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

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Objective To assess whether parenteral nutrition for infants of extremely low birth weight using a mixed lipid emulsion that contains fish oil influences electrophysiological brain maturation.

Study design The study is a prespecified secondary outcome analysis of a randomized controlled trial of 230 infants of extremely low birth weight receiving a mixed (soybean oil, medium-chain triglycerides, olive oil, and fish oil; intervention) or a soybean oil–based lipid emulsion (control). The study was conducted at a single-level IV neonatal care unit (Medical University Vienna; June 2012 to October 2015). Electrophysiological brain maturation (background activity, sleep–wake cycling, and brain maturational scores) was assessed biweekly by amplitude-integrated electroencephalography (birth to discharge).

Results A total of 317 amplitude-integrated electroencephalography measurements (intervention: n = 165; control: n = 152) from 121 (intervention: n = 63; control: n = 58) of 230 infants of the core study were available for analysis. Demographic characteristics were not significantly different. By 28 weeks of postmenstrual age, infants receiving the intervention displayed significantly greater percentages of continuous background activity. Total maturational scores and individual scores for continuity, cycling, and bandwidth were significantly greater. Maximum maturational scores were reached 2 weeks earlier in the intervention group (36.4 weeks, 35.4-37.5) compared with the control group (38.4 weeks, 37.1-42.4) (median, IQR; $P < .001$).

Conclusions Using a mixed parenteral lipid emulsion that contains fish oil, we found that electrophysiological brain maturation was accelerated in infants who were preterm. *(J Pediatr 2019;211:46-53)*.

Trial Registration ClinicalTrials.gov: NCT01585935.

Infants born with extremely low birth weight (ELBW, birth weight <1000 g) are at high risk of adverse neurologic outcome.[1] Current neuroprotective strategies comprise the use of antenatal steroids, magnesium sulfate, and caffeine.[2] Optimized nutrition positively supports brain maturation and neurocognitive development of infants who are ELBW.[3,4] Omega (ω)-3 long-chain polyunsaturated fatty acids (LC-PUFAs) are important for normal brain development.[5-7] The ω-3 LC-PUFA docosahexaenoic acid (DHA) comprises 40% of total brain fatty acids and is considered a main structural and functional component.[5,6] In utero, high amounts of DHA are transferred to the fetus in the last trimester to meet the demands of rapid brain growth.[8,9] In infants born preterm, DHA supply from enteral nutrition falls short of fetal demands,[8] and their capacity to synthesize DHA from ω-3 precursor fatty acids is low.[10] Infants of ELBW are therefore at particular risk due to initially low enteral intake[10] and the absence of DHA in parenteral soybean oil–based lipid emulsions, which are currently the only approved lipid emulsions for parenteral nutrition of infants born preterm in the US.[11]

A mixed lipid emulsion composed of soybean oil, medium-chain triglycerides, olive oil, and fish oil (SMOF-LE)[12] provides DHA and its immediate precursor eicosapentaenoic acid (EPA).[13] In a recent randomized clinical trial,[12] we assigned infants of ELBW to receive either SMOF-LE or a soybean oil–based lipid

aEEG	Amplitude-integrated electroencephalography
DHA	Docosahexaenoic acid
ELBW	Extremely low birth weight
EPA	Eicosapentaenoic acid
LC-PUFA	Long-chain polyunsaturated fatty acids
PMA	Postmenstrual age
SMOF-LE	Lipid emulsion composed of soybean oil, medium chain triglycerides, olive oil and fish oil

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

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emulsion for parenteral nutrition to analyze its preventive effect against parenteral nutrition–associated cholestasis and found no difference. As yet, it is still unknown whether increasing DHA supply by parenteral nutrition using SMOF-LE affects brain maturation in these infants. In this study, we analyzed amplitude-integrated electroencephalography (aEEG) recordings of study participants. Our aim was to investigate the effect of SMOF-LE compared with a soybean oil–based lipid emulsion on electrophysiological brain maturation in infants of ELBW.

