

# Nutrient Intake in the First Two Weeks of Life and Brain Growth in Preterm Neonates

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abstract

**BACKGROUND:** Optimizing early nutritional intake in preterm neonates may promote brain health and neurodevelopment through enhanced brain maturation. Our objectives were (1) to determine the association of energy and macronutrient intake in the first 2 weeks of life with regional and total brain growth and white matter (WM) maturation, assessed by 3 serial MRI scans in preterm neonates; (2) to examine how critical illness modifies this association; and (3) to investigate the relationship with neurodevelopmental outcomes.

**METHODS:** Forty-nine preterm neonates (21 boys, median [interquartile range] gestational age: 27.6 [2.3] weeks) were scanned serially at the following median postmenstrual weeks: 29.4, 31.7, and 41. The total brain, basal nuclei, and cerebellum were semiautomatically segmented. Fractional anisotropy was extracted from diffusion tensor imaging data. Nutritional intake from day of life 1 to 14 was monitored and clinical factors were collected.

**RESULTS:** Greater energy and lipid intake predicted increased total brain and basal nuclei volumes over the course of neonatal care to term-equivalent age. Similarly, energy and lipid intake were significantly associated with fractional anisotropy values in selected WM tracts. The association of ventilation duration with smaller brain volumes was attenuated by higher energy intake. Brain growth predicted psychomotor outcome at 18 months' corrected age.

**CONCLUSIONS:** In preterm neonates, greater energy and enteral feeding during the first 2 weeks of life predicted more robust brain growth and accelerated WM maturation. The long-lasting effect of early nutrition on neurodevelopment may be mediated by enhanced brain growth. Optimizing nutrition in preterm neonates may represent a potential avenue to mitigate the adverse brain health consequences of critical illness.

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Dr Schneider designed and conducted the study, was responsible for the MRI acquisition, collected clinical data, participated in the postprocessing of the MRI data, drafted the initial manuscript, and revised the final manuscript; Dr Fischer Fumeaux supervised nutritional data collection, contributed to data interpretation, and reviewed and revised the manuscript; Dr Duerden performed the postprocessing of the MRI data, contributed to statistical analyses, and reviewed and revised the manuscript; Dr Guo performed the automatic brain segmentation and reviewed the manuscript; Mr Foong performed the diffusion tensor imaging analysis and reviewed the manuscript; Dr Bickle Graz conducted the neurodevelopmental assessments of

**WHAT'S KNOWN ON THIS SUBJECT:** In very preterm neonates, enhancing early nutritional support appears to limit postnatal growth restriction and improve neurodevelopmental outcomes in childhood. Whether the relationship between nutrition and neurodevelopment is mediated by accelerated brain maturation or growth remains uncertain.

**WHAT THIS STUDY ADDS:** In this preterm cohort study, higher energy and enteral feeding during the first 2 weeks of life predict more robust brain growth and accelerated white matter maturation. Optimizing early nutrition in preterm life might promote neurodevelopment through enhanced brain growth.

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Preterm infants are vulnerable to alteration of the expected cerebral neurodevelopmental trajectory and brain injury.<sup>1</sup> Nutrition is emerging as a potential factor to improve growth and outcomes.<sup>2–4</sup> Optimizing early nutritional intake may be brain protective,<sup>5</sup> but the extent to which nutrition leads to improved neurodevelopment through enhanced brain maturation remains to be determined.

Recently, higher nutritional intake in early life was associated with a lower incidence of brain injury at term-equivalent age (TEA).<sup>6</sup> Yet studies in which researchers examine nutrition in relation to brain volumes either at TEA<sup>7–9</sup> or in adolescence<sup>10</sup> are scarce and have conflicting results. Furthermore, enhanced early nutrition appears to improve neurodevelopment,<sup>11,12</sup> but whether this relationship is mediated by accelerated brain maturation remains unclear. Thus, the relationship of early nutrition with brain maturation, as reflected in volume or white matter (WM) fractional anisotropy (FA),<sup>13</sup> over the NICU course needs to be determined.

We studied a very preterm cohort to first determine the association of early energy and macronutrient intake with regional (basal nuclei and cerebellum) and total brain growth and WM maturation. Our secondary objectives were to examine how critical illness modifies this association and the relationship with neurodevelopmental outcomes. All neonates had comprehensive nutritional data collected over the first 2 weeks of life and 3 serial MRI scans from birth to TEA. We hypothesized that greater early nutrient intake would predict enhanced brain growth and accelerated microstructural maturation, and subsequent better neurodevelopment, at 18 months' corrected age (CA).

## METHODS

### Study Design and Subjects

In this prospective cohort study, preterm neonates born at <30 weeks' gestation and admitted to the level III NICU of the University Hospital in Lausanne (Switzerland) between 2011 and 2013 underwent serial brain MRI between birth and TEA. Exclusion criteria included the following: major malformation, severe cardiorespiratory instability preventing MRI completion, and/or intraventricular hemorrhage grade >II on early cerebral ultrasound. This cohort has been described elsewhere.<sup>6,13</sup> The local ethical committee (Commission d'Ethique du Canton de Vaud, Switzerland) approved the study protocol, and parents provided informed written consent.

### MRI Studies

Three serial MRI scans were performed as follows: (1) within the first 2 weeks of life, (2) at an intermediate time point (3 weeks of life for the first two-thirds of the cohort and 34–35 weeks' postmenstrual age [PMA] for the rest), and (3) at TEA on a 3-Tesla MAGNETOM Trio system (Siemens, Erlangen, Germany) using a magnetic resonance (MR)-compatible incubator (Lammers Medical Technology, Luebeck, Germany) with an integrated neonatal head coil. MR scanning lasted ~50 minutes; no sedation was provided.

