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UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE

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Impact of Early Nutritional Intake on Preterm Brain: a Magnetic Resonance Imaging Study

THESE

préparée sous la direction du Professeur Anita C. Truttmann
(avec la co-direction de la Docteure Céline J. Fischer Fumeaux)

et présentée à la Faculté de biologie et de médecine de
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DOCTEUR EN MEDECINE

par

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Impact of Early Nutritional Intake on Preterm Brain: a Magnetic Resonance Imaging Study

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pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Impact of Early Nutritional Intake on Preterm Brain: A Magnetic Resonance Imaging Study

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Objectives To investigate the association between early nutritional intake and brain development assessed by magnetic resonance imaging (MRI).

Study design A cohort of neonates born at ≤30 weeks gestational age underwent MRI at term equivalent age. Brain maturation and injury were assessed using the Kidokoro score. Two groups were defined by severity of the scores. The associations between macronutrients intake during the first 2 weeks of life, clinical factors, and imaging scores were analyzed using logistic regression.

Results MRI 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 (IQR) 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 intake were significantly lower than in group 1. Group 2 also showed higher rates of sepsis and clinical risk scores than group 1. After adjustments in bivariate models, higher energy and lipid intake remained significantly associated with improved scores on MRI. This association was stronger for the gray matter component of the score.

Conclusions Higher energy and lipid intake during the first 2 weeks after birth was associated with a lower incidence of brain lesions and dysmaturation at term equivalent age in preterm neonates. *(J Pediatr 2017;181:29-36).*

Given the rise in rates of preterm birth and survival, it is important to attempt to decrease rates of neurologic 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 2 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 morphologic maturation itself are also poorly understood. Further investigation is 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 neurologic 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[19] 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 (BW) 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 2 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 morphologic brain development, assessed by MRI at TEA, and macronutrient and energy intakes during the first 2 weeks after birth. We used a semiquantitative MRI score,

BW	Birth weight
BPD	Bronchopulmonary dysplasia
CRIB	Critical risk index for babies
DOL	Day of life
GA	Gestational age
GM	Gray matter
MRI	Magnetic resonance imaging
TEA	Term equivalent age
WM	White matter

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described by Kidokoro et al[11] based on whole gray and WM growth, maturation, and lesion assessment.

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 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 (**Figure 1**; available at www.jpeds.com). The study protocol was approved by the local ethics 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 MRI-compatible incubator (Nomag; Lammers Medical Technology, Luebeck, Germany) with integrated neonatal head coil. The MRI-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, 160 mm); (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); and (5) magnetization-prepared dual rapid acquisition of gradient echo (MP2RAGE) (0.7 mm, 1.2 mm, 4000 ms, 3.17 ms, 190 mm, inversion time (TI) 1: 900 ms, TI 2: 2200 ms).

Brain maturation and injuries were assessed using the Kidokoro score.[11] This semiquantitative total score consists of 4 underscores (with a total of 13 scoring items, of which 6 are quantitative [brain metrics]): WM, cortex, deep gray 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 to 40. The scores were assessed by 2 neonatologists trained in MRI reading (J.S., A.T.), blinded for patient's information and supervised by a neuroradiologist (P.Ha.) in case of disagreement.

Nutritional Data Collection and Calculation

During the study, parenteral and enteral nutrients were individualized daily, according to our nutritional protocol, based on the European Society for Paediatric Gastroenterology Hepatology and Nutrition recommendations.[21,22]

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

Discontinuous milk feedings were initiated from DOL 1, at 15 ± 5 mL/kg/day and increased daily by 15 ± 5 mL/kg/day according to the enteral tolerance until 160 mL/kg/day 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, Vevey, Switzerland). Fortification (Aptamil Frauen-Milch-Supplement 4%; Milupa SA, Domdidier, Switzerland) was introduced when 100 mL/kg/day of human milk was tolerated.