Methods

This study is a prespecified secondary outcome analysis of a double-blind randomized controlled trial[12] (ClinicalTrials.gov; NCT01585935) conducted at the Department of Pediatrics and Adolescent Medicine (Medical University of Vienna, Austria) from June 2012 to October 2015. The study design was previously described in detail,[12] and the protocol is accessible at ClinicalTrials.gov. In summary, infants of ELBW without conditions associated with cholestasis were eligible. After consent, participants were randomized and stratified (sex and birth weight <750 vs ≥750 g) within their first 5 days of life. The intervention was blinded for patients and observers, including the analysis of data in this study. Participants received a mixed lipid emulsion (SMOF-LE) composed of 30% soybean oil, 30% medium-chain triglycerides, 25% olive oil, and 15% fish oil (SMOFlipid 20%; Fresenius Kabi, Bad Homburg, Germany) or a soybean oil–based lipid emulsion (Intralipid 20%; Fresenius Kabi).[14] SMOF-LE contains (wt/wt) 2.2% DHA, 2.4% EPA, and 200 mg/L α-tocopherol, whereas the soybean oil–based lipid emulsion is devoid of DHA and EPA and contains 38 mg/L α-tocopherol.[14] Both groups received parenteral vitamins (2 mL/kg Soluvit; 4 mL/kg Vitalipid N Infant, provides 2.6 mg/kg α-tocopherol; Fresenius Kabi) until fortification of human milk feedings. Enteral nutrition was commenced using own mother's milk or human donor milk. If donor milk was used, infants were switched to preterm formula after 32 weeks of postmenstrual age (PMA). Milk feedings were fortified using a fat-free fortifier (Aptamil FMS; Milupa Nutricia GmbH, Frankfurt, Germany) when 100 mL/kg of enteral nutrition was reached. Parenteral nutrition was stopped at 140-160 mL/kg/d of enteral nutrition.

Analysis of Brain Maturation by aEEG

aEEG of study participants was recorded biweekly as part of clinical routine using a single-channel aEEG (Olympic CFM 6000; Natus Medical Incorporated, San Carlos, California).[15] For analysis of brain maturation in this study, infants with severe intraventricular hemorrhage (grade >II) and cystic periventricular leukomalacia (grade > I) were excluded post-hoc (but before analysis) due to the negative impact on aEEG activity and sleep–wake cycling.[16] Only aEEG sequences recorded without sedative or antiepileptic drugs[17] with a duration over 90 minutes and impedance below 20 kΩ were used.[18] Brain maturation was assessed by classification of background pattern and sleep–wake cycles according to Hellstrom-Westas and Rosen and calculation of maturational scores according to Burdjalov et al.[19,20] Analysis was performed by 2 independent investigators. Inter-rater agreement was assessed by the Cohen kappa. Any discordance was dissolved by discussion and consensus. For analysis of background pattern according to Hellstrom-Westas and Rosen,[19] aEEG traces were subdivided in 10-minute periods, rated as continuous, discontinuous, burst suppression, low voltage, or flat trace[19] and reported as percentage distribution. Sleep–wake cycles of individual aEEG records were classified as absent, mature, or immature.[19] Results are reported according to the PMA period (weeks + days) at assessment: 24 + 0 to 27 + 6, 28 + 0 to 29 + 6, 30 + 0 to 31 + 6, 32 + 0 to 33 + 6, 34 + 0 to 35 + 6, and 36 + 0 to 41 + 6.

Brain maturational scores according to Burdjalov et al were calculated from aEEG traces based on continuity (0-2), cycling (0-5), lower border amplitude (0-2), and bandwidth (0-4) and reported according to the PMA period at assessment.[20] Total maturational scores (0-13) were individually plotted with trajectories. To assess the time of full brain maturation, the PMA when individual participants reached their maximum score (13 points) was assessed. For participants who did not reach the maximum score (13 points at the end of the study), the estimated PMA of maximum maturation was plotted as approximated by linear extrapolation according to Hazewinkel.[21]

Baseline Characteristics

A full course of antenatal steroids was defined as 2 doses of 12 mg of betamethasone given 24 hours apart. Surfactant (200 mg/kg Curosurf; Chiesi, Parma, Italy) was administered prophylactically to infants born <28 weeks of PMA using less-invasive surfactant administration[22] or otherwise therapeutically according to European consensus guidelines.[23] Anthropometry was performed by the attending nurses and z scores were calculated using growth curves by Fenton and Kim.[24] Supply with parenteral DHA, EPA, and α-tocopherol was calculated. Necrotizing enterocolitis was diagnosed clinically (Bell stage ≥IIa)[25] or after exploratory surgery. Bronchopulmonary dysplasia was defined as supplementary oxygen after 36 + 0 weeks of PMA. Retinopathy of prematurity was diagnosed by direct ophthalmoscopy. Severe intraventricular hemorrhage (grade >II) and cystic periventricular leukomalacia (grade >I)[26] were diagnosed by cerebral ultrasound scan performed every 7-14 days. The type of enteral feeding at discharge was recorded.

