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Associations between Early Life Nutrient Intakes and Brain Maturation Show Developmental Dynamics from Infancy to Toddlerhood: A Neuroimaging Observation Study

Nora Schneider [1,*], Fabio Mainardi [2], Sanja Budisavljevic [1], Maryann Rolands [3], Sean Deoni [4,5,6]

[1] *Brain Health Department, Nestlé Institute of Health Sciences, Société des Produits Nestlé SA, Vers-Chez-les-Blanc, Lausanne, Switzerland;* [2] *Applied Data Analytics Group, Nestlé Institute of Health Sciences, Société des Produits Nestlé SA, Vers-Chez-les-Blanc, Lausanne, Switzerland;* [3] *Nutrition Science Group, Nestlé Institute of Health Sciences, Société des Produits Nestlé SA, Vers-Chez-les-Blanc, Lausanne, Switzerland;* [4] *Advanced Baby Imaging Lab, Rhode Island Hospital, Providence, RI, USA;* [5] *Department of Radiology, Warren Alpert Medical School at Brown University, Providence, RI, USA;* [6] *Spinn Neuroscience, Seattle, WA, USA*

A B S T R A C T

Background: Myelin imaging has increasingly been applied to study the impact of nutrition on brain development in recent years. Although individual dynamics for nutrient intakes and myelin trajectories previously have been investigated across childhood, the longitudinal interaction between both remains unclear in typically developed children.

Objectives: The objective of this work was to explore the developmental dynamics of nutrient-myelin interactions from infancy to early childhood using myelin imaging as a marker for brain maturation.

Methods: Brain neuroimaging (1 scan per child) and dietary nutrient intake data were analyzed for 88 nutrients from 293 children (127 female, 62% White) from a longitudinal cohort study in the United States. A sliding window approach was used to investigate correlations between nutrient intakes and brain myelination over a continuous set of age windows. Image processing techniques (Sobel-filter vertical edge detection) were applied to determine age windows with unique association profiles, providing novel insight into how these relationships change with child age.

Results: We identified 3 nutrient-myelin windows covering the age range of 1–5 y: window 1 from 6 to 20 mo with 60% positive nutrient correlations, window 2 from 20 to 30 mo with 20% positive correlations, and window 3 from 30 to 60 mo with 37% positive correlations. The windows are aligned with reported myelin and white matter dynamics that change in the first 5 y from fast and steep (window 1) to continued but slower growth (window 3), with window 2 possibly representing the inflection period.

Conclusions: To our knowledge, this is the first study in typically developing children demonstrating the developmental dynamics between early life nutrient intakes and brain maturation in toddlerhood. The knowledge can be applied for identifying targeted and brain-stage–appropriate nutritional interventions for this critical stage of brain development.

Keywords: nutrition, dynamics, myelination, brain development, MRI, toddlers

Introduction

Myelin imaging is a viable noninvasive in vivo technique that has helped to map brain structural maturation in infancy and childhood revealing specific developmental dynamics. Myelination of cerebral axons begins in utero and continues into the second and third decades of life [1]. It advances particularly rapidly over the first 2 y of life following a specific posterior-to-anterior pattern and in close interplay with emerging neurobehavioral development [2–7].

Longitudinal myelin imaging studies report myelin trajectories in neurotypical infants and young children that show a steep initial increase in myelin content in the brain throughout infancy, an inflection point around 18–25 mo depending on the brain region, followed by a continuous but slower increase in myelin content throughout the remainder of childhood and

Abbreviations used: ASA-24, self-administered 24-hour dietary assessment tool; bSSFP, balanced steady-state free precession; mcDESPOT, multicomponent-driven equilibrium single pulse observation; MNI, Montreal Neurological Institute; MWF, myelin water fraction; SPGR, spoiled gradient recalled.

* Address correspondence to (). *E-mail address:* nora.schneider@rdls.nestle.com (N. Schneider).

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adolescence [5, 8–10]. Increasing evidence suggests alterations in myelin trajectories based on health and environmental factors, for example, in children with febrile seizures [11], in young adults with autism [12], and differences between formula-fed and breast-fed children [13, 14]. Differences in myelin development may be linked to developmental outcomes, as myelination has been linked to cognitive [5, 15–17] and social-emotional development in young children [18].

Understanding the dynamics of brain development in relation to influencing factors is critical for identifying and studying early life interventions, such as nutritional opportunities. Myelin imaging has increasingly been applied to study the impact of nutrition on brain development in recent years, particularly in young, preverbal children as well as in animal models of development [13, 14, 19–21]. These studies indicate the relation between nutritional factors and myelin development and suggest the modifiability of brain structural growth with nutritional modification. However, nutrient-brain interactions in development are complex. The high metabolic demand and the high degree of plasticity make early life a sensitive period for nutritional impact. The nonhomogeneous temporal and spatial development of the brain leads to the need for nutritional intervention to be concomitant with age and stage of brain development [22, 23]. However, scientific publications on brain-nutrient findings by age are still scarce for toddlers and preschool children compared with that for infants and school-aged children [24]. For the age group of 1–5 y, for example, observation and intervention studies have mostly explored the impact of nutrients on motor, cognitive, and social-emotional benefits in stunted, autistic, or nutrient-deficient populations, for example, for iron, vitamin D, vitamin B-12, folic acid, spirulina, and polyunsaturated fatty acids [25–34]. No link was made to brain developmental dynamics, nor are the data conclusive for healthy development.

The quantification and mapping of myelin development may, therefore, provide a measurable and developmentally relevant physiologic and empirical link between nutrition and cognitive-behavioral development. Limited knowledge exists of the dynamic interplay and longitudinal association between nutrients and brain growth during development, in a particular comprehensive investigation of multiple nutrients rather than individual compounds. Studies on cognitive development suggest that multinutrient approaches, including multimicronutrient interventions, can yield a positive impact on the brain and cognitive development in young children [35, 36]. To our knowledge, no study has investigated the brain-nutrient dynamics from infancy to early childhood.

