



OPEN ACCESS

EDITED BY

Patrick Noël Pallier,
Queen Mary University of London,
United Kingdom

REVIEWED BY

Domenico Umberto De Rose,
Bambino Gesù Children's Hospital (IRCCS),
Italy
Arista Nienaber,
North-West University, South Africa
Giuseppe De Bernardo,
Ospedale Buon Consiglio Fatebenefratelli,
Italy
Andreas Repa,
Medical University of Vienna, Austria

*CORRESPONDENCE

Andrea Calandrino
✉ andrea.calandrino@edu.unige.it

RECEIVED 11 October 2025

REVISED 14 December 2025

ACCEPTED 19 January 2026

PUBLISHED 04 February 2026

CITATION

Caruggi S, Calandrino A, Corradi B,
Battaglini M, Massirio P, Vinci F, Mongelli F,
Pepe A, Parodi A, Malova M, Zoia A,
Severino M, Resaz M, Rossi A and
Ramenghi LA (2026) Do different lipid
emulsions affect brain development? A
single-center retrospective analysis.
Front. Nutr. 13:1723062.
doi: 10.3389/fnut.2026.1723062

COPYRIGHT

© 2026 Caruggi, Calandrino, Corradi,
Battaglini, Massirio, Vinci, Mongelli, Pepe,
Parodi, Malova, Zoia, Severino, Resaz, Rossi
and Ramenghi. This is an open-access article
distributed under the terms of the [Creative
Commons Attribution License \(CC BY\)](#). The
use, distribution or reproduction in other
forums is permitted, provided the original
author(s) and the copyright owner(s) are
credited and that the original publication in
this journal is cited, in accordance with
accepted academic practice. No use,
distribution or reproduction is permitted
which does not comply with these terms.

Do different lipid emulsions affect brain development? A single-center retrospective analysis

Samuele Caruggi¹, Andrea Calandrino^{1*}, Benedetta Corradi²,
Marcella Battaglini¹, Paolo Massirio¹, Francesco Vinci¹,
Federica Mongelli¹, Alessia Pepe², Alessandro Parodi¹,
Mariya Malova¹, Agata Zoia², Mariasavina Severino³,
Martina Resaz³, Andrea Rossi^{3,4} and Luca Antonio Ramenghi^{1,2}

¹Neonatal Intensive Care Unit, Department of Maternal and Neonatal Health, IRCCS Istituto Giannina Gaslini, Genoa, Italy, ²Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Mother/Child Sciences (DINOGLI), University of Genoa, Genoa, Italy, ³Neuroradiology Unit, Department of Services, IRCCS Istituto Giannina Gaslini, Genoa, Italy, ⁴Department of Health Sciences (DISSAL), University of Genoa, Genoa, Italy

Background: Preterm birth is a critical period for brain development, as extrauterine factors can impair growth and myelination, thereby increasing the risk of neurodevelopmental impairment. Adequate nutrition and rapid weight gain are associated with better cognitive outcomes, and the choice of lipid emulsion during parenteral nutrition may influence these results. SMOFlipid®, enriched with omega-3 long-chain polyunsaturated fatty acids, could reduce inflammation and oxidative stress, potentially lowering bronchopulmonary dysplasia (BPD) risk. This study compared brain maturation at term-equivalent age (TEA) using MRI and neurodevelopment at 2 years in infants receiving either SMOFlipid® or Intralipid®.

Methods: In this single-center retrospective observational cohort study, we included all very low birth weight (VLBW) infants admitted to the NICU of our institution between 2017 and 2021. Infants who underwent brain MRI at term-equivalent age and completed neurodevelopmental assessment at 2 years were included, and those with severe brain lesions were excluded. Patients were categorized into two groups based on the lipid emulsion administered during parenteral nutrition. The primary outcome was neurodevelopment at 24 months of corrected age (CA). The secondary outcome was brain maturation assessed by the total maturation score (TMS) on magnetic resonance imaging (MRI).

Results: A total of 121 VLBW infants were included and categorized into two cohorts based on the lipid formulation administered: multi-component lipid emulsion (MLE) in 62 and soybean lipid emulsion (SLE) in 49 infants. TMS showed non-statistically significant differences among infants treated with SLE compared with those treated with MLE, as well as in neurodevelopmental outcomes assessed using Griffith's scales.

Conclusion: Despite integrating brain imaging and clinical follow-up data, this study could not determine the optimal lipid emulsion for preterm infants.

KEYWORDS

lipid emulsions, MRI, neurodevelopment, parenteral nutrition, preterm

1 Introduction

Preterm infants are born during a critical period of brain development, making them particularly vulnerable to brain injury. Diffuse white matter injury (WMI) is currently recognized as the most common lesion associated with subsequent neurodevelopmental impairment (1–3).

The hallmark neuropathological feature of diffuse WMI is oligodendroglial lineage dysmaturation, mediated by oxidative stress that blocks oligodendrocyte progenitor cell maturation and myelination (1, 4, 5).

Although emerging research suggests a potential protective role of specific antioxidants—administered either *in vitro* or through the maternal diet—no clinical treatment is currently available to counteract these conditions, and it remains unclear whether the extrauterine environment can provide stimuli comparable to those *in utero* to support normal brain maturation (6–9).

Parenteral nutrition is a cornerstone in the management of very low birth weight (VLBW) infants, due to their intestinal immaturity and limited tolerance to enteral feeding (10). Identifying the optimal composition of parenteral nutrition, especially regarding lipid emulsions, is crucial to improving long-term health and quality of life in this vulnerable population. Several studies have highlighted the importance of optimal nutrition management to ensure faster weight gain from birth to term-equivalent age, which is subsequently associated with better neurodevelopmental outcomes in children born preterm (10–14).