Statistical Analyses

Data are expressed as median and IQR or mean and SD. Statistical testing was specified post hoc. The t test or Mann–Whitney U test were used to compare continuous data depending on normality as tested using the Kolmogorov–Smirnov test. The χ^2 test was used to compare

categorical data and frequency distribution of sleep–wake cycles between groups. The Kruskal–Wallis rank test was used to compare background pattern and maturational scores. Inter-rater agreement of aEEG analysts was assessed by Cohen kappa. A P value of $< .05$ was considered statistically significant.

Results

A total of 230 infants of ELBW were assigned randomly (**Figure 1**; available at www.jpeds.com) and 223 infants were available for analysis of the primary outcome.[12] For assessment of electrophysiological brain maturation, aEEG records from 138 of 223 infants were available (missing data: 38%). After we excluded infants with severe intraventricular hemorrhage (grade > II; SMOF-LE: n = 6, soybean oil–based lipid emulsion: n = 5; $P = .83$) or cystic periventricular leukomalacia (grade > I; SMOF-LE: n = 1, soybean oil–based lipid emulsion: n = 1; $P = .96$) and those with sedative/anti-epileptic drugs at all aEEG measurements (SMOF-LE: n = 1, soybean oil–based lipid emulsion: n = 3; $P = .28$), 121 infants (SMOF-LE: n = 63; soybean oil-based lipid emulsion: n = 58) with 317 aEEG traces were retained for analysis (SMOF-LE: n = 165; soybean oil–based lipid emulsion: n = 152). Twenty-four aEEG records were excluded due to short duration (SMOF-LE: n = 2; soybean oil–based lipid emulsion: n = 1) and sedative drugs at measurement (SMOF-LE: n = 10; soybean oil–based lipid emulsion: n = 11), no record had to be excluded due to poor quality.

Demographic characteristics, type of feeding at discharge, and neonatal morbidities of infants eligible for analysis of aEEG did not differ significantly between the groups (**Table I**). Infants of the SMOF-LE group received significantly more parenteral DHA, EPA, and α-tocopherol due to the nature of the intervention.

Table I. Baseline characteristics

Characteristics	SMOF-LE	S-LE	*P* value
Patients, total number	63	58	
aEEG records, total number	165	152	
Male	65 (41/63)	62 (36/58)	.73
Gestational age, wk	26.0 [25.1, 27.4]	26.2 [25.0, 27.9]	.72
Birth weight, g	800 [690, 893]	800 [640, 910]	.92*
Z score	−0.4 [−1.0, 0.2]	−0.5 [−1.2, 0.3]	.35*
Birth length, cm	33.5 [31.3, 35.0]	34.0 [32.0, 35.3]	.37
Z score	−0.3 [−0.9, 0.6]	−0.2 [−0.8, 0.7]	.56
Birth head circumference, cm	23.7 [22.5, 24.9]	23.8 [22.5, 25.0]	.97
Z score	−0.2 [−0.5, 0.6]	−0.2 [−0.8, 0.6)	.34
Antenatal steroids, complete course	62 (39/63)	64 (37/58)	.85
Hypertensive disorder in pregnancy	18 (11/63)	16 (9/58)	.77
Preterm premature rupture of membranes	35 (22/63)	38 (22/58)	.73
Cesarean delivery	92 (58/63)	88 (51/58)	.58
Apgar, 5 min	8 [8, 9]	8 [8, 9]	.70
Apgar, 10 min	9 [9, 9]	9 [9, 9]	.47
Umbilical artery, pH	7.31 [7.27, 7.36]	7.30 [7.27, 7.34]	.44
Received surfactant	91 (57/63)	88 (51/58)	.65
Ventilation during hospital stay	43 (27/63)	45 (26/58)	.88
Ventilation, days per patient	10 [6, 15]	8 [3, 17]	.96
Culture-proven septicemia	17 (11/63)	26 (15/58)	.26
Weight (end of study), g	2660 [2371, 3088]	2503 [2248, 2780]	.09
Length (end of study), cm	45.0 [43.0, 47.8]	44.3 [42.0, 46.0]	.10
Head circumference (end of study), cm	32.5 [31.0, 33.5]	31.9 [31.0, 33.0]	.18
Exclusively mother's milk (discharge)	44 (28/63)	43 (25/58)	.88
Gestational age (end of study), wk	37.9 [36.6, 39.9]	37.4 [36.1, 39.3]	.60
Study medication			
Parenteral lipids, days	18 [13, 31]	18 [12, 25]	.36
Cumulative study lipids, g/kg	40 [25, 69]	35 [25, 52]	.38
Study lipids, g/kg/d	2.2 [1.8, 2.6]	2.1 [1.8, 2.4]	.56
Docosahexaenoic acid, mg/kg/d	48 [39, 57]	–	
EPA, mg/kg/d	53 [43, 62]	–	
α-Tocopherol (lipid emulsion), mg/kg/d	4.4 [3.6, 5.1]	0.8 [0.7, 0.9]	<.001
α-Tocopherol (total parenteral), mg/kg/d	7.0 [6.2, 7.7]	3.4 [3.3, 3.9]	<.001
Short-term outcome			
Necrotizing enterocolitis (stage ≥ II)	6 (4/63)	9 (5/58)	.63
Bronchopulmonary dysplasia	21 (13/63)	14 (8/58)	.32
Retinopathy of prematurity	67 (42/63)	66 (38/58)	.85
Retinopathy of prematurity (stage > II)	13 (8/63)	12 (7/58)	.66
Intraventricular hemorrhage (stage I/II)	14 (9/63)	14 (8/58)	.61
Death	0 (0/63)	2 (1/58)	.96

