
Necrotizing enterocolitis II-III	4.509	0.132	0.152-10.688	5.796	0.036	2.276-13.734	9.202	0.141	0.872-19.273
Late onset sepsis	3.448	0.008	1.246-9.955	2.823	0.356	0.893-3.256	4.191	0.280	0.379-11.346
Bronchopulmonary dysplasia	8.928	0.246	0.254-15.508	7.795	0.031	3.236-14.243	10.136	0.129	0.538-18.859

weeks of age was significantly associated with lower BSID-III index scores at 18–24 months of CA and in fact, the inadequate nutrition in addition to other neonatal morbidities such as NEC, late onset sepsis, and BPD were significant risk factors for neurodevelopmental impairment.

A most critical developmental period for brain growth and function begins during the last trimester of pregnancy and continues during the first two years of postnatal life (Dusick, Poindexter, Ehrenkranz, & Lemons, 2003; Ehrenkranz et al., 2006), including the enhanced neurogenesis, neuron differentiation, myelinosis and synapsis formation that lead to the rapid increase of the cortical grey matter and white matter volume (Carlson et al., 2009). Therefore, the optimal nutrition administration during this vulnerable period is critical for preterm infants and may represent a significant key component for the neurodevelopmental outcome. Previous observational studies have suggested that the improvement of the early nutrition that reduces energy and nutrient deficits could improve brain growth, brain maturation and the neurodevelopment in preterm infants (Christmann et al., 2017; dit Trolli, Kermorvant-Duchemin, Huon, Bremond-Gignac, & Lapillonne, 2012; Stephens & Vohr, 2009). The findings of those studies indicated that greater intakes of protein (Christmann et al., 2017; Stephens & Vohr, 2009) or lipids (dit Trolli et al., 2012) from enteral and parenteral resources were related with a better neurodevelopmental outcome, even after adjusting for any confounding factors. Furthermore, a follow-up study (Strommen et al., 2015) of a randomized control trial on the effect of an early enriched nutrition on the very low birth infant growth (Moltu et al., 2013), showed an enhanced white matter maturation at term-equivalent age.

On the contrary, the nutrition deprivation and malnutrition of preterm infants could lead to a profound growth impairment affecting organogenesis and contributing to long-term consequences on many physiological functions, including neurobehavior (Cooke, 2016). In the study by Georgieff et al. the caloric deprivation of preterm very low birth infants had been directly related to poor head growth and furthermore, the prolonged administration of inadequate nutrition had been associated with neurodevelopmental impairment at 12 months of CA (Georgieff, Hoffman, Pereira, Bernbaum, & Hoffman-Williamson, 1985). In accordance with the previous researchers, our findings suggested that caloric deprived preterm infants had significantly lower BSID-III index scores at two years of CA. With regards to the nutrient components, we found a significant difference in the average daily lipid administration, in favor of the infants with an adequate caloric intake. Infants of the caloric deprivation group were in a higher proportion of a birth weight < 1000 g and, *albeit* statistically insignificant, of a lower GA. Those infants, due to the severity of their clinical condition, could not tolerate a proper advance of their nutrition intake and mainly lipids, during the first two weeks of age. Since both protein and fatty acids are essential for brain growth and development, it is highly plausible that neurodevelopment will be influenced by nutritional status (Bloomfield et al., 2015; Collins et al., 2015). Long-Chain Polyunsaturated Fatty Acids are important structural components of cell membranes in the human brain and retina (Schneider & Garcia-Rodenas, 2017), and multiple studies have evaluated the association of fatty acids administration during infancy and the neurodevelopment (Almaas et al., 2015; Clandinin et al., 2005; Fewtrell et al., 2002; Isaacs et al., 2011; Sabel, Strandvik, Petzold, & Lundqvist-Persson, 2012; van Wezel-Meijler et al., 2002). Despite the heterogeneity of the studies in view of the design and outcomes, the body of evidence suggests a linking of early nutrition and cognitive benefits for preterm infants.