The objective of this work was to identify age- and brain stage–dependent changes in nutrient-myelin associations and to describe the dynamic change in these associations from infancy to early childhood using myelin imaging as a measure for brain maturation. We hypothesized that nutrients from food intake data will show differential association patterns with myelin development based on age and brain stage.

Methods

Participants

Participants in this study were drawn from a larger longitudinal prenatal and postnatal study of child health and neurodevelopment in the United States termed RESONANCE, which is part of the environmental influences on child health outcomes program (echochildren.org). The study aimed to understand the relationships between child genomics, nutrition, and home environmental exposures on brain and cognitive development. Infants and young children were recruited between the ages of birth and 5 y, with study visits scheduled biannually from birth through 30 mo of age and annually thereafter. For this study, a single time point was selected from each child that had high-quality neuroimaging and completed dietary nutrient intake information. Informed consent was obtained from all parents and/or legal guardians, and research activities were performed as approved by the Rhode Island Hospital's ethical review board.

For inclusion in the analysis of the present study, 293 children aged between 6 mo and 5 y were selected who met the following criteria: *1*) singleton full-term (>37 wk) pregnancy; *2*) uncomplicated pregnancy (i.e., no reports of pre-eclampsia, gestational hypertension, or gestational diabetes mellitus); *3*) no reports of abnormalities on fetal ultrasound; *4*) infant 5-min appearance, pulse, grimace, activity, and respiration scores of ≥8; *5*) infant birth weight greater than 1500 g; *6*) no reported history of neurologic trauma in the child; *7*) no reported sibling or parental psychiatric history, including autism; and *8*) no reports of major depressive disorder requiring medication in the mother during pregnancy or in the 6 mo prior to becoming pregnant. In addition, children had to have a successful MRI scan and time-matched nutrition intake information for at least one 24-h period within a week of MRI. Anthropometric and demographic information is summarized in Table 1.

Myelin MRI data acquisition and processing

All MRIs were performed at 3 Tesla (Siemens Tim Trio) during natural and nonsedated sleep. We have previously described our approach to night-time pediatric imaging [37] using noise-derated imaging sequences, sound-insulating MRI bore liners, MiniMuff ear pads, and sound-attenuating ear protectors.

To measure white matter development and myelination, multicomponent-driven equilibrium single pulse observation

TABLE 1
Anthropometric and demographic data of the children studied

	Variable	Value
Biological sex (*N*)	Male	165
	Female	128
Age (mo), mean (SD)		25.5 (4.5)
Birth weight (kg), mean (SD)		3.4 (0.5)
Birth length (cm), mean (SD)		51.3 (4.8)
Maternal education (*N*)	Professional degree	105
	College graduate	74
	Partial college	49
	High school graduate	21
	Partial high school	3
	Not reported	41
Race (*N*)	White	181
	Black or African American	36
	Asian	13
	Mixed	22
	Not reported	41
Cognitive development composite,[1] mean (SD)	MSEL ELC	101 (18)
	MSEL VDQ	99 (22)
	MSEL NVDQ	105 (18)

ELC, early learning composite; MSEL, Mullen scales of early learning; NVDQ, nonverbal developmental quotient; VDQ, verbal developmental quotient.

(mcDESPOT) of T1 and T2 relaxometry data were collected using age-optimized protocols [9] (Table 2). A consistent voxel dimension of ~1.8 × 1.8 × 1.8 mm^3 was used across the age span, with the field of view and imaging matrix adjusted depending on child age and head size. The theoretical basis for DESPOT1 and mcDESPOT has been detailed previously [38, 39] and involves the acquisition of multiflip angle T_1-weighted spoiled gradient recalled (SPGR) images (DESPOT1) as well as T_1/T_2-weighted balanced steady-state free precession (bSSFP) images at 2 differing radiofrequency (RF) phase-cycling patterns. From these data, single-component and multicomponent relaxometry measures are calculated. For multicomponent analysis, a 3-pool tissue model comprising myelin-associated, intracellular and extracellular, and cerebrospinal fluid water pools is fit to the combined SPGR and bSSFP data using an iterative stochastic region approach [40]. The field of view and matrix size were increased with child age to accommodate the growing head size but keeping the voxel size consistent. All other aspects of acquisition were kept constant across the age range.

From the acquired mcDESPOT data, the myelin water fraction (MWF) was calculated using a processing pipeline that includes linear alignment of the SPGR, IR-SPGR, and bSSFP images to account for subtle intrascan head movement [41], nonparenchyma voxel removal [42], and correction of flip angle errors and off-resonance inhomogeneities using DESPOT1-HIFI and DESPOT2-FM [43]. A 3-pool tissue model was fit to the multiangle SPGR and bSSFP data to estimate the MWF, a surrogate and noninvasive measure of myelin content [40]. The MWF images (maps) were then nonlinearly aligned to a common analysis space in approximate Montreal Neurological Institute space using a previously described multistep approach [9] that first aligns the subject's high flip angle T_1-weighted SPGR image to 1 of 14 age-specific templates and then to an overall study-specific template using nonlinear 3-dimensional deformation, advanced normalization tools [44]. The calculated transformation matrices are then applied to the quantitative MWF maps.

Nutritional data collection

Nutrient intake data were collected through the automated self-administered 24-h dietary assessment tool (ASA-24) [45]. The mean daily nutrient intake per scan age was calculated, resulting in 293 observations of 88 nutrients. Fifty-six nutrient intakes were directly yielded from the ASA-24 output. Intake values for amino acids and phospholipids, including sphingomyelin, were retrieved from content information in the relevant USDA databases. The USDA choline database contains contents of free choline, glycerophosphocholine, phosphocholine, phosphatidylcholine, and sphingomyelin for ~630 foods. Ganglioside concentrations for meat and fish were estimated from Khor et al. [46]; for milk concentrations, we assumed 11 mg of ganglioside per liter, as suggested by Vesper et al. [47]. The oligosaccharides 3'SL and 6'SL are found only in milk products; values of 114 mg/100g and 23 mg/100g were used for their respective concentrations in cow's milk [48]. For the estimation of oligofructose content, we based our calculations on the study by Moshfegh et al. [49]. We then mapped the foods reported in ASA-24 to the corresponding items in the USDA database and calculated the daily totals. These nutrient contents and concentration values were included in addition to the ASA-24 calculated intake levels to have a comprehensive assessment of dietary intakes.