S-LE, soybean oil–based lipid emulsion.
Categorical data are presented as percentages with numbers in parentheses and were tested using the χ^2 test. Continuous data are presented as the median [IQR] and were tested using the Mann–Whitney U test or the independent samples t test (*).

aEEG Measurements

The PMA at analysis was 24-41 weeks of PMA. The duration of recordings (median, IQR) did not differ significantly between groups (SMOF-LE: 180 minutes [150, 260]; soybean oil–based lipid emulsion: 180 minutes [140, 240]; $P = .30$). Inter-rater agreement for aEEG analysts was high (Cohen kappa: 0.93 for background pattern, 0.90 for sleep–wake cycles and 0.90 for maturational scores).

Pattern Analysis according to Hellstrom-Westas and Rosen

Analysis of aEEG pattern[19] is shown in Table II. Starting at 28 weeks of PMA, the percentage of continuous background pattern was significantly larger in infants who received SMOF-LE than in infants who received soybean oil–based lipid emulsion. Mature sleep–wake cycles were the dominant pattern after 33 weeks of PMA in all infants, and the percentage of mature sleep–wake cycles did not differ significantly between groups.

Maturational Scores according to Burdjalov et al

The scores for cycling and bandwidth were significantly greater in infants receiving SMOF-LE, starting from 28 weeks of PMA (Table III). In this group, lower border amplitude scores were significantly greater from 28 to 31 weeks and continuity scores were greater from 28 to 33 weeks PMA. The summative total maturational score was significantly greater from 28 to 41 weeks of PMA.

Individual maturational score trajectories revealed accelerated electrophysiological maturation in infants receiving SMOF-LE (Figure 2). As shown in Figure 3 (available at www.jpeds.com), maximum electrophysiological maturation (median, IQR) was reached 2 weeks earlier at 36.4 weeks (35.4, 37.5) PMA in infants receiving SMOF-LE compared with 38.4 weeks (37.1, 42.4) in infants receiving soybean oil–based lipid emulsion ($P < .001$). A significantly lower number of infants who received soybean oil–based lipid emulsion (3/58, 5%) reached the maximum score by the end of the study, compared with infants who received SMOF-LE (17/63, 27%, $P = .001$).

Discussion

Our study of serial aEEG measurements showed accelerated electrophysiological brain maturation in infants of ELBW receiving a mixed lipid emulsion that contains fish oil. Infants receiving SMOF-LE reached significantly greater scores for aEEG activity, cycling, continuity, and bandwidth and presented with significantly more continuous background activity—both sensitive indicators of brain maturation[20,27] and possible predictors of neurodevelopment.[28,29] Sleep–wake cycles were significantly different only using the classification of Burdjalov et al,[20] which is likely due to a more detailed scoring compared with the classification of Hellstrom-Westas and Rosen.[19]

The aim of nourishing the infant born preterm is to achieve growth and body composition similar to a healthy fetus,[30]

Table II. Comparison of background pattern and sleep–wake cycles according to Hellstrom–Westas and Rosen[19]

Study groups	24-27 weeks*			28-29 weeks*			30-31 weeks*			32-33 weeks*			34-35 weeks*			36-41 weeks*		
	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*
aEEG records, n	16	16		27	33		34	33		33	31		29	18		26	21	
Patients, (n)	15	16		26	32		31	33		33	28		28	18		26	20	
Background pattern†			.32			**<.001**			**.002**			**<.001**			**<.001**			**<.001**
Continuous pattern	49 (26)	40 (20)		69 (15)	41 (16)		78 (18)	57 (25)		85 (12)	68 (17)		94 (8)	84 (8)		97 (7)	90 (6)	
Discontinuous pattern	49 (26)	53 (18)		30 (14)	52 (17)		22 (18)	40 (25)		15 (12)	32 (17)		6 (8)	16 (8)		3 (7)	10 (6)	
Burst suppression	2 (6)	7 (13)		1 (3)	7 (15)		0 (0)	3 (10)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Sleep–wake cycles‡			1.0			.44			.16			.21			.67			.83
None	13 (34)	13 (34)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Immature	87 (34)	87 (34)		93 (27)	97 (17)		71 (46)	85 (36)		42 (50)	58 (50)		17 (38)	22 (42)		12 (32)	10 (30)	
Mature	0 (0)	0 (0)		7 (26)	3 (17)		29 (46)	15 (36)		58 (50)	42 (50)		83 (38)	78 (43)		88 (32)	90 (30)	

