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Infant Formula Supplementation With Long-chain Polyunsaturated Fatty Acids Has No Effect on Bayley Developmental Scores at 18 Months of Age—IPD Meta-Analysis of 4 Large Clinical Trials

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ABSTRACT

Objectives: To find out whether supplementation of formula milk by long-chain polyunsaturated fatty acids (LCPUFA) affects neurodevelopment at 18 months of age in term or preterm infants by an individual patient data (IPD) meta-analysis.

Materials and Methods: Data of 870 children from 4 large randomised clinical trials for formula milk with and without LCPUFAs allowed for assessing the effect of LCPUFA with adjustment for potential confounders and extensive subgroup analysis on prematurity, LCPUFA source, and dosage. Any additional clinical trials examining the effect of LCPUFA supplementation on Bayley Scales of Infant Development at 18 months were regarded as relevant. Two relevant studies were identified by MEDLINE, but were not available to us. An IPD meta-analysis was performed with subgroup analyses by preterm delivery, very low birth weight (<1500 g), trials with higher amounts of docosahexaenoic acid (DHA) and arachidonic acid (AA), and specific sources of LCPUFA. The sample size of 870 children was sufficient to detect clinically relevant differences in Bayley Scales even in subgroups.

Results: There were no significant differences in mental or psychomotor developmental indexes between LCPUFA-supplemented and control groups for all children or in subgroups. This was confirmed with adjustment for the possible confounders: sex, gestational age, birth weight, maternal age, and maternal smoking. The adjusted mean differences in mental developmental index and psychomotor developmental index for all of the children were −0.8 (95% confidence interval −2.8 to 1.2) and −1.0 (−2.7 to 0.7), respectively.

Conclusions: These data based on considerable sample size provide substantial evidence that LCPUFA supplementation of infant formula does not have a clinically meaningful effect on the neurodevelopment as assessed by Bayley scores at 18 months. Inclusion of all relevant data should not have led to differing conclusions except, possibly, for very-low-birth-weight infants. ***JPGN 50:000–000, 2010.*** **Key Words:** Bayley Scales—Formula milk—IPD meta-analysis—LCPUFA—Neurodevelopment. © 2010 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

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Human milk contains long-chain polyunsaturated fatty acids (LCPUFA), most notably n-3 docosahexaenoic acid (DHA) and n-6 arachidonic acid (AA). Advantages in cognitive development of breast-fed in comparison with formula-fed infants have been attributed to the lack of these LCPUFAs in the past standard commercially available formulas (1).

Short-term beneficial effects of LCPUFAs such as DHA and AA on cognitive and visual development of

the offspring were shown in several studies (2–4), but the long-term effect of these LCPUFAs on infant mental and psychomotor development at the age of 3 years, for example, is controversial (5,6). Guided by the short-term beneficial effects of LCPUFAs, Koletzko et al have recommended the use of formulas with a proportion of DHA between 0.2% and 0.5% of fatty acids and amounts of AA being at least equal to those of DHA (7).

In 1- to 2-year-old children, in particular, contradictory findings have been reported (8–21). It is unclear whether these differences may be attributed to whether term or preterm infants had been included in the study, to the LCPUFA amount, composition and source, population studied, and outcome measures used (22,23).

Systematic reviews on term and preterm children concluded that there is little evidence for benefits to LCPUFA-supplemented children in neurodevelopment, but small effects of LCPUFA supplementation may have escaped detection because of lack of power, the impossibility to adjust for confounders, and to perform subgroup analyses in the conventional meta-analysis approach (24–26).

These limitations may be overcome by an individual patient data (IPD) meta-analysis on the raw data of relevant original studies. Individual patient data meta-analyses are regarded as providing ''the least biased and most reliable means'' to combine results from different studies (27). However, this advantage may be challenged if data are not available from all relevant studies and if the assessment of relevant covariates differs substantially between the included studies.