Brain-nutrient associations across windows

With the MWF maps in standard space, regional mean values were calculated across the brain in each child. The combined data from all 293 children were used to identify dynamics and window size and to perform a series of MWF-nutrient correlations using a sliding window approach. For each nutrient of interest and each brain region, we set a window size of 25 myelin imaging measurements corresponding to a step size of 72–162 d and fit the following general linear model to the data:

$$\mathrm{MWF}_{i,j} = \beta_{0,j} + \beta_1 \log(\mathrm{age}_{i,j}) + \beta_2 \mathrm{NutrientIntake}_{i,j} + \beta_3 \mathrm{NutrientIntake}_{i,j} \times \log(\mathrm{age}_{i,j}) \quad [1].$$

TABLE 2
Age-optimized imaging protocols for qT_1, qT_2, and myelin water fraction imaging

Sequence	Parameter	Scanning Age				
		3–9 mo	9–16 mo	16–28 mo	28–48 mo	>48 mo
SPGR	Field of view (cm)	14 × 14 × 13	17 × 17 × 14.4	18 × 18 × 15	20 × 20 × 15	20 × 20 × 15
	TE/TR (ms)	5.8/12	5.9/12	5.4/12	5.2/11	4.2/8
	Flip angles (degrees)	2, 3, 4, 5, 7, 9, 11, 14	2, 3, 4, 5, 7, 9, 11, 14	2, 3, 4, 5, 7, 9, 11, 14	2, 3, 4, 5, 7, 9, 12, 16	3, 4, 5, 6, 7, 9, 13, 18
	Bandwidth (Hz/pixel)	350				
	Image matrix	80 × 80 × 72	96 × 96 × 80	104 × 104 × 84	112 × 112 × 84	112 × 112 × 84
IR-SPGR	TI/TE/TR (ms)	(600, 950)/5.8/12	(600, 900)/5.9/12	(500, 850)/5.4/12	(500, 800)/5.2/11	(450, 750)/4.8/10
	Flip angle (degrees)	5				
	Image matrix	80 × 80 × 36	96 × 96 × 40	108 × 104 × 42	112 × 112 × 42	112 × 112 × 42
bSSFP	TE/TR (ms)	5/10	5.1/10.2	5/10	4.4/9.8	3.6/7.2
	Flip angles (degrees)	9, 14, 20, 27, 34, 41, 56, 70				
	Bandwidth (Hz/pixel)	350				
	Image matrix	80 × 80 × 72	96 × 96 × 80	104 × 104 × 84	112 × 112 × 84	112 × 112 × 84
High-resolution IR-SPGR	Field of view (cm)	20 × 20 × 15				
	TI/TE/TR (ms)	950 ms/6.9 ms/16 ms				
	Flip angle (degrees)	5				
	Reconstructed image matrix	224 × 224 × 150				

bSSFP, balanced steady-state free precession; IR, inversion recovery; SPGR, spoiled gradient recalled; TE, echo time; TI, inversion time; TR, repetition time.

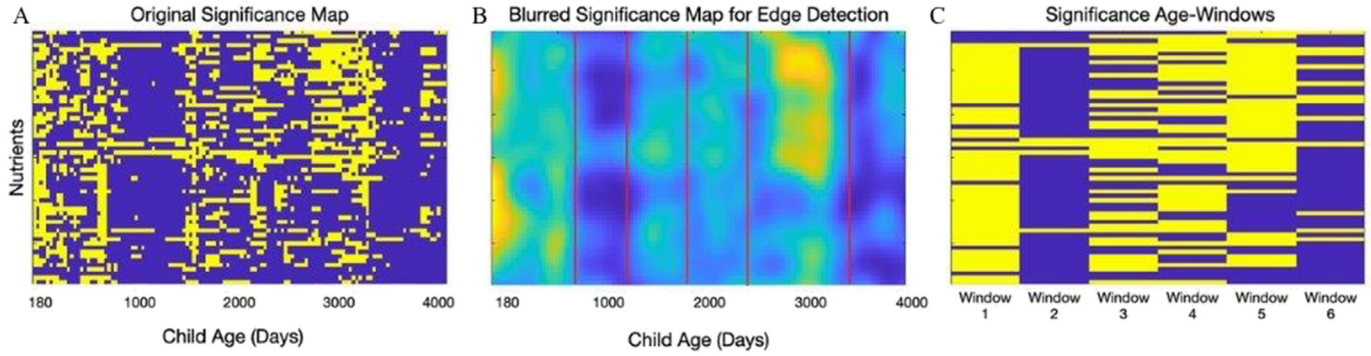

FIGURE 1. Associations for nutrient intakes and brain myelination in the children studied. Child age (x axis) and nutrient (y axis) *P* value map based on the sliding window analyses for original significance map (A), blurred significance map for edge detection (B), and summarized into main age windows (C). Yellow represents statistically significant *P* values; blue indicates nonsignificant values.

In our model, MWFi,j is the mean regional MWF estimate in child j at time point i; $age_{i,j}$ is the corresponding child age at the time point; and βo, β_1, β_2, and β_3 are the regression coefficients. Once our general linear model was fit for all age-nutrient-brain myelin combinations, we then plotted the resultant *P* value "map" (unadjusted $P < 0.05$) associated with the β_2 nutrient intake term, with the age-wise *P* values along the x axis and nutrients along the y axis. We focused on the direct nutrient