P values < .05 were considered statistically significant and printed in bold letters.
*PMA at aEEG recording.
†Values expressed as percentages (SD) and tested using the Kruskal–Wallis rank test.
‡Values expressed as percentages (SD) and tested using the Mann–Whitney *U* test.

Table III. Comparison of maturational scores according to Burdjalov et al[20]

Study groups	24-27 weeks*			28-29 weeks*			30-31 weeks*			32-33 weeks*			34-35 weeks*			36-41 weeks*		
	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*	SMOF	S-LE	*P*
aEEG records, n	16	16		27	33		34	33		33	31		29	18		26	21	
Patients, n	15	16		26	32		31	33		33	28		28	18		26	20	
Total score†	6.2 (1.3)	5.5 (1.6)	.21	8.7 (1.1)	6.3 (1.2)	<.001	9.5 (1.2)	7.8 (1.6)	<.001	10.6 (0.9)	8.8 (1.4)	<.001	12.1 (0.8)	10.7 (1.0)	<.001	12.7 (0.8)	11.4 (1.1)	<.001
Continuity†	0.9 (0.4)	0.8 (0.4)	.42	1.5 (0.5)	1.1 (0.3)	<.001	1.7 (0.4)	1.4 (0.5)	.002	1.9 (0.2)	1.6 (0.5)	.001	2.0 (0.0)	1.9 (0.2)	.20	2.0 (0.0)	2.0 (0.0)	1.00
Cycling†	2.4 (0.5)	2.3 (0.8)	.87	3.4 (0.6)	2.5 (0.5)	<.001	3.8 (0.4)	3.2 (0.7)	<.001	4.0 (0.3)	3.4 (0.6)	<.001	4.7 (0.5)	4.2 (0.5)	.002	4.9 (0.5)	4.4 (0.6)	.001
Amplitude†	1.3 (0.5)	1.1 (0.3)	.08	1.8 (0.4)	1.2 (0.4)	<.001	1.8 (0.4)	1.6 (0.5)	.028	1.9 (0.3)	1.8 (0.4)	.40	2.0 (0.0)	2.0 (0.0)	1.00	2.0 (0.0)	2.0 (0.0)	1.00
Bandwidth†	1.6 (0.5)	1.3 (0.5)	.16	2.0 (0.4)	1.5 (0.6)	<.001	2.2 (0.6)	1.7 (0.6)	.001	2.7 (0.5)	2.0 (0.6)	<.001	3.4 (0.6)	2.6 (0.5)	<.001	3.8 (0.5)	3.0 (0.6)	<.001

*PMA at aEEG recording.
†Values expressed as mean (SD) and tested using Kruskal–Wallis rank test.

coupled with satisfactory neurodevelopment. In this context, optimal nutrition is of great importance, and an adequate supply of DHA is highly relevant for an normal cerebral development.[4,9] After preterm birth, DHA is exclusively supplied by enteral nutrition and falls short of fetal accretion rates.[10] Endogenous synthesis of DHA is insufficient.[11] Parenteral nutrition using soybean oil–based lipid emulsion provides high loads of essential fatty acids (linoleic and linolenic acid), but not DHA. Thus, infants of ELBW (who rely on parenteral nutrition in their first weeks of life) accumulate large DHA deficits.[9,10] To support cerebral development, it seems appropriate to supply DHA with parenteral nutrition in amounts similar to the fetus. Infants who received SMOF-LE in our study (Table I) were provided with DHA comparable with in utero transfer rates (45 mg/kg/d).[10]

Several in vitro studies have provided direct evidence for the important beneficial effects of DHA on neurite growth and synaptic function.[31-35] Electrocortical activity—as it was measured by aEEG in our study—is an aggregate of postsynaptic potentials[15] and thus correlates with the synaptic number and activity. In this context, improved supply with DHA in our trial might have enhanced cerebral neurite growth and/or synaptogenesis, which translated into accelerated electrophysiological brain maturation. In support of this hypothesis, Helland et al have reported an association of DHA levels and the maturity of EEG in infants born at term.[36] In our study, aEEG was analyzed until term-equivalent age but parenteral lipids were used only during the first weeks after birth. Thus, the potential influence of DHA from enteral nutrition needs to be considered. As all infants received exclusively human milk until 32 + 0 weeks PMA, only the type of nutrition thereafter was potentially confounding. We analyzed the percentage of infants fed exclusively mother's milk at discharge but found no significant difference (Table I). A bias from enteral DHA therefore seems unlikely.