We performed an IPD meta-analysis based on 4 independent large clinical trials (8–11) on LCPUFA supplementation in term or preterm infants, assessing neurodevelopment at 18 months using Bayley Scales of Infant Development II (BSID II) (28). The data were provided in the framework of the Early Nutrition Programming Project, a large European Union-funded research consortium exploring long-term consequences of nutrition during pregnancy and infancy on development and health (29). Unfortunately, we did not have access to data from 2 other relevant studies (13,18).

The question addressed was whether there is a global effect of LCPUFA supplementation on neurodevelopment, or a potential effect confined to subgroups of preterm infants, very-low-birth-weight infants (VLBW), boys, girls, or regarding specific composition or sources of LCPUFA.

MATERIALS AND METHODS

Search for Other Relevant Studies

Because this IPD meta-analysis started with the data provided within the Early Nutrition Programming Project consortium, an effort was made to include all of the relevant data. We searched in MEDLINE (November 2007) for other randomised trials examining the effect of LCPUFA supplementation on neurodevelopment of infants measured by BSID II at 18 months of age. Search items were ''Bayley'' or ''development'' and ''LCPUFA.'' From 8 studies with adequate setting (12–19), only 2 proved to be relevant (13,18), because the others had assessed mental developmental index (MDI) and psychomotor development index (PDI) at time points other than 18 months of age; moreover, 2 of those had used BSID I (Table 1). Attempts to access the data from the relevant studies were not successful. We were not aware of other unpublished studies.

Data

The meta-analysis was based on individual patient data from randomised clinical trials from Groningen (8), Leicester, Nottingham (9,10), and Glasgow (11). Two of the British studies involved preterm infants (10,11). Here, the Leicester/Nottingham term and preterm studies will be called Leicester 1 and Leicester 2, respectively. The Leicester 2 children had a gestational age of <37 weeks and a birth weight <1750 g, the infants from the Glasgow study had a gestational age <35 weeks and a birth weight ≤ 2000 g.

In all of the trials, infants were randomised to receive either infant formulas with additional LCPUFA (LF) or a control unsupplemented infant formula (CF) in a double-blind design. The infants were not randomised to other interventions. The trial formulas were supplemented with n-3 DHA and n-6 AA and in the 2 preterm trials additionally with n-6 γ-linolenic acid

TABLE 1. *Other randomised studies on the effect of LCPUFA supplementation on BSID indexed in MEDLINE*

Study	Infants	BSID measured at (mo)	BSID version
Carlson (12)	Preterm	12	I
Birch et al (13)	Term	18	II
Makrides et al (14)	Term	12, 24	II
O'Connor et al (15)	Preterm	12	II
Van Wezel-Meijler et al (16)	Preterm	12, 24	I
Agostoni et al (17)	With phenylketonuria	5, 12	II
Clandinin et al (18)	Preterm	18	II
Fang et al (19)	Preterm	6, 12	II

BSID = Bayley Scales of Infant Development; LCPUFA = long-chain polyunsaturated fatty acids.

TABLE 2. *Formula compositions of LCPUFA-supplemented formulas in grams per 100 g fat and duration of formula feeding in the 4 trials*

	Groningen	Leicester 1	Leicester 2	Glasgow
DHA	0.30	0.32	0.17	0.50
AA	0.45	0.30	0.31	0.04
Other fatty acids	LA: 11.00*	LA: 15.90	GLA: 0.40	LA: 12.30
	GLA: 0.18	ALA: 1.10	EPA: 0.04	GLA: 0.90
	DGLA: 0.03	EPA: 0.01		ALA: 1.50
	ALA: 1.30*			EPA: 0.10
	EPA 0.23			
Duration	2 mo	6 mo	Until discharge (3 wk at minimum)	Until discharge, postdischarge formula

AA = arachidonic acid (n-6); ALA = α-linolenic acid (n-3); DGLA = dihomo-γ-linolenic acid (n-6); DHA = docosahexaenoic acid (n-3); EPA = eicosapentaenoic acid (n-3); GLA = γ-linolenic acid (n-6); LA = linoleic acid (n-6).

* The control group received similar amounts of LA (11.56) and ALA (1.27).