### Volumetric Measurements

Volume segmentation was performed by using three-dimensional T1-weighted images acquired with a MP2RAGE (Magnetization-Prepared Dual Rapid Acquisition of Gradient Echo) sequence. A semiautomated segmentation method using the Multiple Automatically Generated Templates brain pipeline<sup>14</sup> was applied.<sup>15</sup> Manually segmented thalamus, basal ganglia (putamen, globus pallidus, and caudate

nucleus), cerebellum, and total brain (excluding midbrain and ventricles) on multiple images, acquired at appropriate PMA, were used as atlases in the subsequent segmentation pipeline. Templates were propagated to the T1-weighted images of the cohort, producing volumes of each subject's anatomic structure.

### Diffusion-Weighted Imaging

FA values were extracted from the diffusion-weighted imaging sequence in 9 WM regions of interest: the corpus callosum; anterior and posterior limbs of the internal capsule; the anterior, superior, and posterior corona radiata; the posterior thalamic radiations; the superior longitudinal fasciculus; and the corticospinal tract by using the Johns Hopkins University atlas. Diffusion tensor imaging data were analyzed by using the FMRIB Software Library (<http://www.fmrib.ox.ac.uk/fsl>). Extracted FA values were averaged over the Johns Hopkins University atlas regions, and regional evolution was examined over time.

### Nutritional Protocol and Data Collection

For our local nutritional protocol, we followed the European Society for Pediatric Gastroenterology Hepatology and Nutrition recommendations, as described previously,<sup>6</sup> and in the Supplemental Information. Information about exact parenteral and enteral intake from day of life (DOL) 1 to 14 was collected from the electronic medical charts. Enteral and parenteral contributions were summed to obtain total daily intake. Energy intake was computed with proteins and carbohydrates providing 4 kilocalories (kcal) per gram and lipids providing 9 kcal per gram. Breast milk composition was based on the Standardized Reporting of Neonatal Nutrition and Growth checklist,<sup>16</sup> and formula composition

was based on commercial notifications.

### Clinical Data

Prospective collection of clinical variables included mechanical ventilation duration, bronchopulmonary dysplasia (defined as ventilatory or oxygen requirement at 36 weeks' PMA), and sepsis (defined as culture-proven infection or as clinical infection signs with inflammatory syndrome [C-reactive protein >20 mg/L] leading to  $\geq 7$  days of antibiotic treatment). Weight was measured daily on an electronic scale (accuracy  $\pm 5$  g), and crown-heel length and head circumference (HC) were measured weekly with a height gauge and a tape measure, respectively. Being small for gestational age (GA) was determined as a birth weight (BW)  $< 2$  SD according to the Fenton growth chart.<sup>17</sup> Weight gain (in g/kg per day) was calculated with the following formula:  $1000 \times (\text{TEA MRI weight} - \text{BW}) / [(\text{TEA MRI weight} + \text{BW}) / 2] / \text{number of days}$ .

### Neurodevelopmental Outcome

A standardized neurodevelopmental assessment was performed at 18 months' CA by a developmental pediatrician blinded to nutritional and MR data who used the Bayley Scales of Infant Development, Second Edition, which provides 2 indices with a normative mean score of  $100 \pm 15$  SD. The Mental Developmental Index (MDI) comprises language and cognitive items, whereas the Psychomotor Developmental Index (PDI) consists of fine and gross motor items as well as visuospatial items.

### Statistical Analysis

For our data analysis plan, we followed a stepwise strategy given the limited number of intensively studied subjects. The first stage consisted of describing the cohort by separating subjects into 2 groups by the median daily total energy

per kilogram to identify potential confounders. For subsequent analyses, nutritional data were used as continuous variables. In the second stage we analyzed the association of total energy, lipid, protein, or carbohydrate intake separately with total brain growth across the 3 scans. We used generalized estimating equation (GEE) models accounting for repeated measures with independent correlation structures and robust SE adjustment, adjusting for PMA at MRI. Hypothesizing that nutrition would impact gray matter (GM) and WM development differently, we built separate regression models to assess GM maturation using basal nuclei (thalamus and basal ganglia) and cerebellum volume changes over time and WM maturation with FA value changes. For the third stage, we further analyzed the significant relationships from GEEs and we examined the temporal differences by scan using multivariable linear regression models assessing the association between nutritional intake with total or regional brain volume and FA at each scan in separate models that adjusted for PMA at MRI. In the fourth stage we focused on the relative contribution of enteral and parenteral intake to volume and FA value changes; we used separate GEE models for energy and each nutrient, accounting for respective enteral and parenteral intake and PMA at MRI. In the fifth stage, we examined potential confounders in the relationship between nutritional intake and brain maturation: clinical variables identified at the first stage were tested in GEE models using an interaction term (energy intake by clinical factor). Complementary analyses explored the effect of energy and nutrients on weight, length, and HC growth velocities in separate multivariable linear regression models adjusting for birth GA. Finally, the association between each MR metric (in unit change per week)

separately and neurodevelopment (MDI and PDI) at 18 months' CA was examined by using a linear regression model adjusting for birth GA. Given our primary hypothesis that greater early nutrient intake predicts greater brain health, statistical significance was defined as  $P < .05$ ; analyses were performed by using the Statistical Package for the Social Sciences (version 23; IBM SPSS Statistics, IBM Corporation).