Besides DHA, other components of SMOF-LE have a potential impact on cerebral development. EPA, which is provided by SMOF-LE (Table I) in similar amounts, has been shown to promote better myelination in newborn rats than DHA.[37] Improved white matter connectivity has been shown to increase EEG coherence,[38] which corresponds to increased continuous background activity in aEEG. Thus, improved myelination also may explain some of our findings, and magnetic resonance imaging[39] could help to clarify this effect. This was not part of our study but would be of interest in the future. We can only speculate whether provision of EPA was significant for our findings. A shortcoming of every clinical trial investigating ω-3 LC-PUFA supplementation is that effects of DHA and EPA are hard to separate because both are provided in fish oil.[40]

Finally, SMOF-LE contains 5 times more α-tocopherol (Table I) than soybean oil–based lipid emulsion.[35,41] Cerebral α-tocopherol protects neuronal membranes from oxidative damage[42] and is involved in processes related to neuronal plasticity.[43] A recent study showed that parenteral α-tocopherol supply to infants of ELBW was below

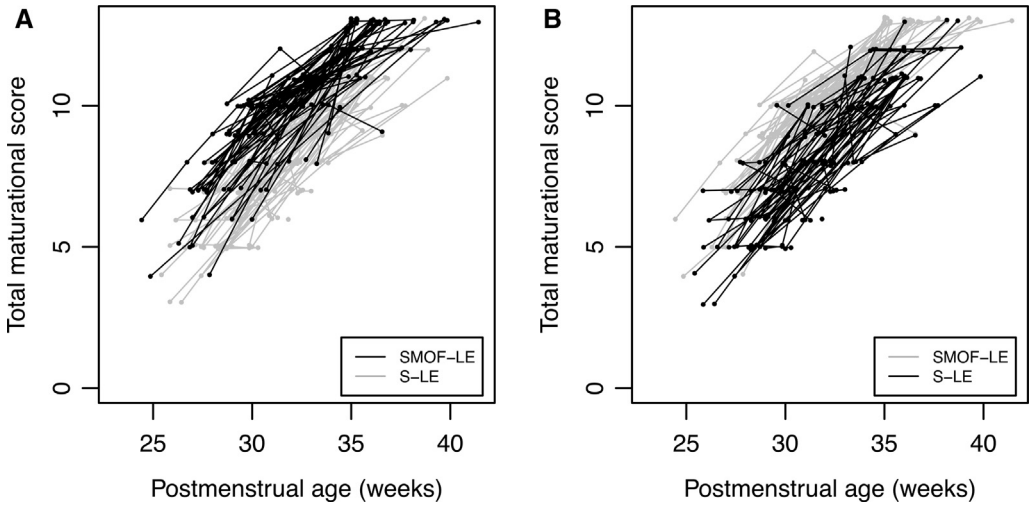

Figure 2. Total maturational scores of participants plotted with trajectories. **A,** Infants in group SMOF-LE (*black lines*) show the greatest scores for most PMAs. **B,** infants in group S-LE (*black lines*) show the lowest scores for most PMAs.

recommendations.[44] Considering the supply with total parenteral α-tocopherol in our study (**Table I**), both groups were sufficiently supplemented (recommended range: 2.8-3.5 mg/kg/d, maximum: 7 mg/kg/d[45]) and infants of the SMOF-LE group exceeded current recommendations. Pharmacologic α-tocopherol supplementation (5-30 mg/kg/d) has been linked to sepsis and necrotizing enterocolitis.[46] We and others[47] did not find any significant influence of SMOF-LE on sepsis or necrotizing enterocolitis,[12] but caregivers should be aware of the high supply of α-tocopherol using SMOF-LE together with parenteral multivitamin preparations.[45] Whether the supra-physiological supply of α-tocopherol contributed to electrophysiological brain maturation in our study is speculative but cannot be excluded.