Actual parenteral and enteral intakes were recorded in the electronic medical charts (Metavision; iMDsoft, Düsseldorf, Germany), allowing an exact record of enteral and parenteral intakes. Daily intake was 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 g, and lipids provide 9 Kcal per g. 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 postmenstrual age; necrotizing enterocolitis as Bell stage ≥2; and sepsis as clinical signs of infection with positive blood culture and/or inflammatory syndrome. Intraventricular hemorrhage was graded according to Papile et al.[24] A BW small for GA was determined by a weight more than 2 SDs below the mean on the Fenton growth chart.[25] Weight gain (in g/kg/day) calculation was {1000 × (weight at TEA MRI−BW)/[(weight at TEA MRI + BW)/2]/number of days}.[26,27]

Statistical Analyses

Continuous variables were summarized by their median and 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 ≥75th percentile (more severe abnormalities). Logistic regression analyses assessed associations between the 2 groups, nutritional intake, GA, BW, sepsis, sex, small for GA status, and comorbidities. The association between each nutrient and the outcome was adjusted on the covariable with a P value of <.05 in univariate analysis or other potential confounders. Statistical analysis was performed using Stata software v 14 (StataCorp, College Station, Texas).

Results

Of the 51 preterm infants included in the initial cohort,[13] 9 were excluded from the final analysis (1 withdrawal, 2 deaths before TEA, 2 missing nutritional data, and 4 noninterpretable MRIs) (**Figure 1**). 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. Goup 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]

Univariate Analysis

Factors that were found to be significantly associated ($P < .05$) 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. ORs (with group 1 as reference group) and corresponding *P* values are presented in **Table I**.

Adjusted Analysis

Bivariate models adjusting for DOL 1-14 cumulative nutritional intake and relevant clinical variables are presented in **Table II**. Clinical variables retained in the bivariate models were selected either from the univariate analysis ($P < .05$; 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

Table I. 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
Baseline clinical data					
GA (wk)	27.4 (26.4-28.4)	27.4 (26.6-28.4)	27.0 (25.5-28.4)	0.95 (0.88-1.02)	.17
Birth weight (g)	890 (763-1045)	900 (775-1093)	844 (738-1030)	1.00 (1.00-1.00)	.47
SGA	0	0	0	—	—
Female sex	23 (54.8)	14 (51.9)	9 (60.0)	1.39 (0.39-5.01)	.61
Chorioamnionitis	16 (38.1)	10 (37.0)	6 (40.0)	1.03 (0.26-4.07)	.97
Antenatal steroids	37 (88.1)	25 (92.6)	12 (80.0)	0.32 (0.05-2.18)	.24
Postnatal clinical data					
CRIB score	4 (1-6.8)	2 (1-5)	6 (4-9)	1.42 (1.10-1.82)	.006*
Postnatal steroids	6 (14.3)	2 (7.4)	4 (26.7)	4.55 (0.72-28.61)	.11
BPD (moderate to severe)	12 (29.3)	5 (19.2)	7 (46.7)	3.68 (0.90-15.01)	.07
Treated PDA	17 (40.5)	10 (37.0)	7 (46.7)	1.6 (0.43-5.94)	.48
Sepsis	19 (45.2)	9 (33.3)	10 (66.7)	4.0 (1.05-15.26)	.04*
NEC	0	0	0	—	—
IVH ≥2	2 (4.8)	1 (3.7)	1 (6.7)	1.86 (0.11-32.00)	.67
ROP ≥2	2 (4.8)	1 (3.7)	1 (6.7)	1.86 (0.11-32.00)	.67
Growth (birth to TEA MRI)					
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)	.35
Length growth (cm/wk)	0.99 (0.87-1.1)	0.97 (0.86-1.09)	1.0 (0.91-1.09)	2.25 (0.16-305.62)	.75
HC growth (cm/wk)	0.78 (0.74-0.83)	0.79 (0.74-0.81)	0.78 (0.76-0.85)	3.54 (0.0-7577.1)	.75
Cumulative nutritional intake (DOL 1-14)					
Energy (Kcal/kg)					
Parenteral	587 (476-776)	555 (418-764)	643 (552-762)	1.00 (1.0-1.0)	.48
Total	1227 (1109-1305)	1286 (1195-1334)	1077 (1035-1227)	0.99 (0.99-0.99)	.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)	.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)	.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)	.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)	.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)	.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)	.19

HC, head circumference; *IVH*, intraventricular hemorrhage; *NEC*, necrotizing enterocolitis; *PDA*, patent ductus arteriosus; *ROP*, retinopathy of prematurity; *SGA*, small for gestational age.
Quantitative variables are indicated in median (Q1,Q3) and qualitative variables in n (%).
*$P < .05$.