## RESULTS

### Subjects

From the original cohort of 51 subjects,<sup>6</sup> complete nutritional and MRI data sets were available for 49 subjects, of whom 2 died before a TEA scan could be performed. The lower- and higher-energy groups differed clinically by multiple gestation rate, length at birth, and respiratory morbidity but not by GA, BW, sex, Apgar score, and sepsis (Table 1). Compared with the parenteral contribution, enteral intake showed higher variability between groups, reflecting greater standardization of the parenteral prescription of nutrition. Over the first 2 weeks of life, lipids contributed 36% of the average total energy intake, compared with 15% and 49% for proteins and carbohydrates, respectively. Breast milk comprised 98% of enteral intake during the first 2 weeks.

### Regional and Total Brain Growth in Relation to Nutrition

Volume segmentation was performed on 129 scans (42 early, 41 intermediary, and 46 TEA scans), and 6 scans were discarded because of a motion artifact. Greater total energy (kcal/kg per day) and lipid (g/kg per day) intake predicted increased total brain ( $\beta = 839.8$ ,  $P = .021$  and  $\beta = 13425.5$ ,  $P = .019$ , respectively) and basal nuclei ( $\beta = 37.6$ ,  $P = .019$  and  $\beta = 616.8$ ,  $P = .017$ , respectively) growth ( $\text{mm}^3$ ) over

**TABLE 1** Clinical and Nutritional Characteristics of the Cohort, Separated by the Median Daily Total Energy per Kilogram in 2 Groups ( $\pm 86.0$  kcal/kg per Day)

	Lower-Energy Group, <i>n</i> = 24	Higher-Energy Group, <i>n</i> = 25	<i>P</i>
<b>Baseline clinical data</b>			
GA (wk), median (IQR)	27.4 (25.9–28.4)	28.1 (26.8–29.0)	.114
Wt at birth (g), median (IQR)	826.0 (679.8–1015.0)	890.0 (764.5–1137.5)	.179
Length at birth, median (IQR)	34.0 (32.3–36.0)	35.5 (34.0–38.0)	.031
HC at birth, median (IQR)	24.0 (23.0–25.4)	24.5 (24.0–26.0)	.243
Boys, <i>n</i> (%)	11 (46)	10 (40)	.680
Small for GA, <i>n</i> (%)	1 (4)	1 (4)	.976
Multiple gestations, <i>n</i> (%)	10 (41)	2 (8)	.006
Apgar at 5 min (IQR)	7.5 (6.0–8.0)	7.0 (6.0–8.0)	.564
Chorioamnionitis, <i>n</i> (%)	10 (42)	10 (40)	.906
<b>Postnatal clinical data</b>			
Postnatal steroid therapy, <i>n</i> (%)	7 (29)	0 (0)	.004
Days of mechanical ventilation, median (IQR)	4.6 (0.3–11.8)	0.5 (0.0–2.0)	.008
Moderate-severe BPD, <i>n</i> (%)	12 (50)	4 (16)	.011
Early-onset sepsis, <i>n</i> (%)	7 (29)	5 (20)	.456
Late-onset sepsis, <i>n</i> (%)	10 (42)	7 (28)	.315
Necrotizing enterocolitis, <i>n</i> (%)	1 (4)	1 (4)	.976
<b>Growth (birth to TEA MRI), median (IQR)</b>			
Wt gain (g/kg per d)	11.7 (11.1–12.2)	12.0 (11.6–13.1)	.126
Length growth (cm/wk)	0.9 (0.8–1.1)	1.0 (0.9–1.1)	.478
HC growth (cm/wk)	0.8 (0.7–0.8)	0.8 (0.8–0.8)	.151
<b>Nutritional intake per d (DOL 1–14), median (IQR)</b>			
Energy total (kcal/kg per d)	77.6 (74.5–83.4)	93.1 (89.5–101.3)	—
Parenteral	45.8 (28.4–62.3)	41.3 (35.9–56.3)	.847
Enteral	31.7 (15.2–45.2)	52.9 (39.1–60.1)	.001
Lipids total (g/kg per d)	3.0 (2.6–3.5)	4.2 (3.8–4.5)	—
Parenteral	1.0 (0.8–1.8)	1.3 (1.0–1.8)	.405
Enteral	1.8 (0.9–2.7)	3.0 (2.2–3.3)	.001
Carbohydrates total (g/kg per d)	9.9 (9.1–10.5)	11.1 (10.3–12.1)	—
Parenteral	6.7 (4.8–8.7)	6.4 (4.4–7.9)	.448
Enteral	3.1 (1.4–4.2)	5.0 (3.6–6.1)	<.001
Proteins total (g/kg per d)	2.8 (2.6–3.1)	3.2 (2.9–3.5)	—
Amino acids, parenteral	2.0 (1.4–2.7)	1.8 (1.5–2.4)	.502
Proteins, enteral	0.8 (0.3–1.0)	1.3 (0.9–1.6)	<.001
Percentage human milk to total enteral intake, % (IQR)	99 (97–100)	95 (77–98)	.015
<b>Age at MRI (wk), median (IQR)</b>			
First MRI	29.2 (27.9–29.6)	29.7 (28.4–31.0)	.035
Second MRI	30.0 (29.2–32.2)	34.1 (31.5–34.9)	<.001
Third (TEA) MRI	40.3 (39.7–41.4)	41.1 (39.9–41.7)	.415

Continuous variables were summarized by their median (IQR), and categorical variables were summarized by frequency. Continuous variables were compared by using Student's *t* test, and categorical variables were compared by using Fisher's exact test. BPD, bronchopulmonary dysplasia; — not applicable.

the NICU course in separate GEE models. Examining volumes at each scan using multivariable linear regression models, we found that the association of energy and lipid intake with total brain, basal nuclei, and cerebellum volumes became visible on intermediary scans and increasingly robust on TEA scans. Similarly, protein and carbohydrate intake were associated with total brain volume at TEA scans (Figs 1 and 2).