In VLBW infants requiring parenteral nutrition with specific nutritional requirements, very long-chain omega-3 polyunsaturated fatty acids (PUFAs) are regarded as conditionally essential, with critical roles in early brain development and anti-inflammatory effects. Because of these factors, the choice of lipid emulsion in parenteral nutrition may influence clinical outcomes in neonates (15–17).

The influence of lipid formulations in parenteral nutrition on preterm neurodevelopment remains debated (18). SMOFlipid is a lipid emulsion combining soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil (60%:30%:25%:15%), providing a balanced fatty acid profile that includes eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with added α -tocopherol for antioxidant protection. Although multicomponent lipid emulsions such as SMOFlipid® have been associated with improved brain growth (16), better white matter organization (19), and anti-inflammatory effects (20–22) compared to pure soy bean oil emulsions, evidence from randomized controlled trials (RCTs) remains limited. To date, two RCTs (17, 23) have failed to demonstrate a clear neurodevelopmental advantage of SMOFlipid® over traditional soybean-based emulsions (Intralipid®), despite early signals of benefit such as enhanced head circumference growth and accelerated brain maturation (24, 25). However, other recent evidence from large cohort studies suggests potential benefits of SMOFlipid® over other lipids emulsions. Torgalkar (26) reported that SMOFlipid® was associated with significantly lower odds of any neurodevelopmental impairment in extremely preterm infants (<29 weeks' gestation), and Chen (27) demonstrated that SMOFlipid® use was associated with a reduced prevalence of epilepsy, cerebral palsy, language delay and autism spectrum disorder at 2 and 5 years of age, particularly in VLBW infants. These findings suggest that, while biologically plausible, the

superiority of fish oil-containing emulsions for long-term neurodevelopment in preterm infants remains unproven, underscoring the need for larger, well-powered studies to confirm their potential role in optimizing neurodevelopmental outcomes.

This study aims to provide new insights into the effects of parenteral lipid emulsions on neurodevelopment in preterm infants by comparing brain morphological maturation at term-equivalent age—assessed using magnetic resonance imaging (MRI)—and neurodevelopmental outcomes at 2 years of corrected age between two different lipid emulsions: a multicomponent lipid emulsion (MLE) (SMOFlipid® 20%, Fresenius Kabi, Italy) and a soybean-based lipid emulsion (SLE) (Intralipid® 20%, Fresenius Kabi, Italy).

2 Materials and methods

Preterm infants admitted to the Neonatal Intensive Care Unit of the IRCCS Giannina Gaslini Institute in Genoa, who underwent MRI at term-equivalent age (TEA) between 2017 and 2021, received two different lipid solutions, and completed a follow-up at 2 years of corrected age (CA), were retrospectively searched and included.

The primary outcome was the evaluation of neurodevelopment outcomes at 24 months of CA.

The secondary outcome was brain maturation assessed by MRI at TEA. We retrospectively included only VLBW infants who underwent MRI at TEA and who were evaluated at 24 months of CA by an expert pediatric neurologist using the Griffiths Scales of Child Development (GMDS) (0–2 years) (28).

The exclusion criteria were major cerebral malformations, brain lesions related to prenatal infection (e.g., from cytomegalovirus); metabolic diseases; arteriovenous malformation; perinatal stroke; and severe brain injury, including grade II and III intraventricular hemorrhage (IVH) according to Papile (29), post-hemorrhagic hydrocephalus (PHVD), periventricular hemorrhagic infarction (PVHI), any grade of periventricular leukomalacia (PVL) including periventricular punctate white matter lesions and any form of cerebellar hemorrhage (CBH)—all lesions with undoubted adverse effects on follow-up. Patients lost to follow-up before 24 months of correct age evaluation were excluded, as were patients whose MRI scans were deemed insufficient for TMS analysis.

In our NICU, the type of lipid emulsion used was changed from Intralipid to SMOFlipid following an institutional decision as part of company policy. Since January 2019, our NICU switched from Intralipid® to SMOFlipid®. Consequently, all parenteral nutrition administered from that date onward contained SMOFlipid® instead of Intralipid®, as these lipid emulsions are an integral component of parenteral nutrition.

According to this, the selected patients were then categorized into two cohorts:

- 1 Patients born between 2017 and December 2018 (inclusive) who received Intralipid®, an SLE.
- 2 Patients born from January 2019 to December 2021 who received SMOFlipid®, an MLE.

For each patient, information on pregnancy, delivery, and clinical course was collected. The need and duration of invasive mechanical ventilation, surfactant administration, bronchopulmonary dysplasia

(BPD), according to NICHD 2001 (30), sepsis confirmed by blood culture or liquor culture, necrotizing enterocolitis (NEC), according to Bell (31), retinopathy of prematurity (ROP), duration of parenteral nutrition, and length of stay were assessed for every patient included.

Each VLBW infant underwent a brain MRI at TEA (between 39 and 41 weeks of CA) according to our internal protocol; MRI scans included axial T2- and T1-weighted images; 3 mm thick, T2-weighted coronal images; sagittal T1-weighted images; axial diffusion-weighted (b -value: 1,000 s/mm²); axial susceptibility weighted imaging (SWI); and diffusion tensor imaging (DTI).

The total maturation score (TMS) (32) was calculated for each patient who underwent MRI at term-equivalent age. TMS consists of four parameters obtained by MRI examination: myelination (M, 1–7 points), cortical convolutions (C, 1–6 points), germinal matrix (GM, 1–4 points), and bands of migrating glial cells (B, 1–4 points). TMS ranges from 4 to 21 points.