Neurodevelopmental safety of new interventions is of importance in infants born preterm.[48] The acceleration of electrophysiological brain maturation as seen using SMOF-LE cannot be considered safe or even beneficial until adequate reports on neurodevelopmental outcome are available. There are studies that show an association of an early presence of sleep−wake cycles and continuous pattern with a favorable neurodevelopment.[19,28] Thus, accelerated electrophysiological brain maturation may point to a neurodevelopmental benefit. This interpretation is supported by studies that showed improved neurodevelopment in subsets of infants born preterm who received preterm formula enriched with DHA.[49] In these studies, the amount of DHA supplied (25-59 mg/kg/d) was quite similar to our study, although parenteral and enteral DHA substitution cannot be compared directly.[50] Along these lines, a retrospective observational study by Tam et al showed that greater levels of DHA were associated with better neurodevelopment and improved microstructural brain maturation.[51] In contrast, acceleration of aEEG maturation also was observed as an effect of the extrauterine environment after preterm birth,[52,53] and thus may not necessarily indicate a beneficial outcome. For now, we can only speculate on the significance of our findings referring to later neurodevelopment. Further trials are necessary to draw firm conclusions of a possible neurodevelopmental influence. imaging studies on possible structural brain changes would be of major interest.

It is a weakness of our study that the analysis of brain maturation by aEEG was a secondary outcome and loss to follow-up (38%) was high, introducing a possibility for bias. The reason for missing data was limited availability of monitors or technicians. Nevertheless, the study population was randomized, investigators were blinded, and the baseline characteristics of infants analyzed were well balanced. Furthermore, the remaining sample size of 121 infants born preterm with 317 aEEG records still represents a large cohort and differences were statistically significant across almost all maturational components of the aEEG, making chance or other influences unlikely.

Overall, our study showed that electrophysiological brain maturation in infants of ELBW was significantly accelerated using SMOF-LE, which may predict a relevant impact on neurodevelopment. Neurodevelopmental follow up of these infants will be performed up to 5 years of age. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *The Journal of Pediatrics*

Occipitofrontal Head Circumference—An Accurate Measure of Intracranial Volume

Bray P, Shields WD, Wolcott GJ, Madsen JA. J Pediatr 1969;75:303-5

Fifty years ago, Bray et al demonstrated that occipitofrontal head circumference (OFC) was highly correlated with intracranial volumes, calculated by internal measurements of the calvarium on skull radiographs. The authors acknowledged that disease conditions associated with ventricular enlargement or space-occupying lesions, however, could limit the extrapolation of these measurements to true brain size. This finding is important to consider now in conditions with improving survival rates that may be associated with cerebral atrophy with ex vacuo changes and decreased cerebral volume. For example, children with complex congenital heart disease frequently have increased extra-axial spaces and subdural hygromas that may increase intracranial volume and OFC; OFC would falsely overestimate brain size.

In otherwise healthy children, OFC is a reliable screening tool and often accurately reflects brain size. Autopsy studies of neonates and infants without central nervous system pathology in the 1970s and 1980s demonstrated strong correlations between brain weight and OFC.[1,2] Magnetic resonance imaging studies in 2002 further demonstrated a strong correlation between OFC and brain volume, particularly in children <6 years of age.[3] Cognitive implications of appropriate brain growth are also relevant, with IQ scores associated with serial OFC measurements in the first year of life, the period with the greatest rate of brain growth.[4]

OFC remains an important measure of intracranial and brain volume. It is critical that this measurement be included in well child visits with the pediatrician, and even specialty visits beyond neurology consultations, to monitor brain growth and development, and to screen for conditions that may alter the typical trajectory of this curve.