### WM Microstructural Maturation and Nutrition

Average FA values were extracted from 115 scans (31 early, 39 intermediary, and 45 TEA scans). Energy and lipid intake predicted WM tract maturation, characterized by increasing FA across the 3 scans in the posterior corona radiata ( $\beta = .001, P < .001$  and  $\beta = .026, P < .001$ , respectively), posterior thalamic radiations ( $\beta = .001, P = .004$  and

$\beta = .013, P < .001$ , respectively), and superior longitudinal fasciculus ( $\beta = .001, P = .026$  and  $\beta = .011, P = .005$ , respectively) in GEE models. Lipid intake was also associated with maturation of the superior corona radiata ( $\beta = .007, P = .041$ ) and corticospinal tract ( $\beta = .017, P = .007$ ). Results from multivariable linear regression models showed similar associations with energy and lipids and temporal evolution (Fig 3, Supplemental Fig 5). No association was found between protein and carbohydrate intake and FA.

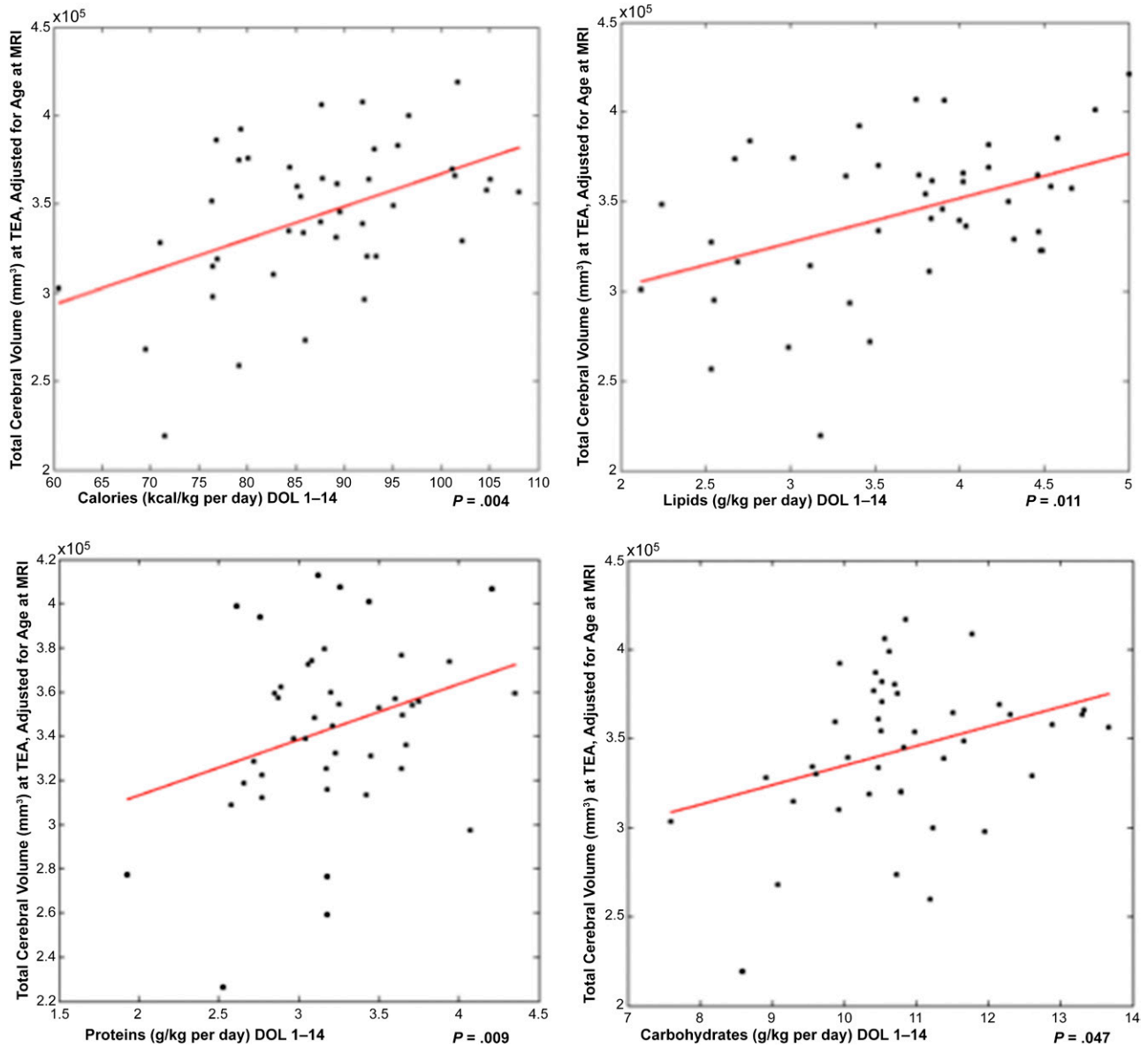
### Enteral Versus Parenteral Contribution in Relation to Brain Development

Compared with its parenteral counterpart, only the enteral component of nutrition showed significant associations with MR metrics (Table 2). In contrast to the preceding analyses, enteral intake of energy and all macronutrients, including proteins and carbohydrates, predicted brain growth and WM maturation, with at times higher effect sizes for enteral proteins. To note, breast milk volume (mL/kg per day) was only associated with FA in WM tracts (Table 2).