Table II. Unadjusted OR, aOR, and 95% CI for more abnormal MRI at TEA (score ≥6) according to cumulative total nutritional intake (day 1-14) and (1) sepsis, (2) GA, (3) BPD, (4) CRIB score, and (5) postnatal steroids (bivariate models)

	Unadjusted		Model 1: Sepsis and nutritional intake		Model 2: GA and nutritional intake		Model 3: BPD and nutritional intake		Model 4: CRIB score and nutritional intake		Model 5: PN steroids and nutritional intake	
	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 +140 kcal/kg (+10 Kcal/kg/d)	0.29 (0.12-0.70)	.01*	0.32 (0.13-0.76)	.01*	0.31 (0.13-0.74)	.008*	0.32 (0.13-0.78)	.01*	0.37 (0.15-0.94)	.036*	0.31 (0.12-0.79)	.015*
sepsis/GA/BPD/CRIB/PN steroids	Cf. Table I†		3.36 (0.74-15.18)	.11	0.97 (0.89-1.06)	.50	1.81 (0.36-9.23)	.47	1.29 (0.99-1.69)	.06	1.36 (0.16-11.2)	.78
Cumulative total fat intake												
by +10 g/kg (+0.7g/kg/d)	0.33 (0.15-0.71)	.01*	0.36 (0.16-0.80)	.01*	0.35 (0.16-0.76)	.008*	0.37 (0.17-0.82)	.015*	0.41 (0.19-0.92)	.03*	0.36 (0.16-0.80)	.012*
sepsis/GA/BPD/CRIB/ PN steroids	Cf. Table I†		2.86 (0.65-12.66)	.17	0.97 (0.89-1.06)	.48	2.00 (0.40-9.92)	.40	1.32 (1.00-1.74)	.05	1.81 (0.24-13.5)	.56
Cumulative total carbohydrate intake												
by +10 g/kg (+0.7g/kg/d)	0.61 (0.38-0.97)	.04*	0.62 (0.38-1.00)	.05	0.62 (0.38-1.01)	.05	0.60 (0.35-1.01)	.05	0.64 (0.37-1.11)	.11	0.65 (0.40-1.05)	.08
sepsis/GA/BPD/CRIB/PN steroids	Cf. Table I†		3.9 (0.94-16.18)	.06	0.96 (0.89-1.04)	.33	2.91 (0.64-13.1)	.17	1.36 (1.06-1.75)	.02*	2.68 (0.38-18.8)	.32
Cumulative total protein intake												
by +10 g/kg (+0.7g/kg/d)	0.49 (0.17-1.42)	.19	0.41 (0.13-1.30)	.13	0.54 (0.19-1.56)	.26	0.66 (0.21-2.09)	.48	0.83 (0.25-2.72)	.76	0.62 (0.20-1.92)	.41
sepsis/GA/BPD/CRIB/PN steroids	Cf. Table I†		4.74 (1.15-19.64)	.03*	0.95 (0.89-1.03)	.23	2.92 (0.63-13.5)	.17	1.40 (1.08-1.82)	.01*	3.48 (0.50-24.2)	.21

PN, postnatal.
*$P < .05$.
†See unadjusted OR for sepsis, GA, BPD, CRIB score or PN steroids, respectively, in Table I.