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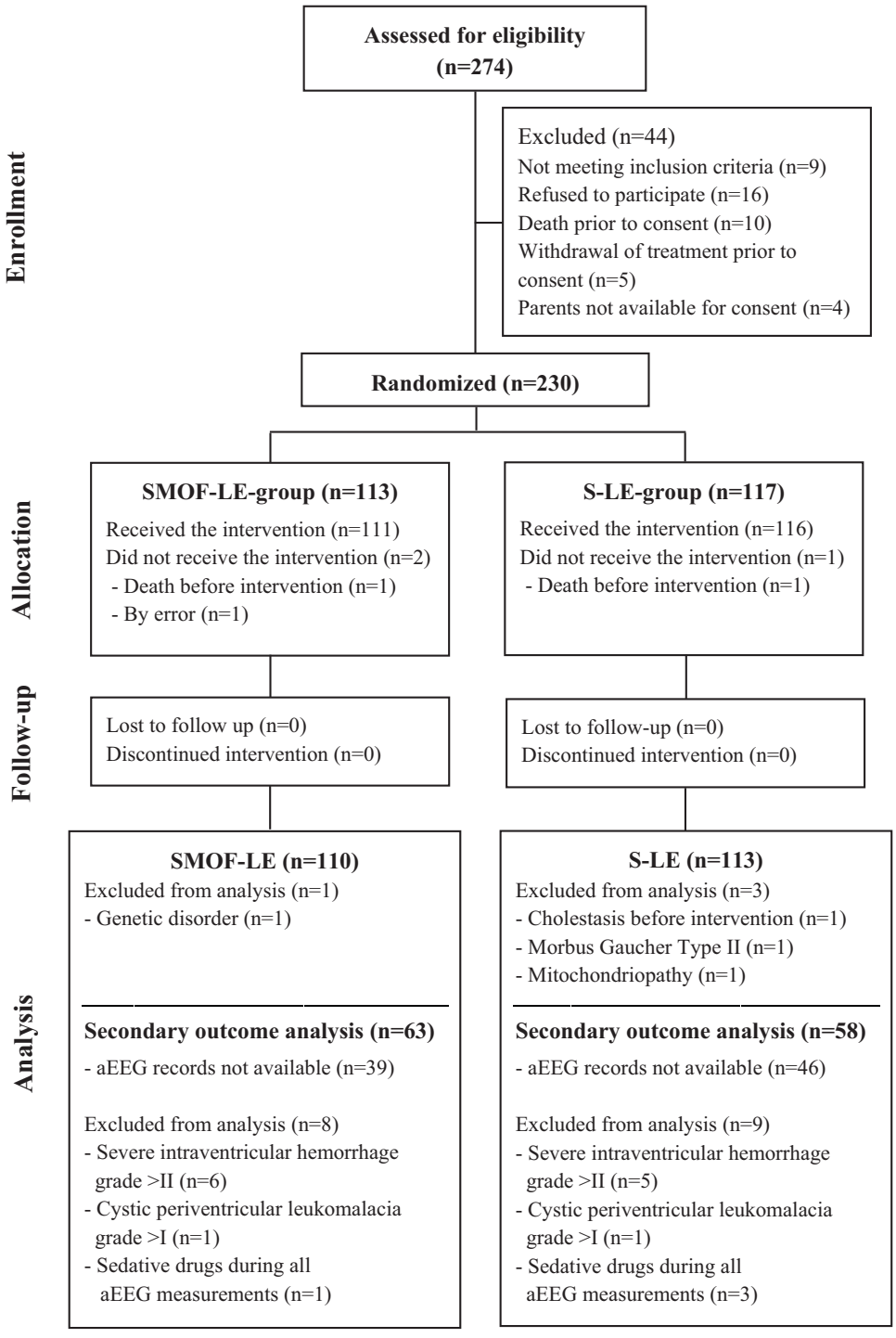

Figure 1. Enrollment with reasons for study exclusion and analysis. *S-LE*, soybean oil–based lipid emulsion.

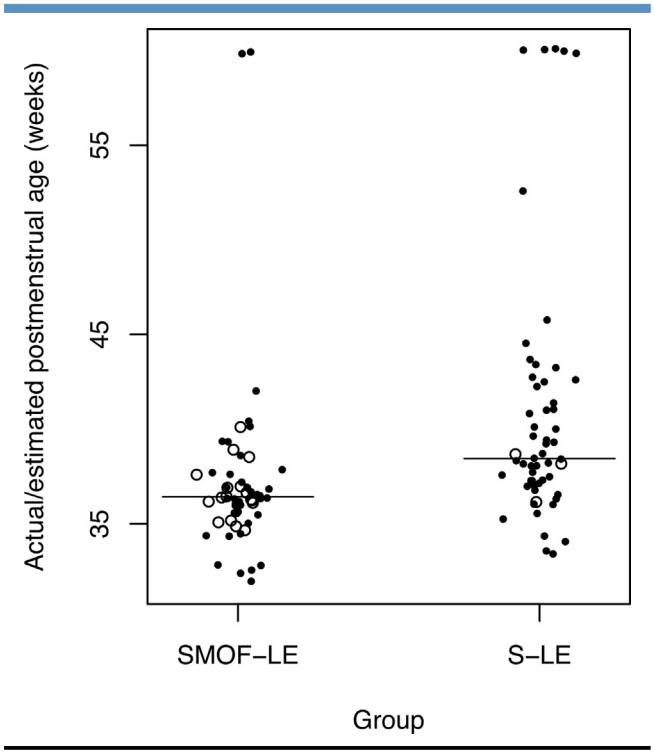

Figure 3. PMA when individual participants reached their maximum maturational score (13 points). The PMA of infants who reached the maximum score by the end of the study (actual age) was marked using *open circles*. The PMA of infants who did not reach the maximum score by the end of the study was approximated by linear extrapolation (estimated age) and marked using *closed circles*.