### Brain Development and Interaction Between Nutrition and Respiratory Morbidity

Considering that variables related to respiratory morbidity differed significantly between higher- and lower-energy groups, ventilation duration (in days) was used in GEE models accounting for energy intake and PMA at MRI and was negatively associated with total brain, basal nuclei, and cerebellum growth ( $\beta = -1608.5, P = .022$ ;  $\beta = -87.9, P = .001$ ; and  $\beta = -139.7, P = .006$ , respectively). However, the interaction of energy intake by ventilation duration in the same models positively predicted total brain, basal nuclei, and cerebellum growth ( $\beta = 150.4, P = .048$ ;  $\beta = 5.7,$





**FIGURE 1**

Graphs reveal the relationships between energy (kcal/kg per day); lipid, protein, and carbohydrate (g/kg per day) intake from DOL 1 to 14 on the x-axis; and total cerebral volumes (in mm<sup>3</sup>; ×10<sup>5</sup>) at TEA, adjusted for PMA at MRI on the y-axis. *P* values result from multivariable linear regression models adjusting for PMA at MRI.

$P = .032$ ; and  $\beta = 15.4$ ,  $P = .044$ , respectively) (Fig 4). Examining FA in GEE models adjusting for ventilation duration and PMA at MRI, we found that energy and lipid intake remained significantly associated with WM development in the posterior corona radiata ( $\beta = .001$ ,  $P = .004$  and  $\beta = .025$ ,  $P < .001$ , respectively) and posterior thalamic radiations ( $\beta = .001$ ,  $P = .049$  and  $\beta = .012$ ,  $P = .016$ , respectively) and in the superior longitudinal

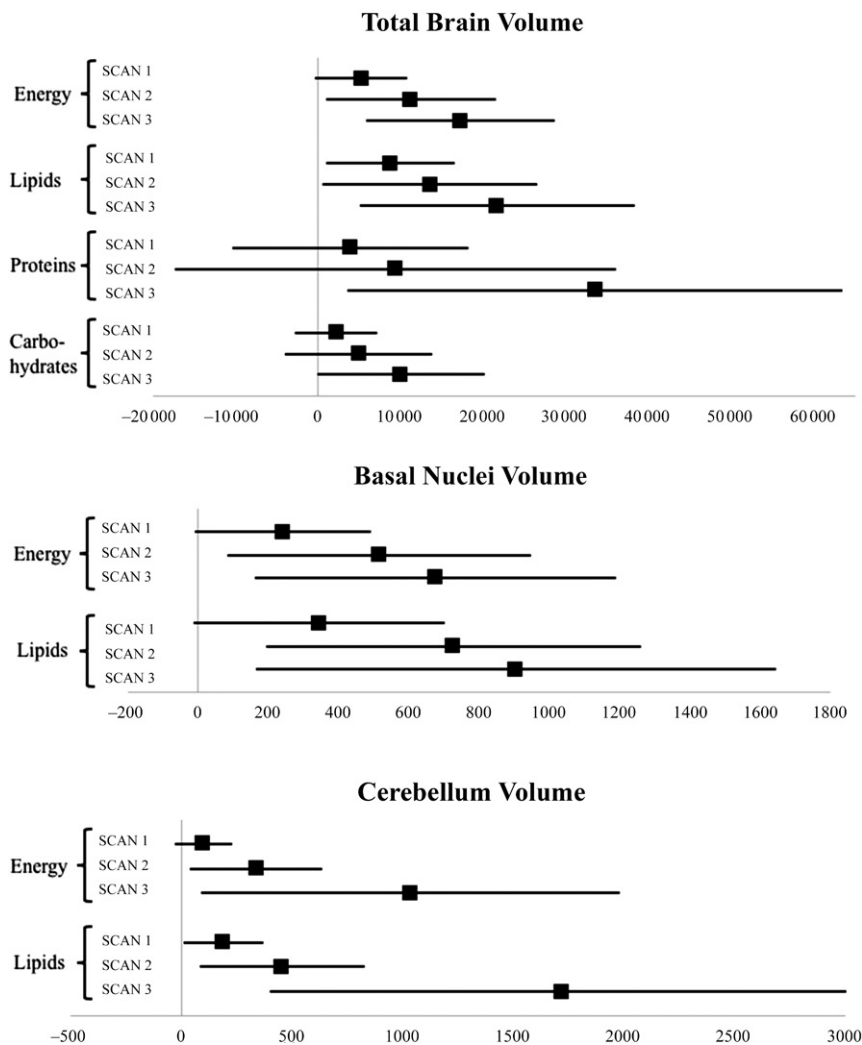
fasciculus with lipid intake only ( $\beta = .009$ ,  $P = .013$ ). Inclusion of birth GA and sepsis did not modify the relationships between energy intake and total brain volume ( $\beta = 787.6$ ,  $P = .048$ ) or FA in the superior ( $\beta = .001$ ,  $P = .017$ ) and posterior corona radiata ( $\beta = .001$ ,  $P < .001$ ), posterior thalamic radiations ( $\beta = .001$ ,  $P = .004$ ), and superior longitudinal fasciculus ( $\beta = .001$ ,  $P = .007$ ) in individual models for each outcome.

### Nutrition and Somatic Growth Velocities

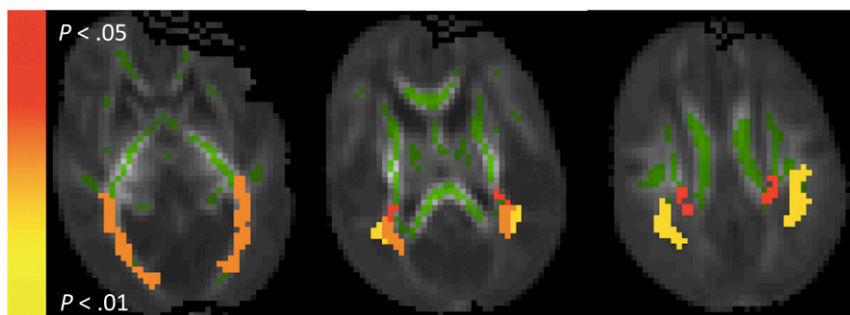
Total protein and carbohydrate intake were positively associated with weight growth velocity in linear regression models. Only protein intake predicted length and HC growth (Table 3).