(GLA). The control formulas were virtually free of DHA, AA, and GLA. The studies differed in formula composition, duration of formula feeding (Table 1), and formula sources: The LCPUFAs in the Groningen trial came from egg, fish oil (DHA), and single cell oil (AA), whereas the LCPUFAs in the UK trials contained mixtures of egg lipid/phospholipid, fish oil, and borage oil. The DHA content of formulas ranged from 0.17% to 0.5% of fatty acids, with varying DHA/AA ratios (Table 2). All 4 studies measured BSID II at 18 months corrected age as outcome variable. The Groningen trial used the Dutch version (BSID-II-NL).

In the term studies from Groningen and Leicester 1, data on MDI and PDI were available in 279 (132 LF + 147 CF) and 250 (125 LF +125 CF) cases, respectively. The preterm trial from Leicester 2 contained 147 (68 LF +79 CF) children, and the Glasgow study contained 194 (103 LF +91 CF). Therefore, the meta-analysis included 529 (257 LF +272 CF) term infants, 341 (171 LF +170 CF) preterm infants, and 870 (428 LF +442 CF) infants in total, with the numbers of LF and CF infants almost equal.

Subgroups

1. Term delivery
2. Preterm delivery as defined in the studies
3. Because different definitions for prematurity had been applied in the respective individual trials, we also generated the subgroup VLBW with children with birth weight of <1500 g (n = 175 = 95 LF + 80 CF), all of whom were born before the 35th week of gestation.
4. Because the level of DHA in the Leicester 2 trial was relatively low (Table 2), we investigated the subgroup "higher DHA levels," including only the other 3 trials, which had used formulas with the recommended level of DHA between 0.2 and 0.5 (7).
5. Equivalently, we examined data from children supplemented with high AA levels (AA ≥ 0.2), leaving out the Glasgow study.
6. For the last subgroup we considered all 3 UK trials only because their LCPUFA sources in the formula differed from those in the Groningen study.
7. Boys
8. Girls

Statistical Methods

For all of the infants as well as for the 8 subgroups defined above, mean differences in Bayley MDI and PDI were calculated, adjusted for confounders, and tested by Student *t* test (2-sided hypothesis). This was done by applying multivariable linear models with BSIDs as outcome variables, LCPUFA supplementation as explanatory variable, and sex, gestational age, birth weight, maternal age, and maternal smoking during the third trimester as confounders. A significant mean difference between LF and CF groups in MDI and PDI was set at an α level of 0.05.

Although information on sociodemographics reported as maternal education (basic school at best vs certificate qualifying for university) was provided in all of the studies, we did not include this potential confounder in the main analyses because of missing data in 42% of the mothers in the Leicester 2 trial (7% in total); however, maternal education was considered in additional sensitivity analyses. Other sensitivity analyses looked for potential differences of the effects in boys and girls in subgroups 1 to 6.

We also examined a potential dose-response effect of DHA on MDI and PDI by calculating confounder-adjusted linear models replacing the explanatory variable LCPUFA supplementation with the variable amount of DHA given in the respective study (set to "0" for the CF group). From these analyses we excluded the data from the Groningen trial because the Bayley scores in this trial were higher than in the UK trials.

Power of the Study

For our power calculations, we assumed an α level of 0.05, a desired statistical power of 0.8, standard deviations of MDI and PDI of 15, and equal sizes of the number of LF and CF infants in every subgroup.

Data of 870 children permitted detection of a difference of 2.9 points in MDI or PDI, whereas 341 preterm children would be enough to find a score difference of 4.6. The subgroup of 175 VLBW infants would still allow detection of a difference of 6.4 score points in MDI or PDI.