Brain MRI images were independently reviewed by two neonatologists, each with over 5 years of clinical experience, including specific expertise in neonatal neuroimaging and neuroradiological interpretation. The TMS was assigned according to standardized criteria, and discrepancies were resolved by consensus. The presence of posterior limb of internal capsule (PLIC) was also assessed in T1 and T2 MRI sequences and classified as usual (2 points), equivocal (1 point), and absent (0 points) (33).

After discharge from our NICU, all VLBW infants were enrolled in the anthropometric and neurodevelopmental follow-up program, which continued until they reached pre-school age. We retrospectively collected data from Griffiths Scales of Child Development (GMDS) (0–2 years) assessment performed at 24 months of correct age. GMDS yields five subscales: locomotor, personal-social, hearing and speech, eye and hand coordination, and performance. Each domain generates a standardized score, and a general developmental quotient (GDQ) is calculated by combining all subscale scores. The mean GDQ is 100 (SD ± 12), with higher scores indicating better developmental performance. Cognitive outcomes were classified as normal when GDQ was >85, borderline when GDQ ranged from 70 to 85, and delayed when GDQ was lower than 70 (28).

Statistical analyses were performed using Jamovi, an open-source statistical software based on the R language. Based on the variability observed in Gallini (17), the sample size required to detect clinically relevant differences in GDQ at 24 months of corrected age was estimated. Assuming a two-sided α of 0.05, 80% power, and equal allocation between groups, the required sample size varies according to the expected effect size: for a 5-point difference, approximately 253 infants per group (total ≈ 506) are required; for a 10-point difference, the required sample size decreases to 64 infants per group (total ≈ 128). Continuous variables were tested for normality and summarized as medians with interquartile ranges. We checked normality using the Shapiro–Wilk test and plots, but since most variables were not normally distributed, we used non-parametric methods such as the Mann–Whitney U test for analysis.

Inter-rater reliability for MRI evaluations was assessed using Cohen's kappa coefficient. Group comparisons for continuous variables were conducted using the Mann–Whitney U test, while categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. A p -value of <0.05 was considered statistically significant. To account for the increased risk of false positives due to multiple comparisons, the Benjamini–Hochberg

procedure was applied to control the false discovery rate (FDR). This approach allows for a more balanced interpretation of statistical significance, particularly in exploratory analyses involving numerous p -values.

3 Results

During the study period, 933 neonates admitted to our NICU underwent brain MRI. Of these, 298 were VLBW infants. We excluded neonates with prenatal hemorrhagic lesions, congenital malformations, or congenital infections ($n = 13$), along with 47 VLBW infants with white matter lesions (23 in the Intralipid® group and 25 in the SMOFLipid® group), 16 with cerebellar hemorrhage of any grade, and 23 with grade II and III IVH, PHVD, or PVHI, resulting in a total of 123 excluded patients. Among the remaining 199 infants, in 41 patients, the MRI performed was not considered to be of sufficient quality for accurate TMS analysis and was therefore excluded, and in 37 cases, data were incomplete or the Griffiths assessment scheduled at 24 months of corrected age was not performed.

The two cohorts were composed as follows: 59 patients born between 2017 and December 2018 (inclusive) were included in the SLE group and 62 patients born from January 2019 (inclusive) to December 2021 (inclusive) were included in MLE group.

The two-cohort comparison showed no statistically significant differences in anthropometric characteristics (birth weight and gestational age), maternal characteristics (artificial insemination, twin birth, intrauterine growth retardation, preeclampsia, placental abruption, twin-to-twin transfusion syndrome, and complete corticosteroid prophylaxis). Clinical outcomes were analyzed across the two groups (Table 1).

The incidence of BPD was higher in the Intralipid® group compared to the SMOFLipid® group (41% vs. 22.5%) but was not statistically significant after Benjamini–Hochberg correction with an adjusted p -value of 0.26. No statistically significant differences were observed in the rates of culture-proven sepsis (34.6% vs. 25.5%, adjusted $p = 0.5$), treated retinopathy of prematurity (5.1% vs. 9.2%, adjusted $p = 0.5$), or necrotizing enterocolitis (4.1% vs. 3.2%, adjusted $p = 0.87$). Similarly, the duration of parenteral nutrition (median [IQR] 17 (11) vs. 21 (14) days, adjusted $p = 0.5$) and length of hospital stay (median [IQR] 46 (16) vs. 49 (19) days, adjusted $p = 0.5$) did not differ significantly between the two groups. The incidence of germinal matrix hemorrhage was comparable between the two groups, with 6.7% in the Intralipid® group and 7.9% in the SMOFLipid® group ($p = 0.87$), indicating no statistically significant difference.

The two cohorts were then compared regarding TMS using the Griffiths scales (Table 2).

The Intralipid® group showed a higher TMS on MRI at term-equivalent age (median 13 vs. 12, adjusted $p = 0.09$), with a difference in PLIC visibility on T2-weighted sequences (median 2 vs. 1, adjusted $p = 0.07$). In contrast, no difference was found on T1-weighted sequences (adjusted $P = 0.5$). The inter-rater agreement for MRI assessments was high, with a Cohen's kappa of 0.87, reflecting almost perfect concordance between the two evaluators. At 2 years of corrected age, Griffiths III developmental scores were similar between groups across most domains: total score (92 vs. 92, $p = 0.87$), locomotor (90 vs. 92.5, $p = 0.5$), personal social (95 vs. 96, $p = 0.5$), hearing and speech (91 vs. 90, $p = 0.58$), and foundations of learning

TABLE 1 Clinical characteristics of the two cohorts.