TABLE 3
Nutrient-myelin associations by age[1] for the children studied

Nutrients	Window 1 ($N = 56$)	Window 2 ($N = 20$)	Window 3 ($N = 35$)
Macronutrients	Carbohydrate, protein, dietary fiber, total fat	Carbohydrate	Carbohydrate, protein
Micronutrients (vitamins)	Vitamin E as α-tocopherol, folic acid[2], folate[3], food folate[4], niacin, retinol, β-cryptoxanthin, vitamin A, thiamine, vitamin B-12, riboflavin, vitamin B-6, vitamin C, vitamin D, vitamin K, choline	—	Retinol, vitamin C, choline
Micronutrients (minerals)	Calcium, iron, magnesium, phosphorus, potassium, selenium, zinc	—	—
Other compounds	Gangliosides, oligofructose, sphingomyelin, lycopene, theobromine, cholesterol	Sphingomyelin	Gangliosides, oligofructose, sphingomyelin
Fatty acids	Hexadecenoic (palmitoleic, 16:1), octadecenoic (Oleic, 18:1), docosenoic (erucic, 22:1), total monounsaturated fatty acids, octadecadienoic (linoleic, 18:2), octadecatrienoic (α-linolenic acid, 18:3), eicosatetraenoic (eta, 20:4), docosapentaenoic (DPA, 22:5), docosahexaenoic (DHA, 22:6), Total polyunsaturated fatty acids, butanoic acid (4:0), hexanoic acid (6:0), octanoic acid (8:0), decanoic acid (10:0), dodecanoic acid (12:0), tetradecanoic (14:0), hexadecanoic (16:0), octadecanoic (18:0), total saturated fatty acids	Eicosatetraenoic (ETA, 20:4), docosapentaenoic (DPA, 22:5)	Hexadecenoic (palmitoleic, 16:1), eicosenoic (20:1), octadecatetraenoic (18:4), eicosatetraenoic (ETA, 20:4), eicosapentaenoic (EPA, 20:5), docosapentaenoic (DPA, 22:5), docosahexaenoic (DHA, 22:6), total polyunsaturated fatty acids
Phospholipids	Phosphatidylcholine, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine	Phosphatidylcholine, phosphatidylinositol	Phosphatidylcholine, phosphatidylinositol, phosphatidylserine, phosphatidylethanolamine
Amino acids	—	Alanine, aspartic acid, cysteine, glutamic acid, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, tyrosine, valine	Alanine, aspartic acid, cysteine, glutamic acid, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine, valine

[1] Age window 1 from 6 to 20 mo, window 2 from 20 to 30 mo, and window 3 from 30 to 60 mo.
[2] Folic acid is the fully oxidized monoglutamate form of the vitamin that is used in fortified foods and most dietary supplements.
[3] Folate is the generic term for naturally occurring food folates and folates in dietary supplements and fortified foods, including folic acid.
[4] Food folates naturally occur in food and are in the tetrahydrofolate form and usually have additional glutamate residues, making them polyglutamates.

TABLE 4
Nutrient intake patterns[1] for the children studied

Nutrients	Window 1 6–20 mo	Window 2 20–30 mo	Window 3 30–60 mo
Macronutrients: Total Fat, Others: Oligofructose, Phosphatidylinositol, Total Phospholipids Micronutrients (minerals): Iron, Micronutrients (vitamins): Niacin, Vitamin B-6, Folate, folic acid, Vitamin A, β-carotene, α-carotene, Vitamin Dü Fatty acids: Butanoic acid (4:0), Octanoic acid (8:0), Decanoic acid (10:0), Dodecanoic acid (12:0), Palmitoleic acid (16:1), Gondoic acid (20:1), Erucic acid (22:1), Stearidonic acid (18:4), Eicosapentaenoic acid [EPA] Amino acids: Threonine, Leucine, Lysine, Methionine, Cystine, Phenylalanine, Valine, Arginine, histidine, Glutamic Acid, Glycine	−→	−→	−→
Macronutrients: Energy, Protein, Others: α-lactalbumin, Gangliosides, Phosphatidylserine Micronutrients (minerals): Calcium, Zinc, Copper Micronutrients (vitamins): Vitamin B-12 Fatty acids: Saturated Fat, Hexadecanoic acid (16:0), Octadecanoic acid (18:0), Octadecenoic acid (18:1) Amino acids: Isoleucine, Tyrosine, Alanine, Aspartic acid, Proline, Serine	↑	−→	−→
Fatty acids: Arachidonic acid (20:4)	↓	−→	−→
Macronutrients: Moisture, Fiber Micronutrients (minerals): Potassium, Micronutrients (vitamins): α-tocopherol, Others: Lycopene, Cholesterol	−→	↓	−→
Fatty acids: Polyunsaturated Fat, Linolelaidic acid (18:2), γ-Linolenic acid 18:3), Docosapentaenoic acid (22:5) Others: Phosphatidylethanolamine	−→	−→	↑
Fatty acids: Monounsaturated Fat, Amino acids: Tryptophan	−→	−→	↓
Micronutrients (vitamins): Vitamin K	↑	↓	↑
Others: Choline	↑	↑	↓
Micronutrients (minerals): Phosphorus, Others: Sphingomyelin, Phosphatidylcholine	↑	−→	↑
Macronutrients: Carbohydrate Micronutrients: Vitamin C, Others: Oligosaccharide 6'SL Fatty acids: Hexanoic acid (6 :0), Tetradecanoic acid (14:0)	↑	−→	↓
Micronutrients (minerals): Magnesium, Selenium, Micronutrients (vitamins): Vitamin B-1, Vitamin B-2, Cryptoxanthin	↑	↓	−→
Micronutrients (minerals): Sodium	−→	↓	↑
Fatty acids: Docosahexaenoic acid [DHA]	↓	−→	↑
Others: Oligosaccharide 3'SL	↑	↓	↓

[1] The pattern indicates the direction of intake changes within the age window, that is, decreasing (↓), stable (−), or increasing (↑) intake for each nutrient.

intake term since the sliding window approach provided information on the relationship with age.

Finally, we used Sobel-filter vertical edge detection with a threshold of 25 to identify age windows with differing patterns of nutrient associations. Nutrients per window were selected on the basis of a threshold of 50% of significance for positive associations in each window (i.e., within the age window, they had an unadjusted P value of <0.05 for at least half the age points).

Potential confounders, such as gender, socioeconomic status, and maternal education were not included in any of the models, as gender and maternal education were not found to be significantly associated with MWF (data not shown).