### MR Metrics and Neurodevelopment

All surviving patients returned for neurodevelopmental assessment



**FIGURE 2** Plots reveal results from multivariable linear regression models examining brain volumes at each scan and adjusting for PMA at MRI. Effect sizes (95% confidence interval) of total brain, basal nuclei, and cerebellum volumes ( $\text{mm}^3$ ) are shown separately for energy (per 10 kcal/kg per day) and lipid, protein, and carbohydrate (per 1 g/kg per day) intake at each scan.



**FIGURE 3** DTI analysis of TEA scans, with the mean FA skeleton shown in green.  $P$  values by tracts (ranging from red to yellow) from the multivariate linear regression models correspond to the positive association between lipid intake and average FA values at TEA. DTI, diffusion tensor imaging.

at 18 months' CA ( $n = 47$ ). Median (interquartile range [IQR]) MDI and PDI scores were 93 (14) and 83 (16), respectively. Total brain, basal nuclei, and cerebellum growth (in  $\text{mm}^3$  per week) were positively associated

with PDI scores at 18 months' CA ( $\beta = .002, P = .020$ ;  $\beta = .036, P = .041$ ; and  $\beta = .016, P = .027$ , respectively). Brain volume changes did not predict MDI scores. Similarly, FA in WM tracts was not associated with MDI or PDI scores (all  $P > .05$ ).

## DISCUSSION

To our knowledge, this is the first preterm cohort study in which brain growth as measured on 3 serial scans in relation to early nutrition is examined. Higher energy intake during the first 2 weeks of life predicted enhanced brain development, with a positive effect on both GM and WM, as indicated by more robust growth of the subcortical structures, the cerebellum, and the total brain and accelerated WM microstructural maturation to term age, with remarkable consistency across brain measures. Among the macronutrients, lipid intake was predominantly associated with MR metrics. Variations of nutritional intake were mostly due to the enteral component, which was composed of >95% breast milk in the study population. Although respiratory morbidity was a strong predictor of adverse outcome, improved nutrition appeared to mitigate its negative impact on brain development. Moreover, brain growth predicted psychomotor outcome at 18 months' CA, suggesting that the long-lasting effect of early nutrition on neurodevelopment might be mediated by enhanced brain maturation.

### Brain Vulnerability to Nutritional Deficit

As placental supply is discontinued, neonatal intensive care is accompanied by a nutritional deficit,<sup>18</sup> which occurs during a critical period

**TABLE 2** GEE Models Examining Associations Between Enteral Energy Intake (kcal/kg per Day), Enteral Nutrient Intake (g/kg per Day), and Breast Milk Volume (mL/kg per Day) as Predictor Variables and Regional or Total Brain Volume (mm<sup>3</sup>) and FA in WM Tracts as Outcome Variables

	Predictor Variable: Enteral Intake of	Effect Size: Volume in mm <sup>3</sup> , Ø Unit for FA	95% CI	P
Total cerebral volume (mm <sup>3</sup> )	Energy	841.5	112.1 to 1570.9	.024
	Lipids	13856.6	2800.6 to 24912.5	.014
	Proteins	25101.5	-1546.5 to 51749.4	.065
	Carbohydrates	6228.4	64.7 to 12392.0	.048
	Breast milk volume	45.9	-278.4 to 370.1	.782
Basal nuclei volume (mm <sup>3</sup> )	Energy	37.7	5.2 to 70.3	.023
	Lipids	624.1	121.6 to 1126.5	.015
	Proteins	1081.3	-37.4 to 2200.1	.058
	Carbohydrates	293.9	16.1 to 571.7	.038
	Breast milk volume	6.4	-7.5 to 20.3	.366
FA in posterior corona radiata	Energy	0.001	0.001 to 0.002	<.001
	Lipids	0.025	0.007 to 0.030	<.001
	Proteins	0.035	0.014 to 0.055	.001
	Carbohydrates	0.010	0.003 to 0.017	.004
	Breast milk volume	0.001	2.9E-4 to 0.001	<.001
FA in posterior thalamic radiations	Energy	0.001	0.000 to 0.001	.003
	Lipids	0.012	0.005 to 0.020	.001
	Proteins	0.019	0.002 to 0.037	.032
	Carbohydrates	0.007	0.002 to 0.012	.006
	Breast milk volume	3.0E-4	4.8E-5 to 0.001	.020
FA in superior longitudinal fasciculus	Energy	0.001	5.1E-5 to 0.001	.003
	Lipids	0.011	0.002 to 0.019	.011
	Proteins	0.012	-0.001 to 0.026	.080
	Carbohydrates	0.005	-7.4E-5 to 0.010	.053
	Breast milk volume	2.2E-4	3.48E-5 to 4.0E-4	.020
FA in corticospinal tract	Energy	0.001	-4.1E-5 to 0.002	.061
	Lipids	0.025	0.003 to 0.047	.025
	Proteins	0.030	0.004 to 0.056	.024
	Carbohydrates	0.005	-0.004 to 0.013	.254
	Breast milk volume	1.2E-4	-2.3E-4 to 4.7E-4	.507

All models are adjusting for parenteral intake of energy or nutrients, respectively, and PMA at MRI.