Patients' characteristics	INTRALIPID®	SMOFLIPID®	<i>p</i> -value	Adjusted <i>p</i> -value
Number of patients	59	62		
Gestational age at birth (median, IQR, and weeks)	29.5 (3.0)	29.8 (2.8)	0.43	0.65
Birth weight (median, IQR, and grams)	1,160 g (335)	1,190 g (318)	0.52	0.75
Medically assisted reproduction	18.4%	14.5%	0.59	0.76
Twin birth	42.9%	35.5%	0.43	0.65
Intrauterine growth retardation	26.5%	27.4%	0.91	0.91
Preeclampsia	16.3%	25.8%	0.22	0.50
Placental abruption	8.2%	9.7%	0.78	0.87
Twin-to-twin transfusion syndrome	8.1%	11.3%	0.58	0.76
Bronchopulmonary dysplasia (percentage)	41.1%	22.50%	0.04	0.26
Culture-proven sepsis (percentage)	34.60%	25.50%	0.17	0.50
Treated retinopathy of prematurity (percentage)	5.10%	9.20%	0.17	0.50
Necrotizing enterocolitis (percentage)	4.10%	3.20%	0.81	0.87
Germinal matrix hemorrhage (percentage)	6.7%	7.9%	0.84	0.87
Parenteral nutrition length (median, IQR, days)	17 (10)	21 (14)	0.18	0.50
Length of stay (median, IQR, and days)	46 (16)	49 (19)	0.23	0.50

Significant *p*-values are reported in bold.

TABLE 2 MRI and Griffith's outcomes.

Patients' characteristics	INTRALIPID®	SMOFLIPID®	<i>p</i> -value	Adjusted <i>p</i> -value
Number of patients	59	62		
Age at MRI (median, IQR, and weeks)	40.3 (2.3)	39.9 (1.7)	0.18	0.50
Weight at MRI (median, IQR, and grams)	2,970 g (725)	2,870 g (700)	0.24	0.50
Z-Score weight at MRI (median)	-1.13	-1.10	0.24	0.50
Total maturation score (median and IQR)	13 (3)	12 (2)	0.007	0.09
PLIC T1 (median)	2	2	0.184	0.50
PLIC T2 (median)	2	1	0.005	0.07
Griffiths at 2 years correct age (median and IQR)				
Total score	92 (9)	92 (8)	0.71	0.87
Locomotor (A)	90 (12)	92.5 (8)	0.27	0.50
Personal social (B)	95 (9)	96 (2)	0.27	0.50
Hearing and speech (C)	91 (11)	90 (13)	0.34	0.58
Eye and hand coordination (D)	85 (16.5)	93 (12)	<0.001	0.02
Performance (E)	92 (15)	88 (12)	0.74	0.87

PLIC, posterior limb internal capsula; MRI, magnetic resonance imaging. Significant *p*-values are reported in bold.

(92 vs. 88, *p* = 0.87). A statistically significant difference was observed only in the eye and hand coordination domain, where the SMOFLipid® group had higher scores (median 93 vs. 85, adjusted *p* = 0.02).

4 Discussion

Unlike the majority of previous studies that focused solely on clinically assessed neonatal outcomes (17, 23, 34), this research incorporated a validated morphological neuroimaging assessment using TMS, aiming to provide a more comprehensive and objective evaluation of brain morphological development (35–40). When

focusing on lipids, the evaluation becomes particularly intriguing to examine the stages of myelination, as visualized on MRI.

At first glance, infants treated with Intralipid® showed higher TMS scores compared to those receiving SMOFLipid® (median 13 vs. 12); similarly, a more detailed analysis of the TMS distribution revealed slightly higher signal intensity in the PLIC on T2-weighted sequences in the Intralipid® group, but no differences were found on T1-weighted sequences, where myelination appear earlier than on T2-weighted images (41–43). PLIC plays a crucial role in routine clinical practice, as neuroradiologists often rely on its appearance to assess the normality of brain MRIs in term-equivalent neonates. Moreover, PLIC myelination may serve as a potential marker of

nutritional quality during pregnancy in the offspring (44). However, after applying Benjamini–Hochberg correction for multiple comparisons, the statistical significance was lost, suggesting that this finding may be due to chance.

Neurodevelopmental outcomes, assessed using the GMDS scale, were similar between infants who received Intralipid® and those who received SMOFLipid®, both in total score and across subscales. The only exception was Scale D (eye and hand coordination), where infants in the SMOFLipid® group achieved significantly higher scores. After applying correction for multiple testing, the statistically significant difference observed in Scale D was confirmed. This domain encompasses fine motor skills, manual dexterity, and visuoperceptual abilities, where a slight but statistically significant difference was noted.

The GMDS scores assessed at 2 years of corrected age were lower than those reported in some comparable cohorts of preterm infants (17, 23). However, in other cohorts (45, 46), GMDS scores may be broadly similar to ours, suggesting variability across studies. These differences could be influenced by unmeasured confounding factors such as parental educational level or other sociodemographic variables that were not considered. Nevertheless, the two study groups in our cohort were comparable to each other, and the similarity of their GMDS outcomes reinforces the conclusion that the type of lipid emulsion used for parenteral nutrition did not significantly influence neurodevelopmental outcomes. Compositional differences between SMOFLipid® and Intralipid® may influence brain development and clinical outcomes. The finding of a better performance in Scale D (eye and hand coordination) may be partially explained by the effects of fish oil-based emulsions on retinal maturation. Yalagala (47) observed improved retinal development in infants of mothers with DHA-rich diets, and Turner et al. (48) demonstrated enhanced retinal function in piglets fed SMOFLipid®. Although Binder et al. (25) did not find significant differences in visual evoked potentials, a trend toward faster neural conduction in the SMOFLipid® group was noted. The absence of similar findings in other studies, such as that by Gallini et al., could reflect the timing of these effects—potentially manifesting later in development—or simply chance, given the small sample sizes and the complexity of neurodevelopmental trajectories in preterm infants.