Although the impact of nutritional deprivation on neurodevelopmental outcome has been documented, the data regarding the role of early enteral, as opposed to parenteral, nutrition in premature infants have been less consistent (Chan, Johnson, Leaf, & Vollmer, 2016; Lucas et al., 1990). In our study, infants with caloric deprivation were receiving a significantly lower proportion of enteral feeding at two weeks of age. A recent meta-analysis by Chan et al suggested that increased parenteral nutrition during the early period after birth may result in suboptimal neurodevelopmental outcomes at 24 months of CA, while increased enteral nutrition

may result in increased number of very low birth weight infants surviving without neurodevelopmental impairment (Chan et al., 2016). However, the authors concluded that the direct relationship between neurodevelopmental outcome and nutrition after birth remains unclear, as the neurologic development of premature infants is subject to multiple influences.

Besides optimal nutrition, several confounders for the neurodevelopment have been identified. In general, a number of clinical factors that may be related to each other have been shown to link to adverse neurodevelopmental outcomes in preterm infants (Leijon, 2010). The development of NEC, late onset sepsis or BPD, in addition to caloric deprivation, were found significant risk factors for suboptimal composite index scores in our study. Current evidence supports the association of clinical morbidities such as NEC with poor neurodevelopmental outcome; mechanisms including the leaky gut (Borre et al., 2014) and the disturbance of the gut-brain connection (Hintz et al., 2005) have been proposed to explain pathogens that enter the bloodstream and reach the brain, with significant consequences for the nervous system functions. Furthermore, accumulating evidence indicates that bacterial infection triggers inflammatory pathways that damage the preterm brain even in the absence of direct bacterial entry to the central nervous system (Strunk et al., 2014). White matter injury is a typical lesion associated with perinatal or neonatal infection, caused by the loss of the immature preoligodendrocytes that are particularly susceptible to oxidative stress and inflammation (Haynes, Folkerth, Trachtenberg, Volpe, & Kinney, 2009; Rezaie & Dean, 2002). Moreover, BPD is characterised by prolonged respiratory support, periods of hypoxia and the exposure to free radicals and oxidative stress. Experimental data have shown that chronic hyperoxia is associated with spatial and memory deficits and infants with BPD are at increased risk for neurodevelopmental impairment (Anderson & Doyle, 2006; Felderhoff-Mueser et al., 2004; Ramani, van Groen, Kadish, Bulger, & Ambalavanan, 2013). In overall, the clinical course of preterm infants includes the combination of such related factors and therefore, it is difficult to evaluate the effect of a single determinant such as the nutritional intake.

The current study has some limitations that should be addressed. Firstly, it was a single center prospective study with a relatively small sample size. However, the differences noted in the neurodevelopmental outcomes were strongly significant between the two groups of our study, and therefore, the sample size was powered enough to detect such a difference. Secondly, we were not able to compare the BSID-III scores in our preterm population with the results from a cohort of term infants. However, several studies have been published since 2006 when BSID-III was introduced in clinical practice (Adams-Chapman et al., 2013; Anderson et al., 2010; Doyle et al., 2010; Duncan et al., 2012; Payne et al., 2013; Serenius et al., 2013; Vohr et al., 2012) and thus, we interpreted our results based on the stratified reference values for each composite index score. Furthermore, in accordance to previous researchers, we reported similar findings in terms of the average composite index scores (Velikos et al., 2015) and the ratio of neurodevelopmental delay, ranged from 11% to 30% in cognitive domain, from 16% to 41% in language domain and from 15% to 16% in motor domain (Adams-Chapman et al., 2013; Anderson et al., 2010; Doyle, Roberts, Anderson, Victorian Infant Collaborative Study, & G., 2010; Duncan et al., 2012; Payne et al., 2013; Serenius et al., 2013; Vohr et al., 2012). Finally, the ultimate neurodevelopmental outcome depends on multiple clinical and environmental factors such as the social economic status or the education of the parents. Since those data were not available in our study, the interpretation of the neurodevelopmental outcome based on the effect of a single factor such as the caloric deprivation may not be precise.

In conclusion, the current study suggests that the caloric intake during the first two weeks of age and the development of specific neonatal co-morbidities have a significant role in the neurodevelopment of preterm infants. The caloric deprivation during infancy in addition to severe neonatal morbidities such as NEC, late onset sepsis or BPD is associated with adverse neurodevelopmental outcomes. Further randomized studies are warranted to evaluate ideal strategies to provide adequate energy supply in these high-risk infants. These will need to be coupled with optimal approaches to prevent common neonatal complications to further optimize neurodevelopmental outcomes.

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