for brain development. Critically timed nutrient deficiency can influence normal developmental trajectories of neurons and glial cells, potentially leading to disrupted brain maturation and/or slower growth.<sup>5</sup> This deficit partly results from the gap between international nutritional recommendations and actual nutrient intake, which is influenced by factors such as feeding intolerance, fluid restriction, and venous access.<sup>2,19</sup> Variations in early nutritional provision seem sufficient to influence brain development. In our study, this variability was attributed to the

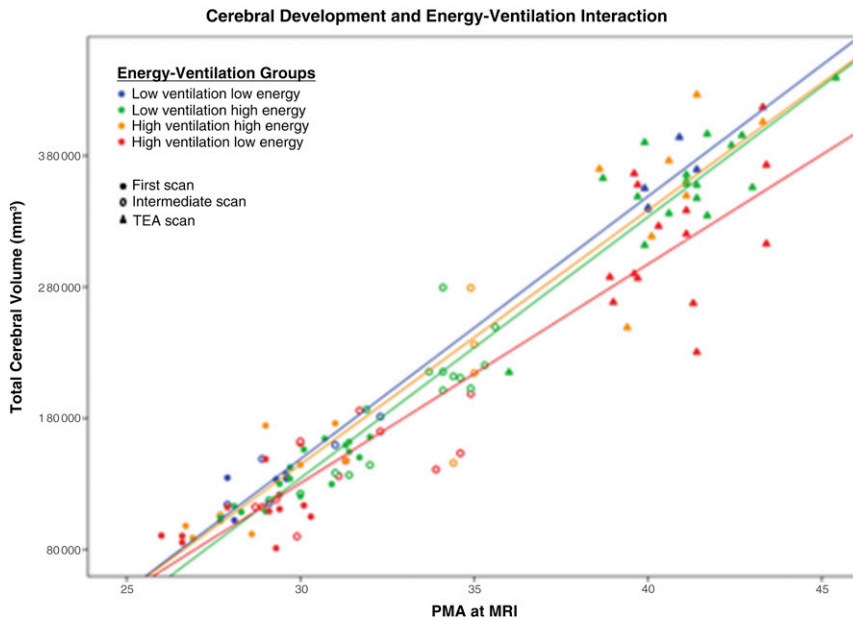
enteral nutritional component. This may reflect the clinical condition of subjects receiving lower enteral supply, but ultimately it might help developing nutritional interventions to optimize enteral feeding.

### Early Nutrition and MR Metrics

Our findings relating brain growth with nutrition are in line with previous studies in which researchers assessed brain volumes at TEA<sup>9</sup> or in adolescence.<sup>10</sup> GM might be specifically vulnerable

to nutritional deficit, as nutrients support neuronal metabolism and proliferation and subsequently regulate differentiation.<sup>5,20</sup> Likewise, our group recently demonstrated a positive association of early energy and lipid intake with the GM component of an injury score performed on TEA scans.<sup>6</sup> Elsewhere, preterm neonates experiencing postnatal growth restriction, potentially resulting from nutritional deficits, showed impaired cortical microstructure development.<sup>21</sup> Nevertheless, GM and WM maturation are intertwined,<sup>1,22</sup> and the association between nutrition and WM development in the current work was consistent with these previous findings and with a study revealing lower WM mean diffusivity in 14 infants exposed to an enriched diet.<sup>23</sup>

In our study, lipids and energy contributed the most to the beneficial effect of nutrition, considering that lipids provided a third of total energy. Whether the impact of lipids is due to their high energy content (reducing energy deficit and sparing protein catabolism) and/or due to fatty acids provision remains to be determined. Disentangling the relative contribution of energy or lipids in enhancing maturation was limited by variable collinearity and would require further interventional trials. Nevertheless, lipids are essential for brain development and participate in neuronal membrane structure formation and myelin synthesis.<sup>5,20</sup> Among them, long-chain polyunsaturated fatty acids (LC-PUFAs), especially docosahexaenoic acid, play a central role,<sup>20,24,25</sup> as demonstrated in a recent preterm cohort with an association between levels of LC-PUFAs and rate of intraventricular hemorrhage, microstructural WM development, and neurodevelopment.<sup>26</sup> Yet protein and carbohydrate intake were significantly associated with brain



**FIGURE 4**

The graph reveals total brain growth in the population, which is divided into 4 groups by median energy intake ( $\pm 86$  kcal/kg per day) and median mechanical ventilation duration ( $\pm 0.8$  day), with 1 = low ventilation and low energy ( $n = 7$ ), 2 = low ventilation and high energy ( $n = 17$ ), 3 = high ventilation and high energy ( $n = 8$ ), and 4 = high ventilation and low energy ( $n = 17$ ).

**TABLE 3** Multivariable Linear Regression Analysis Examining the Associations of Total Energy Intake (kcal/kg per Day) and Lipid, Protein, and Carbohydrate (g/kg per Day) Intake Separately With Weight (g/kg per Day), Length, and HC (cm per Week) Growth Velocities After Adjustment to Birth GA

	Predictor Variable	Effect Size: Wt (g/kg per d) and Length and HC (cm/wk)	95% CI	<i>p</i>
Wt gain (g/kg per d)	Energy	0.039	-0.002 to 0.080	.062
	Lipids	0.173	-0.414 to 0.760	.555
	Proteins	1.684	0.744 to 2.624	.001
	Carbohydrates	0.381	0.036 to 0.725	.031
Length growth (cm per wk)	Energy	0.001	-0.003 to 0.005	.523
	Lipids	0.007	-0.048 to 0.062	.804
	Proteins	0.104	0.008 to 0.199	.034
	Carbohydrates	0.005	-0.029 to 0.040	.747
HC growth (cm per wk)	Energy	0.002	-3.6E-4 to 0.004	.098
	Lipids	0.010	-0.021 to 0.041	.520
	Proteins	0.089	0.039 to 0.140	.001
	Carbohydrates	0.016	-0.003 to 0.035	.097

metrics but not in all analyses; this may relate to less variable supply of those nutrients in our population.