Given the known influence of omega-3 long-chain polyunsaturated fatty acids on fetal brain development, it is relevant to consider maternal dietary intake as a parallel factor. Maternal dietary supplementation with omega-3 polyunsaturated fatty acids has been shown to modulate fetal oxidative stress and inflammatory status (8), as well as brain development and maturation (44, 45, 47). Bruschi et al. (8) demonstrated that such supplementation in women at risk of preterm delivery was associated with improved redox balance and proteomic signatures associated with neurodevelopmental protection in preterm neonates. Yalagala (47) showed that maternal dietary enrichment with DHA could be a promising strategy to improve brain and retinal health in infants. Similarly, De Bernardo (46) demonstrated that the DHA content of human milk from mothers who supplement DHA during pregnancy remains consistent regardless of gestational age at delivery. However, the impact of different lipid formulations in parenteral nutrition on the neurodevelopment of preterm infants remains controversial (24, 34, 49, 50).

In a recent meta-analysis (48), SMOFLipid® offers a promising option for preterm infants compared to Intralipid®, particularly for reducing cholestasis and PDA, but no differences were found for the

prevention of several other neonatal outcomes, including growth, mortality, ROP, and BPD, confirming the findings of a recent Cochrane review (18).

Several studies have reported that the inclusion of omega-3 s may have beneficial effects on neurodevelopment in preterm infants (26, 27). A study by Ottolini et al. (19) reported that very preterm infants supported with SMOFLipid® demonstrated improved regional brain growth and evidence of enhanced white matter microstructural organization and neurobehavioral regulation at term-corrected age.

Neurodevelopmental data of our study were consistent with those of Gallini et al. (17), who found no significant differences at 24 months between infants treated with MLE and those treated with SLE. However, their study focused on anthropometric evaluation at 12 and 24 months CA, short-term neurodevelopmental outcomes at 6 and 12 months CA using the Hammersmith infant neurological examination (HINE), and long-term neurodevelopmental outcomes at 24 months CA using GMDS, while our study expands the analysis to include brain maturation at term-equivalent age using the TMS.

The two cohorts showed no statistically significant differences in anthropometric measures, maternal characteristics, or preterm complications. A particular mention should be made regarding BPD. Previous studies have suggested that different lipid formulations may modulate the pulmonary inflammatory response (22).

Regarding BPD, although the incidence appeared higher in the Intralipid® group, this difference did not reach statistical significance after Benjamini–Hochberg correction (adjusted $p = 0.26$) and is therefore unlikely to have affected neurodevelopmental results. The numerically greater percentage of BPD in the Intralipid® group can be explained by a gradual change in clinical practice during the study period, with reduced use of invasive mechanical ventilation in favor of non-invasive respiratory support—a strategy well documented to lower BPD risk. However, emerging evidence suggests that newer-generation lipid emulsions enriched with omega-3 long-chain polyunsaturated fatty acids, such as SMOFLipid®, may exert anti-inflammatory effects and reduce oxidative stress—both of which are implicated in the pathogenesis of BPD. Several studies have reported a trend toward lower BPD incidence in infants receiving fish oil-containing emulsions, potentially due to their favorable fatty acid profile and antioxidant content (21, 22).

Finally, patients with cerebellar lesions and white matter injuries of any grade were excluded, given their well-established association with adverse neurodevelopmental outcomes in preterm infants (3, 6, 7). Severe hemorrhagic lesions were also excluded, while GMH were retained. Although our recent study have suggested a potential role of low-grade GMH in influencing neurodevelopment (51), there are contrasting data on this subject (52). Moreover, in our cohort, the prevalence of GMH was similarly distributed across groups, making it an unlikely confounding factor in our analysis.

This study has several significant limitations that should be considered. First, its retrospective design inherently limits the ability to establish causal relationships, as data were collected from past records rather than through prospective observation. Additionally, being conducted at a single center may reduce the generalizability of the results to broader populations, as institutional practices, patient demographics, and regional factors may differ significantly from those in other settings. Moreover, the treatment groups were enrolled at different time periods, which could introduce bias due to changes in NICU protocols. However, during this timeframe, the only relevant

change was the pharmacological treatment for patent ductus arteriosus (PDA), which shifted from ibuprofen to paracetamol (53)—a modification not expected to influence neurodevelopment at 2 years of corrected age.

Several potential confounders could have influenced brain maturation during the 2-year follow-up, despite our efforts to minimize bias by excluding infants with major brain lesions and severe complications. Although the two groups were comparable in terms of common complications of prematurity, we lacked complete data on important sociodemographic variables such as maternal age at birth, parental educational level, and ethnic background. These factors are well recognized as potential determinants of neurodevelopment in preterm infants after discharge. Since this information was unavailable for all participants, it could not be included in our analysis and may have introduced residual confounding. Furthermore, the sample size was too small to detect clinically relevant differences of 5 points in the GDQ and was also insufficient to identify differences in TMS scores. Based on our calculations, detecting a 5-point difference in GDQ would require approximately 253 infants per group (total \approx 506), and detecting differences in TMS would require even larger samples. These limitations could result in underestimating potential associations or failing to identify clinically relevant trends. Additionally, maternal dietary data and detailed nutritional intake were not available, which could influence outcomes. These calculations suggest that future prospective trials should either focus on larger clinically meaningful differences or adopt a multicenter design to achieve adequate power.

5 Conclusion

Despite integrating brain imaging and clinical follow-up data, the retrospective nature of the study and the change in lipid emulsion use over time indicate that our findings do not allow us to determine the optimal lipid emulsion for preterm infants. This question would require prospective randomized controlled trials to be adequately addressed.