Nutrient intake dynamics per nutrient-myelin window

The samples were split after window identification according to the following age windows: [6, 20] mo, [20, 30] mo, and [30, 60] mo. For each nutrient, and within each window, a linear model was fit to the data, with the nutrient intake as a response and the scan age as an independent variable. An increasing trend was defined as a positive and a decreasing trend as a negative slope in the linear model, with a P value of <0.05. A nonsignificant slope was considered a "stable trend." In addition, a linear model was fit to the data for all ages, for each nutrient. In this analysis, the P values were not adjusted, as the objective was to describe the age trend of each nutrient intake, within and between windows, and emphasize the nonlinearity of these trends.

Association of myelin with nutrient intakes across windows

A linear model, such as [1], was fitted to the data set, all ages included, for each nutrient. Linear models with significant and positive coefficients for the nutrient intake terms were considered indicative of a linear positive correlation with myelin. The MWF was Box-Cox transformed to make it more symmetric. In addition, to account for possibly nonlinear associations and for correlations between the nutrients, we performed a regression model using a random forest algorithm [50] and used a feature selection algorithm [51] for finding all relevant variables. We used random forests because of their robustness to collinearity

TABLE 5
Nutrientintake ranges and medians for nutrient intakes per age window for the children studied

Nutrients	Window 1 nutrient intake ($N = 56$) (6–20 mo)			Window 2 nutrient intake ($N = 20$) (20–30 mo)			Window 3 nutrient intake ($N = 35$) (30–60 mo)			Dietary reference intakes or adequate intake		
	min	max	median	min	max	median	min	max	median	EAR	AI	UL
Macronutrients												
Carbohydrates (g/d) [4]	25.9	255	133	71.9	287	178	3.1	296	156	100[2]	95[1]	—
Protein (g/d) [4]	1	108	37.2	—	—	—	0.5	82	45.1	—	—	—
Total fat (g/d) [4]	8.8	81.3	35.3	—	—	—	—	—	—	—	30[1]	—
Dietary Fiber (g/d) [4]	0.3	22.7	7.8	—	—	—	—	—	—	—	19[3]	—
Micronutrients (vitamins)												
Vitamin E α- tocopherol (mg/d) [5]	1.3	10.6	3.9	—	—	—	—	—	—	5[2]	5[1]	200[2]
Folic acid (μg/d)	0.9	296	97.3	—	—	—	—	—	—	—	—	—
Folate, DFE (μg/d)	20.9	805	306	—	—	—	—	—	—	120[2]	80[1]	
Food folate (μg/d)	3.5	300	132	—	—	—	—	—	—	—	—	—
Niacin (mg/d) [6]	0.2	45.9	11.9	—	—	—	—	—	—	5[2]	4[1]	—
Retinol (mg/d)	16.7	783	330	—	—	—	0	1000	342	—	—	—
β-Cryptoxanthin (mg/d)	0	644	48.2	—	—	—	—	—	—	—	—	—
Vitamin A, RAE (mg/d) [7]	30.6	2600	399	—	—	—	—	—	—	210[2]	500[1]	—
Thiamine (mg/d) [6]	0	1.7	0.8	—	—	—	—	—	—	0.4[2]	0.3[1]	—
Vitamin B-12 (μg/d) [6]	0.1	6.2	2.2	—	—	—	—	—	—	0.7[2]	0.5[1]	—
Riboflavin (mg/d) [6]	0.3	2.6	1.3	—	—	—	—	—	—	0.4[2]	0.4[1]	—
Vitamin B-6 (mg/d) [6]	0.2	4	0.9	—	—	—	—	—	—	0.4[2]	0.3[1]	—
Vitamin C (mg/d) [5]	0.9	154	45.4	—	—	—	0	116	31.9	13[2]/22[3]	50[1]	400[2]/650[3]
Vitamin D (μg/d) [8]	0	11.5	3.4	—	—	—	—	—	—	10[2]	10[1]	38[1]/63[2]
Vitamin K (mg/d) [7]	0.2	443	32.9	—	—	—	—	—	—	—	2.5[1]/30[2]	—
Choline (mg/d) [7]	0	6.6	1.9	—	—	—	0	8.1	2.8	—	150[1]/ 200[2]/ 250[3]	1[2,3]
Micronutrients (minerals)												
Calcium (mg/d) [8]	76.9	1100	667	—	—	—	—	—	—	500[2]	260[1]	1500[1]/2500[2]
Iron (mg/d) [7]	0.6	23	8.2	—	—	—	—	—	—	6.9[1]/3[2]	—	40 [1,2]
Magnesium (mg/d) [8]	33.2	295	143	—	—	—	—	—	—	65[2]	75[1]	65[2]
Phosphorus (mg/d) [8]	164	1350	731	—	—	—	—	—	—	380[2]	275[1]	3000[2]
Potassium (mg/d) [9]	131	3270	1270	—	—	—	—	—	—	—	700[1]/ 3000[2]	—
Selenium (mg/d) [5]	6.2	150	51.6	—	—	—	—	—	—	17[2]	20[1]	60[1]/90[2]
Zinc (mg/d) [7]	0.2	13	6	—	—	—	—	—	—	2.5[1,2]	—	5[1]/7[2]
Other compounds												
Gangliosides (mg/d)	0	8.6	0.4	—	—	—	0.1	13	2.3	—	—	—
Oligofructose (g/d)	0	25	0.4	—	—	—	0	25.9	2.4	—	—	—
Lycopene (mg/d)	0	13.1	1.6	—	—	—	—	—	—	—	—	—
Cholesterol (mg/d)	0	404	94.6	—	—	—	—	—	—	—	—	—
Sphingomyelin (mg/d)	0	18.5	2.4	0	43.9	3.2	0.1	76.6	5.2	—	—	—
Fatty acids												
Hexadecenoic acid (Palmitoleic, 16:1) (g/d)	0	1.1	0.5	—	—	—	0	1.5	0.4	—	—	—
Eicosenoic acid (20:1) (g/d)	—	—	—	—	—	—	0	0.5	0.1	—	—	—
Octadecenoic acid (Oleic 18:1) (g/d)	1.1	23.8	12.5	—	—	—	—	—	—	—	—	—