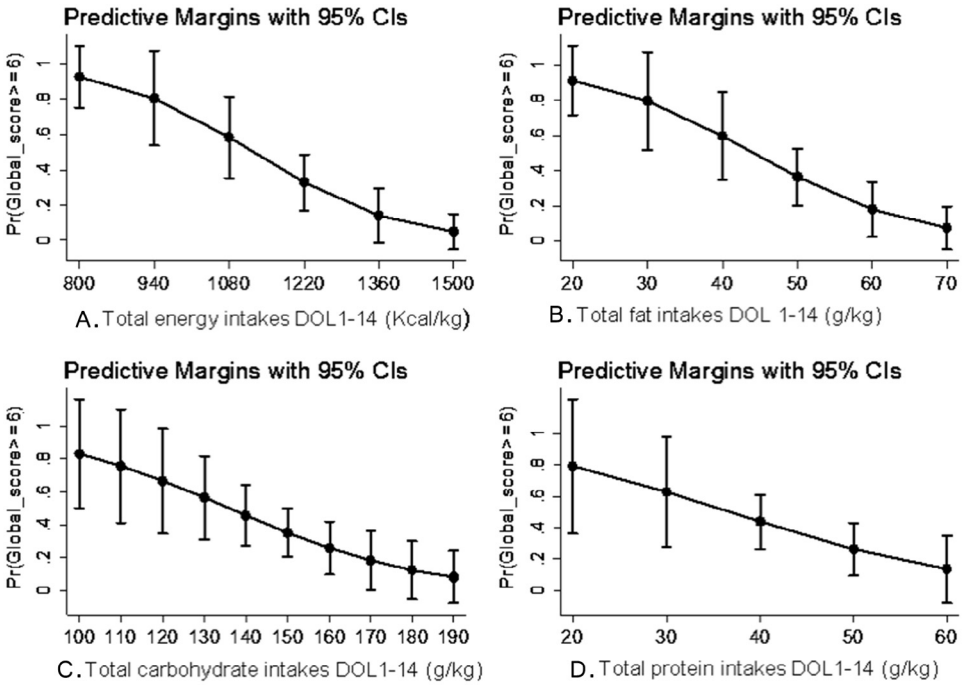

Figure 2. Probability of having a more severe MRI at TEA (score ≥6) according to the cumulative total intake of **A,** energy, **B,** fat, **C,** carbohydrates, and **D,** proteins during the first 2 weeks of life (DOL1-14), after adjustments on sepsis.

remained significant after adjustments. The construction of multivariable models adjusting for all these nutritional and clinical variables was not possible because of the limited number of patients in the study groups.[28]

Figure 2 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 2 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/day) in lipids would reduce this risk by 64%, respectively.

Finally, considering the 2 components of the total score separately, we found a significant association of total energy, fat, carbohydrate, and protein intakes with the GM score (cortical, deep grey matter, cerebellum) component, but no significant association was found with the WM score. (**Figure 3**).

Discussion

This study showed an association between early nutrition and morphologic 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 2 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, GA, BPD, and postnatal steroids in bivariate models. Adjusted models estimated that a 10 Kcal/kg/day increase in energy or a 0.7 g/kg/day 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 2 postnatal weeks. Our study suggests that insufficient nutritional support may be harmful for brain maturation. Despite the existing guidelines, actual nutritional intake is often lower than recommended for preterm neonates, as noted in our population.[29-32] 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 intrauterine growth restriction.[33] Compared with MRI studies on early postnatal nutrition, similar positive effects were observed on cortical[34] and subcortical GM,[19] although MRI 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 intake. GM involvement in addition to that of WM in preterm brain injury is a relatively new concept that was well described by Volpe[14] in the encephalopathy of prematurity.[15] Regarding the WM involvement, we were not able to show an association, contrary to Strømmen et al[18] who found a correlation between nutrient supply and maturation of the WM using diffusion MRI. This could be due to a lack of power in our small and