The widespread adoption of MLE by clinicians, despite limited supporting evidence, may reflect the perceived health benefits of fish and olive oil. From a nutritional perspective, soy-based lipids—central to Intralipid®—are not typically prominent in maternal diets, raising questions about their suitability for fetal brain development. Conversely, emerging evidence recommends that SMOFLipid®, enriched with omega-3 long-chain polyunsaturated fatty acids, may reduce inflammation and oxidative stress, potentially lowering brain oxidative stress and BPD risk. Both groups had a median gestational age of 29 weeks—a critical period for myelination (54)—highlighting the importance of optimizing parenteral lipid composition during this vulnerable window, when infants rely primarily on intravenous nutrition as a substitute for placental support. Further research is essential to clarify these associations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Regional Institutional Ethics Committee of Liguria, Italy. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

SC: Visualization, Formal analysis, Data curation, Methodology, Software, Writing – original draft, Conceptualization. AC: Project administration, Formal analysis, Data curation, Visualization, Methodology, Software, Conceptualization, Funding acquisition, Writing – review & editing, Investigation, Writing – original draft. BC: Methodology, Conceptualization, Writing – original draft, Formal analysis. MB: Investigation, Methodology, Conceptualization, Writing – original draft, Writing – review & editing. PM: Writing – original draft, Validation. FV: Validation, Writing – original draft, Investigation. FM: Software, Visualization, Validation, Writing – review & editing. APe: Writing – original draft, Methodology, Investigation. APa: Data curation, Methodology, Software, Writing – review & editing. MM: Writing – review & editing. AZ: Writing – review & editing. MS: Investigation, Visualization, Data curation, Writing – review & editing. MR: Writing – original draft, Visualization. AR: Supervision, Writing – review & editing. LR: Funding acquisition, Writing – review & editing, Resources, Supervision, Project administration, Validation, Conceptualization.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by the European Union - Next Generation EU, Mission 4 Component 1 CUP D93C22000930002.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that Generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated

organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Janson E, Willemsen MF, Van Beek PE, Dudink J, Van Elburg RM, ESPR Nutrition council members, et al. The influence of nutrition on white matter development in preterm infants: a scoping review. *Pediatr Res.* (2023). doi: 10.1038/s41390-023-02622-1 [Epub ahead of print].
- Pascal A, Govaert P, Oostra A, Naulaers G, Ortbuis E, Van den Broeck C. Neurodevelopmental outcome in very preterm and very-low-birthweight infants born over the past decade: a meta-analytic review. *Dev Med Child Neurol.* (2018) 60:342–55. doi: 10.1111/dmcn.13675
- Khawaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. *Arch Dis Child Fetal Neonatal Ed.* (2007) 93:F153–61. doi: 10.1136/adc.2006.108837
- Panfoli I, Candiano G, Malova M, de Angelis L, Cardiello V, Buonocore G, et al. Oxidative stress as a primary risk factor for brain damage in preterm newborns. *Front Pediatr.* (2018) 6:6. doi: 10.3389/fped.2018.00369
- Buonocore G, Perrone S, Bracci R. Free radicals and brain damage in the newborn. *Neonatology.* (2001) 79:180–6. doi: 10.1159/000047088
- Parodi A, Malova M, Cardiello V, Raffa S, Re M, Calevo MG, et al. Punctate white matter lesions of preterm infants: risk factor analysis. *Eur J Paediatr Neurol.* (2019) 23:733–9. doi: 10.1016/j.ejpn.2019.06.003
- Malova M, Morelli E, Cardiello V, Tortora D, Severino M, Calevo MG, et al. Nosological differences in the nature of punctate white matter lesions in preterm infants. *Front Neurol.* (2021) 12:12. doi: 10.3389/fneur.2021.657461
- Bruschi M, Santucci L, Petretto A, Bartolucci M, Marchisio M, Ghiggeri GM, et al. Association between maternal omega-3 polyunsaturated fatty acids supplementation and preterm delivery: a proteomic study. *FASEB J.* (2020) 34:6322–34. doi: 10.1096/fj.201900738RR
- Scacco S, Acquaviva S, França Vieira e Silva F, Zhang JH, Lo Muzio L, Corso G, et al. Bioactivity and neuroprotective effects of extra virgin olive oil in a mouse model of cerebral ischemia: an in vitro and in vivo study. *Int J Mol Sci.* (2025) 26:1771. doi: 10.3390/ijms26041771
- De Rose DU, Cota F, Gallini F, Bottoni A, Fabrizio GC, Ricci D, et al. Extra-uterine growth restriction in preterm infants: neurodevelopmental outcomes according to different definitions. *Eur J Paediatr Neurol.* (2021) 33:135–45. doi: 10.1016/j.ejpn.2021.06.004
- Zozaya C, Díaz C, de Saenz Pipaón M. How should we define postnatal growth restriction in preterm infants? *Neonatology.* (2018) 114:177–80. doi: 10.1159/000489388
- Massirio P, Battaglini M, Bonato I, de Crescenzo S, Calevo MG, Malova M, et al. Early extra-uterine growth restriction in very-low-birth-weight neonates with Normal or mildly abnormal brain MRI: effects on a 2–3-year neurodevelopmental outcome. *Nutrients.* (2024) 16:449. doi: 10.3390/nu16030449
- Cormack BE, Harding JE, Miller SP, Bloomfield FH. The influence of early nutrition on brain growth and neurodevelopment in extremely preterm babies: a narrative review. *Nutrients.* (2019) 11:2029. doi: 10.3390/nu11092029
- Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics.* (2006) 117:1253–61. doi: 10.1542/peds.2005-1368
- Deshpande GC, Cai W. Use of lipids in neonates requiring parenteral nutrition. *J Parenter Enter Nutr.* (2020) 44:S45–S54. doi: 10.1002/jpen.1759
- Costa S, Cocca C, Barone G, Catenazzi P, Gallini F, Maggio L, et al. Growth of head circumference and body length in preterm infants receiving a multicomponent vs a soybean-based lipid emulsion: a randomized controlled trial. *J Parenter Enter Nutr.* (2021) 45:94–101. doi: 10.1002/jpen.1968
- Gallini F, Pelosi MS, De Rose DU, Coppola M, Costa S, Romeo DM, et al. Neurodevelopmental outcomes in preterm infants receiving a multicomponent vs. a soybean-based lipid emulsion: 24 month follow-up of a randomized controlled trial. *Nutrients.* (2022) 15. doi: 10.3390/nu15010058
- Kapoor V, Malviya MN, Soll R. Lipid emulsions for parenterally fed preterm infants. *Cochrane Database Syst Rev.* (2018). doi: 10.1002/14651858.CD013163
- Ottolini KM, Ngwa J, Basu SK, Kapse K, Liggett M, Murnick J, et al. Brain development using a multicomponent intravenous lipid emulsion in preterm infants. *BMC Pediatr.* (2024) 24:847. doi: 10.1186/s12887-024-05330-9
- Kasirer Y, Bin-Nun A, Raveh A, Schorrs I, Mimouni FB, Hammerman C. SMOFlipid protects preterm neonates against perinatal nutrition-associated cholestasis. *Am J Perinatol.* (2019) 36:1382–6. doi: 10.1055/s-0038-1676977
- Guthrie G, Premkumar M, Burrin DG. Emerging clinical benefits of new-generation fat emulsions in preterm neonates. *Nutr Clin Pract.* (2017) 32:326–36. doi: 10.1177/0884533616687500
- Papandreou P, Gioxari A, Ntountaniotis D, Korda ON, Skouroliakou M, Siahaidou T. Administration of an intravenous fat emulsion enriched with medium-chain triglyceride/ω-3 fatty acids is beneficial towards anti-inflammatory related fatty acid profile in preterm neonates: a randomized, double-blind clinical trial. *Nutrients.* (2020) 12:3526. doi: 10.3390/nu12113526
- Thanhaeuser M, Fuiko R, Oberleitner-Leeb C, Brandstaetter S, Binder C, Thajer A, et al. A randomized trial of parenteral nutrition using a mixed lipid emulsion containing fish oil in infants of extremely low birth weight: neurodevelopmental outcome at 12 and 24 months corrected age, a secondary outcome analysis. *J Pediatr.* (2020) 226:e5:142–8. doi: 10.1016/j.jpeds.2020.06.056
- Binder C, Giordano V, Thanhaeuser M, Kreissl A, Huber-Dangl M, Longford N, et al. A mixed lipid emulsion containing fish oil and its effect on electrophysiological brain maturation in infants of extremely low birth weight: a secondary analysis of a randomized clinical trial. *J Pediatr.* (2019) 211:46–53.e2. doi: 10.1016/j.jpeds.2019.03.039
- Binder C, Schned H, Longford N, Schwindt E, Thanhaeuser M, Thajer A, et al. A mixed-lipid emulsion containing fish oil for the parenteral nutrition of preterm infants: no impact on visual neuronal conduction. *Nutrients.* (2021) 13:4241. doi: 10.3390/nu13124241
- Torgalkar R, Shah J, Dave S, Yang J, Ostad N, Kotsopoulos K, et al. Fish oil-containing multicomponent lipid emulsion vs soy-based lipid emulsion and neurodevelopmental outcomes of children born < 29 weeks' gestation. *J Perinatol.* (2020) 40:1712–8. doi: 10.1038/s41372-020-0710-5
- Chen IL, Hung CH, Huang HC. Smoflipid is better than Lipofundin for long-term neurodevelopmental outcomes in preterm infants. *Nutrients.* (2021) 13:2548. doi: 10.3390/nu13082548
- Green E, Stroud L, Bloomfield S, Cronje J, Foxcroft C, Hurter K, et al. Griffiths III: Griffiths scales of child development. 3rd ed. Florence: Hogrefe Ltd (2016).
- Leijser LM, de Vries LS. Preterm brain injury: germinal matrix–intraventricular hemorrhage and post-hemorrhagic ventricular dilatation In: Handbook of clinical neurology, Amsterdam, The Netherlands: Elsevier. vol. 162 (2019)
- Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med.* (2001) 163:1723–9. doi: 10.1164/ajrccm.163.7.2011060
- Sheikh Y, Gaillard F (2010). Necrotising enterocolitis (staging). Amsterdam, The Netherlands: Elsevier. Available online at: <https://radiopaedia.org> (Accessed June 26, 2025).
- Childs AM, Ramenghi LA, Cornette L, Tanner SF, Arthur RJ, Martinez D, et al. Cerebral maturation in premature infants: quantitative assessment using MR imaging. *AJNR Am J Neuroradiol.* (2001) 22:1577–82.
- Rutherford M, Ramenghi LA, Edwards AD, Brocklehurst P, Halliday H, Levene M, et al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic–ischaemic encephalopathy: a nested substudy of a randomised controlled trial. *Lancet Neurol.* (2010) 9:39–45. doi: 10.1016/S1474-4422(09)70295-9
- Thanhaeuser M, Steyrl D, Fuiko R, Brandstaetter S, Binder C, Thajer A, et al. A secondary outcome analysis of a randomized trial using a mixed lipid emulsion containing fish oil in infants with extremely low birth weight: cognitive and behavioral outcome at preschool age. *J Pediatr.* (2023) 254:68–74.e3. doi: 10.1016/j.jpeds.2022.10.014
- Licht DJ, Shera DM, Clancy RR, Wernovsky G, Montenegro LM, Nicolson SC, et al. Brain maturation is delayed in infants with complex congenital heart defects. *J Thorac Cardiovasc Surg.* (2009) 137:529–37. doi: 10.1016/j.jtcvs.2008.10.025
- Licht DJ, Jacobowitz M, Lynch JM, Ko T, Boorady T, Devarajan M, et al. Impaired maternal-fetal environment and risk for preoperative focal white matter injury in neonates with complex congenital heart disease. *J Am Heart Assoc.* (2023) 12. doi: 10.1161/JAHA.122.025516
- Katz JA, Levy PT, Butler SC, Sadhwani A, Lakshminrusimha S, Morton SU, et al. Preterm congenital heart disease and neurodevelopment: the importance of looking beyond the initial hospitalization. *J Perinatol.* (2023) 43:958–62. doi: 10.1038/s41372-023-01687-4
- Ramenghi LA, Fumagalli M, Righini A, Bassi L, Groppo M, Parazzini C, et al. Magnetic resonance imaging assessment of brain maturation in preterm neonates with punctate white matter lesions. *Neuroradiology.* (2007) 49:161–7. doi: 10.1007/s00234-006-0176-y