(*continued on next page*)

TABLE 5 (*continued*)

Nutrients	Window 1 nutrient intake ($N = 56$) (6–20 mo)			Window 2 nutrient intake ($N = 20$) (20–30 mo)			Window 3 nutrient intake ($N = 35$) (30–60 mo)			Dietary reference intakes or adequate intake		
	min	max	median	min	max	median	min	max	median	EAR	AI	UL
Docosenoic Erucic 22:1) (g/d)	0	0.1	0	—	—	—	—	—	—	—	—	—
Total Monounsaturated fatty acids (g/d)	1.1	24.2	11.7	—	—	—	—	—	—	—	—	—
Octadecadienoic acid (Linoleic, 18:2) (g/d)	0.1	19.3	5.6	—	—	—	—	—	—	—	4.6[1]/7[2]/10[3]	—
Octadecatrienoic acid (α-linolenic acid 18:3) (g/d)	0.1	1.9	0.8	—	—	—	—	—	—	—	0.5[1]/0.7[2]/0.9[3]	—
Octadecatetraenoic (18:4) (g/d)	—	—	—	—	—	—	0	0.1	0	—	—	—
Eicosatetraenoic acid (ETA, 20:4) (g/d)	0	0.3	0.1	0	0.3	0.1	0	0.2	0.1	—	—	—
Eicosapentaenoic (EPA 20:5) (g/d)	—	—	—	—	—	—	0	0.1	0	—	—	—
Docosapentaenoic acid (DPA 22:5) (g/d)	0	0	0	0	0	0	0	0	0	—	—	—
Docosahexaenoic acid (DHA, 22:6) (g/d)	0	0.2	0	—	—	—	0	0.3	0	—	—	—
Total polyunsaturated fatty acids (g/d)	1.3	21.8	7	—	—	—	0.2	22.7	10.6	—	—	—
Butanoic acid (4:0) (g/d)	0	1.1	0.3	—	—	—	—	—	—	—	—	—
Hexanoic acid (6:0) (g/d)	0	0.6	0.3	—	—	—	—	—	—	—	—	—
Octanoic acid (8:0) (g/d)	0	2.2	0.2	—	—	—	—	—	—	—	—	—
Decanoic acid (10:0) (g/d)	0	1.2	0.3	—	—	—	—	—	—	—	—	—
Dodecanoic acid (12:0) (g/d)	0	5	0.6	—	—	—	—	—	—	—	—	—
Tetradecanoic acid (14:0) (g/d)	0.2	3.3	1.4	—	—	—	—	—	—	—	—	—
Hexadecanoic acid (16:0) (g/d)	0.6	16.4	6	—	—	—	—	—	—	—	—	—
Octadecanoic acid (18:0) (g/d)	0.3	8.2	2.7	—	—	—	—	—	—	—	—	—
Total Saturated fatty acids (g/d) [4]	4.2	30.8	12.7	—	—	—	—	—	—	As low as possible[1,2,3]		
Phospholipids												
Phosphatidylcholine (g/d)	0	1.2	0.1	0	3.5	0.3	0	3.2	0.4	—	—	—
Phosphatidylinositol (g/d)	0	0	0	0	0	0	0	0.2	0	—	—	—
Phosphatidylserine (g/d)	0	0.1	0	—	—	—	0	0.3	0	—	—	—
Phosphatidylethanolamine (g/d)	0	0.3	0	—	—	—	0	0.7	0.1	—	—	—
Amino acids												
Alanine (g/d)	—	—	—	0	1.4	0.5	0	1.4	0.5	—	—	—
Aspartic acid (g/d)	—	—	—	0	3.4	1.2	0	3	1.2	—	—	—
Cystine (g/d)	—	—	—	0	0.3	0.1	0	0.5	0.1	—	—	—
Glutamic acid (g/d)	—	—	—	0	8.7	3	0	8.4	2.4	—	—	—
Glycine (g/d)	—	—	—	0	1	0.3	0	1.2	0.4	—	—	—
Isoleucine (g/d)	—	—	—	0	2.1	0.5	0	1.7	0.5	—	—	—
Leucine (g/d)	—	—	—	0	3.6	0.9	0	2.9	1	—	—	—

(*continued on next page*)

TABLE 5 (*continued*)

Nutrients	Window 1 nutrient intake ($N = 56$) (6–20 mo)			Window 2 nutrient intake ($N = 20$) (20–30 mo)			Window 3 nutrient intake ($N = 35$) (30–60 mo)			Dietary reference intakes or adequate intake		
	min	max	median	min	max	median	min	max	median	EAR	AI	UL
Lysine (g/d)	—	—	—	0	2.3	0.8	0	2.3	0.7	—	—	—
Methionine (g/d)	—	—	—	0	1	0.2	0	0.8	0.2	—	—	—
Phenylalanine (g/d)	—	—	—	0	2	0.6	0	1.7	0.6	—	—	—
Proline (g/d)	—	—	—	0	4.3	1.1	0	3.3	1	—	—	—
Serine (g/d)	—	—	—	0	1.7	0.7	0	1.9	0.6	—	—	—
Threonine (g/d)	—	—	—	—	—	—	0	1.4	0.4	—	—	—
Tyrosine (g/d)	—	—	—	0	2	0.5	0	1.6	0.5	—	—	—
Valine (g/d)	—	—	—	0	2.6	0.6	0	2	0.7	—	—	—

AI, adequate intake; DFE, dietary folate equivalent; EAR, estimated average requirement; RAE, retinol activity equivalent; UL, tolerable upper intake level.

[1] Recommendations for children aged 7–11 mo.

[2] Recommendations for children aged 1–3 y.

[3] Recommendations for children aged 4–8 y.

[4] All macronutrient Dietary Recommended Intakes are from Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids [54].

[5] Dietary Recommended Intakes are from Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids [55].

[6] Dietary Recommended Intakes are from Dietary reference intakes for thiamine, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, pantothenic acid, biotin, and choline [56].