Furthermore, our findings suggest a positive role for enteral feeding, particularly breast milk. Breast milk's

impact on brain development and neurodevelopment was previously reported<sup>27,28</sup> and could partly be explained by the greater amount of LC-PUFAs compared with formula.<sup>29</sup> Additionally, higher enteral intake may reflect a less severe neonatal course, which may foster earlier enteral feeding initiation with better intestinal tolerance.

### Respiratory Morbidity, Nutrition, and MR Metrics

Respiratory illness is a major risk factor for adverse neurodevelopmental outcomes, independent of GA,<sup>30</sup> and is potentially mediated through disrupted brain maturation, with detrimental effects observed on brain volumes,<sup>31-33</sup> WM tract development,<sup>34,35</sup> and cortical growth.<sup>36,37</sup> The negative impact of prolonged ventilation was confirmed in our study, in which slower brain growth was observed. However, with our findings we suggest that enhanced nutritional intake might attenuate the impact of respiratory illness on brain development.

### Nutrition and Somatic Growth Velocity

In contrast with MR measures of brain volume, somatic growth was predominantly predicted by protein intake, as previously reported.<sup>38</sup> Our findings suggest that growth parameters and MR metrics of brain size are not equivalent measurement tools. In addition to variability in the measure of HC clinically, in the context of the "encephalopathy of prematurity,"<sup>39</sup> increased size of the extra-axial spaces might artificially increase HC measures, supporting the value of measuring brain volumes themselves with MRI.

### Brain Growth and Psychomotor Outcome

In line with previous studies revealing an association of brain volumes at TEA and measures of brain



maturation with neurodevelopment during childhood,<sup>40–42</sup> we demonstrated that brain growth over the preterm period predicted psychomotor outcome at 18 months' CA, suggesting that brain growth may serve as an intermediary between early nutrition and neurodevelopment. Relationships with cognitive outcome were not observed, pointing out the need for longer-term assessment to detect differences in domains more robustly assessed later in childhood.

### Limitations

In this observational cohort study, we cannot infer causality between nutrition and brain development. Although our sample size limited the number of variables in the regression analysis, we examined the role of prolonged ventilation, GA, and sepsis in the relationship between nutrition and brain development. However, other potential differences in clinical characteristics between higher- and lower-energy groups may exist, so we acknowledge the potential of other unmeasured confounding variables. Given a single primary hypothesis, we did not adjust *P* values for multiple comparisons. Although this approach may have inflated type I error risk, significant *P* values are low and are congruent across the different stages of analysis. This consistency of findings across outcome measures further supports our conclusions. Additionally, measurement of breast milk composition was not available. Instead, the nutrient content of breast milk was estimated according to recent guidelines.<sup>16</sup> We acknowledge the potential imprecision of this approach, which may not exclude that the beneficial effect of nutrition was related to breast milk provision rather

than a specific nutrient. However, increasing random variability of our measure should have biased our analyses toward the null hypothesis and should not account for the significant findings detected. Actual nutritional support in the cohort remained lower than the international guidelines' requirements, despite the upgrade of our nutritional protocol during the study. This has been previously reported<sup>43</sup> and emphasizes the importance of optimizing nutrition and avoiding underfeeding. Future studies will aim at better defining the link between nutrition and neurodevelopment and the predictive role of neuroimaging as this cohort is being followed throughout childhood.

### CONCLUSIONS

In very preterm neonates, greater energy intake and enteral feeding (mostly with breast milk) during the first 2 weeks of life predicted more robust brain growth, particularly in the subcortical structures and the cerebellum, and accelerated WM maturation. Nutrition in the first weeks after preterm birth appears to have long-lasting effects on neurodevelopment, which may be mediated by advanced brain maturation, as suggested by the association between brain growth and psychomotor outcome at 18 months' CA. Optimizing early nutrition in preterm life warrants further attention as a potential avenue to mitigate the adverse cerebral consequences of critical illness and NICU course. Future adequately powered interventional studies are required to determine the optimal nutritional support in preterm neonates, which would

promote brain health and ultimately improve neurodevelopmental outcomes of this vulnerable population.

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### ABBREVIATIONS

BW: birth weight  
CA: corrected age  
DOL: day of life  
FA: fractional anisotropy  
GA: gestational age  
GEE: generalized estimating equation  
GM: gray matter  
HC: head circumference  
IQR: interquartile range  
kcal: kilocalorie  
LC-PUFA: long-chain polyunsaturated fatty acid  
MDI: Mental Developmental Index  
MR: magnetic resonance  
PDI: Psychomotor Developmental Index  
PMA: postmenstrual age  
TEA: term-equivalent age  
WM: white matter

the cohort and critically reviewed the manuscript; Dr Hagmann designed the MRI protocol and reviewed the manuscript; Dr Chakravarty contributed to the volume segmentation analysis in which the Multiple Automatically Generated Templates brain pipeline was used and critically reviewed the manuscript; Dr Hüppi acquired funding for the research project, contributed to data interpretation, and reviewed the manuscript; Dr Beauport collected the nutritional data and reviewed the manuscript; Dr Truttmann supervised patient enrollment and MRI acquisition, contributed to data interpretation, and reviewed and revised the manuscript; Dr Miller designed the imaging analyses, contributed to data interpretation and statistical analyses, and reviewed and revised the final manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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