RESULTS

As expected, the term children showed higher birth weight and gestational age and a smaller percentage of

TABLE 3. *Means (standard errors) and numbers of cases (%) of maternal and infant characteristics of term, preterm, and all children of all 4 included studies*

	Term		Preterm		All	
	LCPUFA (n = 257)	Control (n = 272)	LCPUFA (n = 171)	Control (n = 170)	LCPUFA (n = 428)	Control (n = 442)
Males	139 (54%)	149 (55%)	79 (46%)	82 (48%)	218 (51%)	231 (52%)
Gestational age, wk	39.8 (1.3)	39.8 (1.2)	30.8 (2.2)	30.9 (2.2)	36.2 (4.7)	36.4 (4.7)
Birth weight, g	3595 (482)	3537 (438)	1426 (316)	1459 (307)	2725 (1145)	2731 (1087)
Maternal age, y	28.8 (4.7)	28.4 (4.7)	28.4 (4.7)	27.7 (5.5)	28.8 (4.7)	28.1 (5.0)
Higher maternal education*	45 (18%)	30 (11%)	41 (28%)	19 (15%)	86 (21%)	49 (12%)
Maternal smoking†	68 (27%)	85 (32%)	67 (40%)	70 (43%)	135 (32%)	155 (36%)

LCPUFA = long-chain polyunsaturated fatty acids.
* Missing values in UK 2 (42%).
† During third trimester; missing values in the Netherlands (6%) and UK 2 (6%).

mothers smoking in the third trimester compared with the preterm children, whereas there were no significant differences in any of these variables for LCPUFA versus control infants (Table 3). Maternal age was comparable across all groups. However, the proportion of mothers with high levels of education was significantly higher in children randomised to LCPUFA supplementation.

Crude analyses are presented in Table 4. There were no significant differences between LF and CF groups in MDI and PDI overall and in any subgroups. Also, after adjustment for sex, gestational age, birth weight, maternal age, and maternal smoking, no significant mean differences were found between LCPUFA supplemented and control groups in MDI (difference −0.8 [95% confidence interval −2.8 to 1.2]) and PDI (−1.0 [−2.7 to 0.7]). Furthermore, there were no significant findings in any of the defined subgroups (Table 5).

Sensitivity analyses revealed identical findings in boys and girls overall, in all subcategories, and with inclusion of higher maternal education as a potential confounder (data not shown). The variable ''amount of DHA'' was no significant predictor in the dose response analyses.

DISCUSSION

In contrast to classical meta-analyses based on aggregated data from different studies, this IPD meta-analysis on a large sample size allowed adjustment for confounders and to perform subgroup analyses. The absence of any detectable benefit or disadvantage in neurodevelopment assessed with BSID at the age of 18 months for all of the children or in any subgroup therefore provides evidence against beneficial effects of LCPUFA supplementation on BSID at 18 months under the conditions of the trials included here. The strength of the evidence depends substantially on the sample size of the data included and on the results of studies for which data were not available. In any case, our results do not exclude potential benefits under specific conditions, such as the reported improvement of BSID at 18 months in male

TABLE 4. *Mean values of MDI and PDI and unadjusted mean differences of LCPUFA vs control children in subgroups with term, preterm, and VLBW infants, high DHA and AA levels, children from the UK trials (receiving LCPUFAs from sources of egg lipid/phospholipid, fish oil and borage oil), boys, girls, and all infants*

	MDI			PDI		
	LCPUFA	Control	Mean difference	LCPUFA	Control	Mean difference
All (n = 870)	93.9 (92.4–95.4)	94.5 (92.9–96.1)	−0.6 (−2.8 to 1.6)	93.3 (92.0–94.6)	94.4 (93.1–95.8)	−1.1 (−3.0 to 0.7)
Term (n = 529)	98.7 (96.9–100.5)	100.5 (98.7–102.4)	−1.8 (−4.4 to 0.7)	97.5 (96.1–99.0)	98.9 (97.5–100.4)	−1.4 (−3.4 to 0.6)
Preterm (n = 341)	86.8 (84.6–89.0)	84.9 (82.6–87.2)	1.9 (−1.3 to 5.0)	86.9 (84.9–88.9)	87.2 (85.0–89.4)	−0.2 (−3.2 to 2.7)
VLBW (n = 175)	85.7 (82.8–88.6)	83.6 (79.9–87.4)	2.0 (−2.7 to 6.8)	86.2 (83.4–89.0)	84.3 (80.7–87.8)	2.0 (−2.6 to 6.6)
DHA ≥ 0.2 (n = 733)	95.2 (93.6–96.8)	96.7 (95.0–98.5)	−1.6 (−3.9 to 0.8)	94.0 (92.7–95.4)	95.9 (94.4–97.3)	−1.8 (−3.8 to 0.2)
AA ≥ 0.2 (n = 676)	96.3 (94.6–98.0)	96.9 (95.1–98.6)	−0.6 (−3.0 to 1.8)	95.8 (94.5–97.2)	96.4 (95.0–97.9)	−0.6 (−2.6 to 1.4)
UK trials (n = 591)	89.9 (88.3–91.6)	89.1 (87.3–90.8)	0.8 (−1.6 to 3.2)	90.7 (89.2–92.1)	91.1 (89.5–92.6)	−0.4 (−2.5 to 1.7)
Boys (n = 449)	91.7 (89.7–93.7)	92.2 (90.1–94.3)	−0.5 (−3.4 to 2.4)	92.1 (90.2–93.9)	93.6 (91.7–95.5)	−1.5 (−4.1 to 1.1)
Girls (n = 421)	96.2 (94.1–98.4)	97.1 (94.7–99.5)	−0.9 (−4.1 to 2.4)	94.6 (92.8–96.4)	95.4 (93.5–97.3)	−0.8 (−3.4 to 1.8)