[7] Dietary Recommended Intakes are from Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc [57].

[8] Dietary Recommended Intakes are from Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride [58].

[9] Dietary Recommended Intakes are from Dietary reference intakes for water, potassium, sodium, chloride, and sulfate [59].

between the predictor variables [52]. They are well-suited to model nonlinear relationships between the outcome and the predictors and are known to deal well with modest sample sizes and high-dimensional feature spaces while being statistically consistent [53].

Results

Brain-nutrient associations (nutrient-myelin windows)

The majority of nutrients assessed (60%) were positively associated with brain maturation over the early developmental period from 6 to 20 mo of age (window 1); then, a period of relative stability, during which only one-fifth of nutrients (20%) had a significant association with brain myelination (20–30 mo, window 2); and, finally, a refractive period of growth during which the 37% of nutrients were positively associated with brain development (30–60 mo, window 3). We note that in all cases, the associations were positive, that is, higher nutrient intakes associated with higher measures of brain myelin. This likely reflects the study samples, which are healthy, neuro-typically developing children living in a high-resource area of the United States. Figure 1 displays the nutrient versus age *P* value map calculated from our sliding window analysis and summarized into our main age windows. The analysis was initially performed on the full sample up to 12 y of age until the windows were identified that cover the target age range from 1 to 5 y. Lastly, we observed differences in nutrient-myelin dynamics across age windows, for example, amino acids were positively associated with myelin at later ages only (windows 2 and 3), unlike minerals (window 1) or vitamins (windows 1 and 3, but not window 2), see Table 3.

Nutrient intake dynamics for nutrients per window

The pattern of dietary nutrient intake variation per window is displayed in Table 4 for each investigated nutrient. Nutrient intake ranges and medians are summarized in Table 5 [54–59].

Five nutrients were identified with a positive and significant association with myelin according to the linear model (Table 6). The variables selected by the random forest model and sorted by mean importance for nutrients across ages were as follows: logAge; gangliosides (mg/d); sphingomyelin (mg/d); 18:2, octadecadienoic acid (g/d); 22:6 *n*-3, docosahexaenoic acid (g/d); phosphatidylcholine (g/d); phosphatidylinositol (g/d); 20:4, eicosatetraenoic acid (g/d); fatty acids, total saturated (g/d); 3'-SL (mg/d); phosphorus (mg/d); fatty acids, total polyunsaturated (g/d); food folate (μg/d); isoleucine (g/d); methionine (g/d); total fat (g/d); total phospholipids (g/d); carotene, β (μg/d); serine (g/d); calcium (mg/d); and phosphatidylserine (g/d).

Figure 2 compares the values of the transformed MWF with the values predicted by the random forest on a test set. The Pearson correlation between predictions and original values is 0.88 (95% CI: 0.81, 0.92), indicating that the model predicts myelin values appropriately.

Discussion

To our knowledge, this is the first longitudinal association study describing nutrient-myelin windows and their dynamics in

TABLE 6
Nutrient intakes across ages in the children studied with a positive and significant myelin association

Nutrient	Term	Estimate	Standard error	*P* value
Lysine	(Intercept)	−0.168	0.012	<0.001
	nutIntake	0.033	0.017	0.048
	logAge	0.036	0.002	<0.001
	nutIntake × logAge	−0.005	0.002	0.049
3'SL	(Intercept)	−0.168	0.008	0.000
	nutIntake	0.002	0.000	<0.001
	logAge	0.036	0.001	<0.001
	nutIntake × logAge	0.000	0.000	<0.001
6'SL	(Intercept)	−0.168	0.008	0.000
	nutIntake	0.009	0.002	<0.001
	logAge	0.036	0.001	<0.001
	nutIntake × logAge	−0.001	0.000	<0.001
Oligofructose	(Intercept)	−0.156	0.008	<0.001
	nutIntake	0.004	0.002	0.039
	logAge	0.034	0.001	<0.001
	nutIntake × logAge	−0.001	0.000	0.043
α-Lactalbumin	(Intercept)	−0.166	0.010	0.000
	nutIntake	0.097	0.040	0.015
	logAge	0.036	0.001	<0.001
	nutIntake × logAge	−0.014	0.006	0.016

well-nourished young children applying myelin imaging to identifying windows of sensitivity for brain stage–related nutrients. Although 4 of the evaluated nutrients were significantly associated with myelin development at all age windows up to 5 y, most nutrients followed a dynamic association pattern over time. We identified 3 nutrient-myelin windows across the age range of 6–60 mo that follow previously defined brain development dynamics of a steep increase in myelin in the first 1.5 postnatal years, followed by a transition to slower growth around 2 y of age and then continued slower myelin increase at 3–5 y [8, 60, 61].

Relations between brain growth and emerging skills or behaviors [5, 15–18, 62–64] as well as between brain growth and influencing factors [13, 14, 65, 66] have been well described. The dynamic relations between nutrition, brain, and cognitive development have been highlighted by Georgieff et al. [22, 23]. Our findings add to these ideas by supporting new hypotheses and observational data for age and brain-stage–appropriate nutritional opportunities, in alignment with the dynamic needs of the developing brain. Timing is critical for both nutritional deficiencies as well as effective support and nutritional intervention during development [67–70]. Understanding sensitive periods for the specific link between nutrients and brain development are foundational for developing effective nutritional solutions and credible recommendations for brain nutrients. Interestingly, all classes of nutrients showed dynamic patterns and sensitive windows. Micronutrients and fatty acids appear particularly relevant in the first 1.5 y of life during the time of steep myelin increase, whereas both nutrient classes phase out during the brain development window of myelin rate change; fatty acids phase back in after 2.5 y of age when myelin increase continues at a slower rate. This may indicate the relevance of fatty acids in myelin accumulation. The formation of the myelin sheath requires high levels of fatty acid and lipid synthesis as well as the uptake of extracellular fatty acids [71]. Preclinical studies suggest a diet deficient in essential fatty acids during development causes hypomyelination [72] and dietary fatty acids are important in central nervous system myelinogenesis [73]. In contrast, amino acids gain importance in toddlerhood in our study when the myelin spurt slows down and transitions to slower continued growth. Amino acids may be more indirectly relevant for developmental myelination. Amino acid abnormalities have been linked to disturbed