39. Ramenghi LA, Martinelli A, De Carli A, Brusati V, Mandia L, Fumagalli M, et al. Cerebral maturation in IUGR and appropriate for gestational age preterm babies. *Reprod Sci.* (2011) 18:469–75. doi: 10.1177/19337191110388847
40. Massirio P, Cardello V, Andreato C, Caruggi S, Battaglini M, Calandrino A, et al. Ventilatory support, extubation, and cerebral perfusion changes in pre-term neonates: a near infrared spectroscopy study. *Neurotrauma Rep.* (2024) 5:409–16. doi: 10.1089/neur.2023.0092
41. Welker K, Patton A. Assessment of normal myelination with magnetic resonance imaging. *Semin Neurol.* (2012) 32:015–28. doi: 10.1055/s-0032-1306382
42. Barkovich AJ, Kjos BO, Jackson DE, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Radiology.* (1988) 166:173–80. doi: 10.1148/radiology.166.1.3336675
43. Dietrich R, Bradley W, Zaragoza E, Dietrich RB, Bradley WG, Zaragoza EJ, et al. MR evaluation of early myelination patterns in normal and developmentally delayed infants. *AJR Am J Roentgenol.* (1988) 150:889–96. doi: 10.2214/ajr.150.4.889
44. Na X, Glasier CM, Andres A, Ou X. Maternal diet quality during pregnancy is associated with neonatal brain white matter development. *Nutrients.* (2023) 15:5114. doi: 10.3390/nu15245114
45. Liu Y, Zhong L, Sun Z, Feng Y, Ding Q, Zhang Y. N–3 fatty acid supplementation in mothers and infants for childhood psychomotor and cognitive development: an updated systematic review and meta-analysis. *Matern Child Nutr.* (2025) 21:e13767. doi: 10.1111/mcn.13767
46. De Bernardo G, Leone G, Izzo F, Giovengo M, Basilicata MG, Centanni F, et al. Fatty acid profiling of breast milk at different gestational ages. *Nutrients.* (2025) 17:2672. doi: 10.3390/nu17162672
47. Yalagala PCR, Sugasini D, Chantapim S, Caal K, Sun H, Nicastro S, et al. Efficient enrichment of docosahexaenoic acid (DHA) in mother's milk and in the brain and retina of the offspring by lysophosphatidylcholine (LPC)-DHA in the maternal diet. *Nutrients.* (2025) 17:1864. doi: 10.3390/nu17111864
48. He T, Huang J, Ren D, Yang S. Impact of SMOFlipid on clinical outcomes in neonates receiving parenteral nutrition: a systematic review and meta-analysis of randomized controlled trials. *Br J Hosp Med.* (2024) 48:1–20. doi: 10.12968/hmed.2024.0303
49. Skouroliakou M, Konstantinou D, Koutri K, Kakavelaki C, Stathopoulou M, Antoniadi M, et al. A double-blind, randomized clinical trial of the effect of ω -3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. *Eur J Clin Nutr.* (2010) 64:940–7. doi: 10.1038/ejcn.2010.98
50. Biagetti C, Correani A, D'Ascenzo R, Ferretti E, Proietti C, Antognoli L, et al. Is intravenous fish oil associated with the neurodevelopment of extremely low birth weight preterm infants on parenteral nutrition? *Clin Nutr.* (2021) 40:2845–50. doi: 10.1016/j.clnu.2021.02.036
51. Uccella S, Parodi A, Calevo MG, Nobili L, Tortora D, Severino M, et al. Influence of isolated low-grade intracranial haemorrhages on the neurodevelopmental outcome of infants born very low birthweight. *Dev Med Child Neurol.* (2023) 65:1366–78. doi: 10.1111/dmcn.15559
52. Reuhsaet P, Brouwer AJ, van Haastert IC, Brouwer MJ, Koopman C, Groenendaal F, et al. The impact of low-grade germinal matrix-intraventricular hemorrhage on neurodevelopmental outcome of very preterm infants. *Neonatology.* (2017) 112:203–10. doi: 10.1159/000472246
53. Caruggi S, Calandrino A, Cipresso G, Battaglini M, Massirio P, Vinci F, et al. Second attempt for patent ductus arteriosus (PDA) closure: room for acetaminophen? A retrospective single-center experience at Gaslini children's hospital. *Children.* (2025) 12:577. doi: 10.3390/children12050577
54. Van Steenwinckel J, Bokobza C, Laforge M, Shearer IK, Miron VE, Rua R, et al. Key roles of glial cells in the encephalopathy of prematurity. *Glia.* (2024) 72:475–503. doi: 10.1002/glia.24474