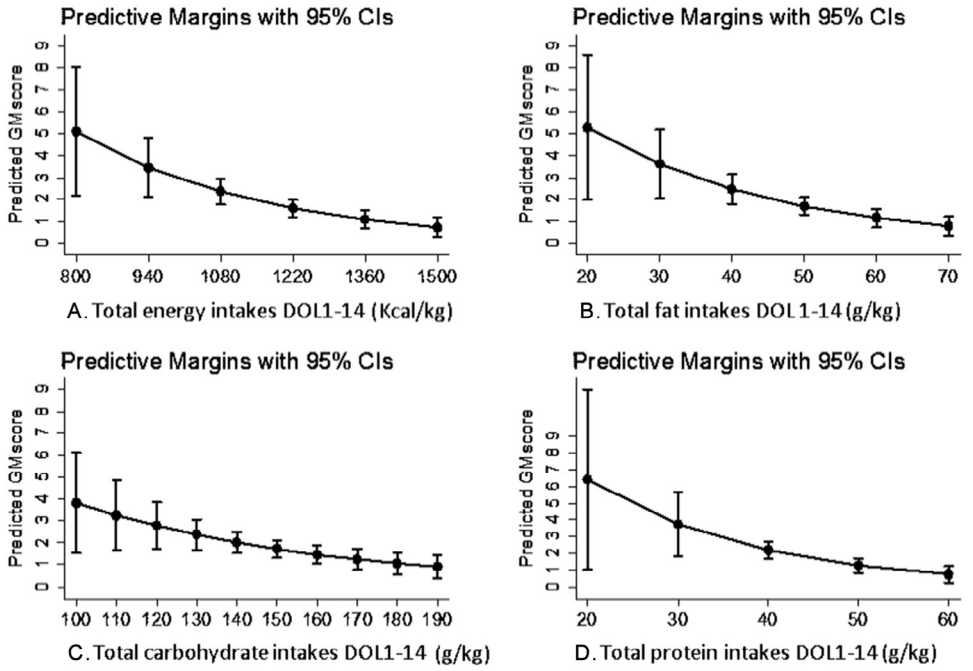

Figure 3. Predicted MRI gray matter scores according to the cumulative total intake of **A,** energy, **B,** fat, **C,** carbohydrates, and **D,** proteins during the first 2 weeks of life (DOL1-14), after adjustments on sepsis.

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,[34] using diffusion tensor imaging, demonstrated a correlation between postnatal growth and cortical structural development. Interestingly, we did not observe a similar correlation between growth and MRI outcome in our study. This difference could be due to the distinctive MRI 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/day). Recently, Horbar et al[29] 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. Likewise, weight growth rate velocity from Martin et al,[35] from birth to DOL 28 was 10-11 g/kg/day. 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 semiquantitative 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, because of the lack of sensitive tools. Compared with new techniques, such as segmentation or diffusion tensor imaging, the semiquantitative 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,[36] 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 dit Trolli et al[7] who showed a positive correlation between early lipid intake and neurologic outcome. 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[37,38] showed that lower intake of calories and lipids were significantly associated with an increased risk of retinopathy of prematurity. However, our study was not adequately powered to assess this issue, as only 2 patients (1 in each group) developed retinopathy of prematurity. The importance of energy supply was also stressed by Stephens et al,[4] who reported that an increase of 10 Kcal/kg/day during the first week was associated with a 4.6-point increase in the mental development index of the Bayley Scales of Infant Development.[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 intake 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.[7,39]

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 intake in the first 2 weeks of life could be the reflection of more babies who are sick,[40] 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 bivariate models. Adjusting for other additional possible confounders, as GA 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,[16,35,41] 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 intake and morphologic brain development evaluated by TEA MRI in very preterm infants. Increased calorie intake or lipid intake 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 intake may increase the risk of poorer brain maturation. Optimizing nutritional intake 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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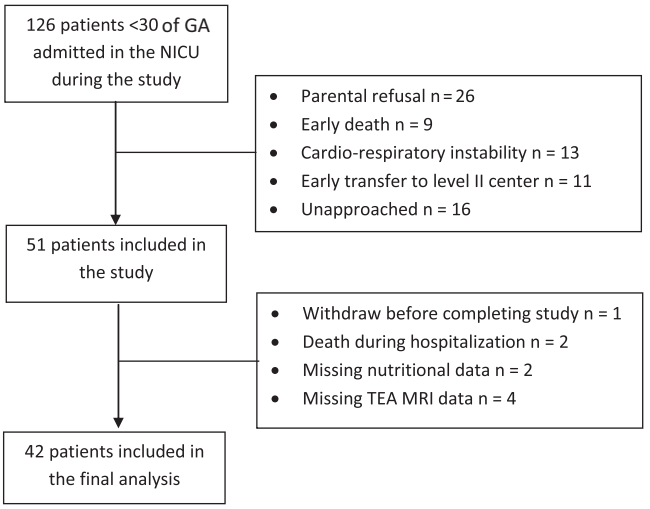

Figure 1. Flow chart.