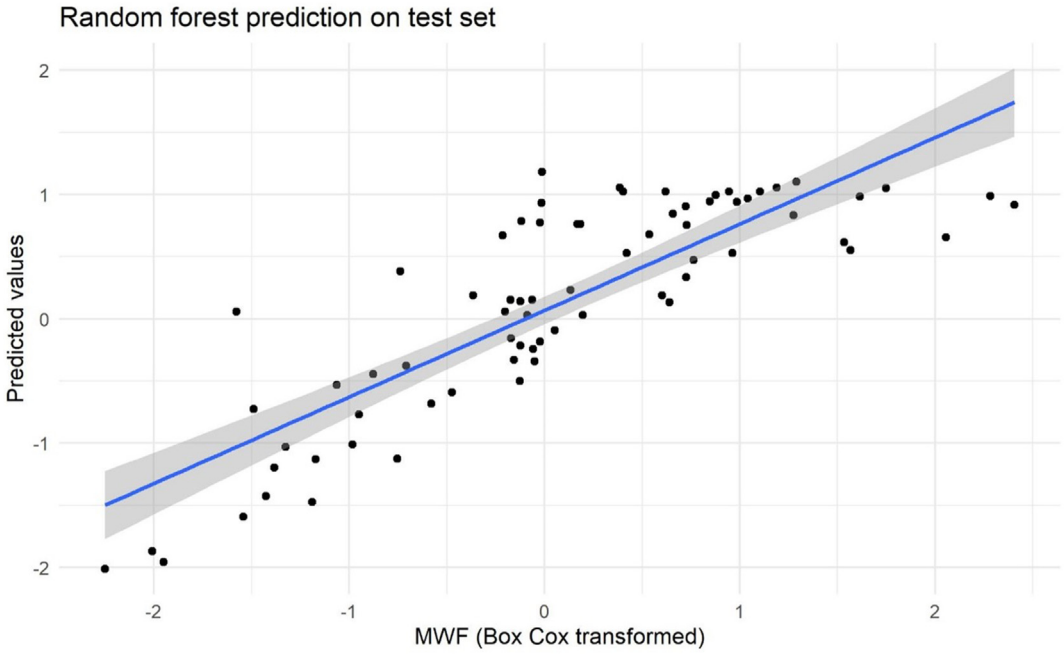

FIGURE 2. Random forest prediction on the test set for nutrient intakes across ages. Actual myelin water fraction (MWF) versus predicted values for the tested random forest model.

protein synthesis, which may affect myelin synthesis [74]. Dietary essential amino acids such as tryptophan and tyrosine may play a role in neurodevelopment, including motor and sensory functions [75]. A study in 2- to 5-y-old Japanese children suggested that ingestion of >800-mg tyrosine or phenylalanine at breakfast results in higher mental health scores than in children who ingested less than 800 mg [76]. The branched-chain amino acids, leucine, isoleucine, and valine, can also influence brain function [77] but have not been investigated yet further for their impact on developmental myelination in normal development.

Of the 52 nutrients significantly associated with myelin development in age window 1, 23 nutrients have dietary intake recommendations for the United States that were met by most of the explored nutrients (18 nutrients). The nutrients that did not meet the recommendations for children aged 6–20 mo were dietary fiber, vitamin E, vitamin D, vitamin A, and choline (Table 5). This is in line with previously reported consumption below dietary recommendations for dietary fiber, vitamin E, and vitamin D among US children aged 12–23.9 mo [78]. For age window 2, only carbohydrates have dietary recommendations (of the 18 nutrient associations) that were met in the study population. In age window 3, of the 33 nutrients associated with myelin, 6 nutrients have dietary recommendations. Nutrient intakes were met in the study population, except for choline and α-linolenic acid. The observed correlations in our study, indicating higher levels of specific nutrients to be associated with higher levels of myelin, must therefore be interpreted taking observed intake ranges as well as nutritional adequacy into account.

For children aged 6–20 mo (window 1), a predominant contribution to higher myelin levels came from fatty acids and micronutrients (vitamins and minerals). In contrast, for children aged 20–30 mo (window 2), mostly amino acids contributed to myelination; for children aged 30–60 mo (window 3), mixed contributions from both fatty acids and amino acids were identified. In addition, age-adjusted models exploring nutrient-myelin associations across age windows suggest the oligosaccharides 3'SL and 6'SL, lysine, α-lactalbumin, and oligofructose to be linked with higher myelin levels. Little is known about the role of these nutrients in developmental myelination. However, 6′SL has been recently shown to impact myelination in a preclinical study, potentially via a reduction in sialylated binding targets for the myelin-associated glycoprotein [79].

Strengths of the study include the sample size with combined nutritional intake and brain imaging data. Furthermore, the longitudinal cohort study design allows for longitudinal associations with more relevance for development than cross-sectional explorations alone. The myelin imaging measure has been previously used in nutrition studies that facilitates the interpretation of the findings. To our knowledge, this is the first analysis of nutrient-myelin associations in relation to age in healthy development.

Limitations of our work include the limitation to a US population. Nutritional intakes vary across geographies; therefore, generalization of the findings to other populations is limited unless intake values are comparable. The novel approach to brain-nutrient dynamics is limited to myelination as a relevant and measurable brain development process. Other markers or behavioral end points were not included in the study and would need further exploration. Future investigations should explore potential interactions or synergistic effects between nutrients on the developing brain.

In conclusion, nutrient-brain development associations are dynamic across child development and suggest the need for age- and brain-stage–appropriate nutritional needs. Although nutrient recommendations are typically targeted at overall health and development, very limited longitudinal data exist for brain benefits during development. The approach described here may provide new insights into nutritional opportunities and their dynamic windows of sensitivity across early life development. Myelin imaging has shown to be an important enabler in fostering the understanding of nutrient-brain interactions.

Author disclosures

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Data Availability

Data described in the manuscript and analytic code will be made available upon request pending application and approval.

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