95% CIs in parentheses. AA = arachidonic acid (n-6); CI = confidence interval; DHA = docosahexaenoic acid (n-3); LCPUFA = long-chain polyunsaturated fatty acids; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index; VLBW = very-low-birth-weight infants.

TABLE 5. *Mean differences in MDI and PDI of LCPUFA vs control children in subgroups with term, preterm; and VLBW infants, high DHA and AA levels, children from the UK trials (receiving LCPUFAs from sources of egg lipid/phospholipid, fish oil, and borage oil), boys, girls, and all infants*

	MDI	PDI
All (n = 870)	−0.8 (−2.8 to 1.2)	−1.0 (−2.7 to 0.7)
Term (n = 529)	−2.2 (−4.8 to 0.4)	−1.2 (−3.3 to 0.9)
Preterm (n = 341)	2.1 (−1.2 to 5.4)	−0.3 (−3.3 to 2.7)
VLBW (n = 175)	1.2 (−3.7 to 6.1)	1.0 (−3.7 to 5.7)
DHA >0.2 (n = 733)	−1.5 (−3.7 to 0.7)	−1.3 (−3.1 to 0.5)
AA >0.2 (n = 676)	−1.2 (−3.5 to 1.1)	−0.7 (−2.6 to 1.2)
UK trials (n = 591)	0.6 (−1.7 to 2.9)	−0.6 (−2.6 to 1.4)
Boys (n = 449)	−1.0 (−3.7 to 1.7)	−1.8 (−4.3 to 0.7)
Girls (n = 421)	−0.1 (−3.1 to 2.9)	0.0 (−2.5 to 2.5)

95% CIs in parentheses. Adjusted for sex (as appropriate), gestational age, birth weight, maternal age, and maternal smoking. AA = arachidonic acid (n-6); CI = confidence interval; DHA = docosahexaenoic acid (n-3); LCPUFA = long-chain polyunsaturated fatty acids; MDI = Mental Developmental Index; PDI = Psychomotor Developmental Index; VLBW = very-low-birth-weight infants.

preterm infants provided with a higher dosage of DHA of 0.5% of fatty acids (11).

The strength of our meta-analysis is its sample size with sufficient power to detect meaningful differences in Bayley scores, not only in the entire sample but also in subgroups. A difference of at least 5 points in the Bayley scores was considered as clinically relevant, taking account of the standard errors of measurement of MDI (4.27) and PDI (5.69) at 18 months given in the test manual (28). The sizes of the total sample and of the subgroups are large enough to find such a relevant difference, except for the subgroup of VLBW infants with a detectable difference of slightly above 5 points.

The only relevant data of term children not included in the IPD meta-analysis were those from the Birch et al (13) study, which had shown beneficial effects of LCPUFA supplementation on neurodevelopment; however, this trial included only 56 children. In our meta-analysis, supplemented term infants tended to have lower Bayley scores than controls. Therefore, inclusion of the Birch et al (13) data would be unlikely to change the results of our meta-analysis substantially (30).

The nonavailability of the data from the study of Clandinin et al (18), however, was a bigger concern. In the mentioned study, a control group (n = 54) was compared with 2 groups supplemented with different LCPUFAs (N = 104). All of the children included were born preterm, and almost all of them were born with VLBW (≤1500 g). In the control group, mean values of 77.2 in MDI and 83.0 in PDI were observed, in contrast to 85.1 (MDI) and 90.7 (PDI) in the combined group of supplemented children (26). Based on these results and the unadjusted mean differences from our study, weighted mean differences (95% confidence intervals) of preterm children were 3.1 (0.3–6.0) in MDI and 2.1 (−0.8 to 5.1) in PDI and were therefore of no clinical relevance (as defined above). In respect of VLBW infants only, differences of 4.2 (0.5–7.9) and 4.7 (0.8–8.7) were detected in MDI and PDI, respectively. Although these appraisements did not consider possible confounding effects, they indicate that inclusion of the Clandinin et al (18) data would probably not have led to differing conclusions in other subgroups than the VLBW group.

These conclusions are in accordance with those from 2 recently published Cochrane reviews (24,25), which were based on the studies included in our IPD meta-analysis (8–11) and those from Birch et al (13) and Clandinin et al (18). These classical meta-analyses did not detect significant benefits in MDI and PDI of term and preterm children at 18 months of age. Another review on the effect of LCPUFA supplementation (26) on neurodevelopment included 2 additional studies that had assessed BSID II earlier than 18 months (15,19). This meta-analysis found a significant increase of MDI by 3.4 points, but no significant change in PDI. Again, it is disputable whether the observed change in MDI is of clinical relevance. Furthermore, the observed effects disappeared when the results of 2 studies with BSID I as outcome (12,16) were additionally considered.

Other possible weaknesses of this study may arise from limitations regarding the data provided. One of the trials lacked information on maternal education in about half of the mothers; however, including higher maternal education into multivariable analyses as an additional covariate where available had no considerable effects on the results. Furthermore, systematically higher MDI and PDI were reported in the Groningen trial. This may be because of different reference norms in the original and translated version of the Bayley test, but is unlikely to interfere with supplementation effects because of almost equal numbers of LF and CF groups in the Groningen trial.

Other studies detected benefits of LCPUFA supplementation on other neurological outcomes, such as general movements (2) or visual acuity (3,4) in children younger than 12 months during infancy. A previous trial in 18-month-old children detected effects of prenatal fatty acid status on neurologic optimality scores, but none on BSID (21). The reason may be that BSIDs, the most frequently used scores to assess neurodevelopment of infants (31), are a less subtle measurement than neurologic optimality scores and may have limitations in detecting differences in ''excellence.''

Measurements based on BSID at 18 months may miss subtle differences related to LCPUFA supplementation and may miss effects manifesting at later ages. For example, in a large double-blind randomised trial providing 200 mg DHA per day or placebo to breast-feeding women, Bayley scores at 18 months were not affected, but the supplemented group showed significantly better

psychomotor development scores at 2½ years (32). Similarly, randomised clinical trials providing oils with considerable amounts of DHA to women beginning in pregnancy found improved cognitive development at later ages of 2½ years (33) and at 4 years (34), whereas another study showed no improvement of visual acuity and intelligence quotient for LCPUFA-supplemented children at 3 years of age (23). A dose-response effect between maternal n-3 LCPUFA intake from seafood and children's verbal intelligence quotient at the age of 8 years, after adjustment for 28 confounding factors, was reported in the Avon Longitudinal Study of Parents and Children (35).

This IPD meta-analysis provides substantial evidence that there are no clinically relevant effects of LCPUFA supplementation on neurodevelopment as assessed by BSID at 18 months in almost all subgroups except for VLBW children. For these, additional inclusion of data from all of the relevant studies in this field may have resulted in the detection of relevant beneficial effects. Possible effects of LCPUFA on other outcomes, including outcomes at later ages, deserve further study.

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