Visual outcome at 2.5 years of age in ω-3 and ω-6 long-chain polyunsaturated fatty acid supplemented preterm infants: a follow-up of a randomized controlled trial

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Summary

Background We investigated ophthalmological outcomes at 2.5 years of corrected age in children born extremely preterm (EPT) to evaluate the effects of postnatal enteral supplementation with ω-3 and ω-6 long-chain polyunsaturated fatty acids.

Methods In the Mega Donna Mega clinical trial, EPT infants born at less than 28 weeks of gestation were randomized to receive an enteral supplementation of docosahexaenoic acid (DHA) and arachidonic acid (AA) from birth to 40 weeks postmenstrual age. In this exploratory follow-up at 2.5 years of corrected age, we assessed visual acuity (VA), refraction, manifest strabismus, and nystagmus. Satisfactory VA was defined as ≥20/63. Multiple imputation (MI) was used to address the issue of missing data.

Findings Of 178 children in the trial, 115 (with median gestational age (GA) of 25 + 4/7 weeks and median birth weights of 790 g) were ophthalmologically assessed at a median corrected age of 2.7 years (range 2.0–3.9 years). VA assessment was missing in 42.1% (75/178), in 41.7% (35/84) of the AA/DHA supplemented infants, and in 42.6% (40/94) of the control infants. After MI and adjustments for GA, study center, plurality, and corrected age at VA exam, no significant effect of AA/DHA supplementation was detected in VA outcome (≥20/63) (odds ratio 2.16, confidence interval 95% 0.99–4.69, p = 0.053).

Interpretation In this randomized controlled trial follow-up, postnatal supplementation with enteral AA/DHA to EPT children did not significantly alter VA at 2.5 years of corrected age. Due to the high loss to follow-up rate and the limited statistical power, additional studies are needed.

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Keywords: Preterm infant; Ophthalmological outcome; Fatty acid supplementation; Docosahexaenoic acid; Arachidonic acid

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Research in context

Evidence before this study

We searched Web of Science and PubMed for primary research literature using the terms "preterm infant", "extremely preterm infant", "fatty acid supplementation", "long-chain polyunsaturated fatty acids (LC-PUFA)", "arachidonic acid (AA)", "docosahexaenoic acid (DHA)", "visual acuity" and "opthalmological outcome". We limited our search to studies supplementing preterm infants with a few exceptions. Variations in study design, intervention regimen, and regimen duration made literature research challenging, and we found study results conflicting. We found two recent reviews concerning visual outcomes after LC-PUFA supplementation in preterms with contradictive conclusions. Moon et al. in their Cochrane review, found no improvement in visual outcomes after LC-PUFA supplementation, while Shulkin et al. reported positive effects of supplementation. Shulkin et al. concluded that varying supplementation regimes and assessment methods prohibited meta-analysis in their review.

Added value of this study

The statistical power is an issue in this study; however, we believe this study may inspire to further research if postnatal fatty acid supplementation with AA and DHA to extremely preterm is beneficial for neural components in the visual system.

Implications of all the available evidence

We believe available studies presented evidence for the importance of AA and DHA supplementation to extremely preterm infants for improved neurovascular development.

Introduction

Infants born extremely preterm (EPT) have a high risk of developing sight-threatening retinopathy of prematurity (ROP) and later ophthalmological disorders in childhood.[1–3] In patients with severe ROP, both retinal abnormalities and altered development of the primary visual pathways and visual cortex may cause visual impairment.[4,5] Regardless of previous ROP, children born EPT are more frequently affected by ophthalmological problems, including subnormal/low visual acuity (VA), refractive errors, and strabismus than term children.[1,2,6,7] Visual impairment is frequently associated with additional neurological deficits in the most immature EPT infants.[7]

The development of many organs depends on an adequate supply of long-chain polyunsaturated fatty acids (LC-PUFAs), including the ω-6 LC-PUFA arachidonic acid (AA; 20:4 ω-6) and the ω-3 LC-PUFA docosahexaenoic acid (DHA; 22:6 ω-3).[8] After EPT birth, the supply of LC-PUFAs from the mother stops abruptly, and the postnatal regimen for optimal supplementation has not been determined.[9] LC-PUFAs are important in the developing retina and brain as they are actively incorporated into neuronal cell membranes, especially during the last trimester and in the first years of life.[10–12] In a recent Swedish multicenter study, Mega Donna Mega, postnatal enteral supplementation with both AA and DHA reduced severe ROP by 50% in EPT infants.[13] Whether LC-PUFA supplementation to EPT infants favourably affects later visual development remains unclear.[14–18]

This study assessed if postnatal enteral LC-PUFA supplementation to infants in the Mega Donna Mega trial impacted the ophthalmological outcomes at 2.5 years of corrected age. We hypothesized that the beneficial effects of supplementation would include visual outcome, as LC-PUFAs are suggested to be involved in the functional maturation of the retina and visual cortex.[19]

Methods

This exploratory cohort study was a follow-up at 2.5 years of the Mega Donna Mega study, a randomized clinical trial (ClinicalTrials.gov Identifier: NCT03201588), conducted at three neonatal intensive care units in Sweden, including EPT born at less than 28 weeks of gestational age (GA) in 2016–2019. The primary aim of the Mega Donna Mega study was to evaluate if an enteral fatty acid supplementation with AA and DHA from birth to 40 weeks postmenstrual age reduced severe ROP. All included infants received nutritional support according to national guidelines. The AA/DHA intervention aimed to correspond to fetal accretion.[20] Half of the infants were randomized to the treatment and received the trial supplement, a triglyceride oil containing AA (from fungi) and DHA (from algae) (Formulaid, DSM Nutritional Products Inc), at a daily dose of 0.39 mL/kg/day, corresponding to 100 mg/kg/d AA and 50 mg/kg/d DHA. The AA/DHA supplementation was initiated within 72 h after birth and continued up to a postmenstrual age of 40 weeks, as described by Hellström et al.[13,21] The study was an open-label study.

The Regional Ethical Board at the University of Gothenburg approved the study (trial protocol in Supplement document 1), and the principles of the Declaration of Helsinki were followed. This study followed the Consolidation Standards of Reporting Trials (CONSORT) reporting guidelines (Supplement document 2).

Ophthalmological outcomes

Swedish national guidelines recommend an ophthalmologic examination at 2.5 years of corrected age of EPT born less than 28 weeks of GA. A follow-up study protocol is available at https://www.medscinet.com/rop/, which was used in this study. The child's current eye clinic was identified, the study protocols at 2.5 years of corrected age were assessed, and outcomes were verified

in the children's medical records. If no follow-up protocol was available, children's medical records were scrutinized. VA was assessed with prescribed refractive correction if present and measured monocularly or binocularly with HVOT, KM (Konstantin Moutakis), Kays or Lea Hyvärinen linear optotype charts. VA was assessed in some children with preferential-looking tests such as Teller acuity cards, Cardiff, and Kasper tests which require less active participation. The examiner had the choice of the method for visual assessment depending on the child's ability to cooperate. VA results were converted to Snellen acuity before statistical analysis. The best monocular VA was recorded. If only binocular VA was available, this was recorded. We divided the results into VA categories; VA <20/63 or ≥20/63, as this is considered a stringent threshold for normal VA in children at 30–35 months of age.[22] If the child could not complete or participate in the VA test, the examiner was to test (according to the study protocol) if the child could follow and fixate a light or toy at a 30 cm distance. Referral to a low-vision clinic was recorded. The study protocol included five screening questions for cerebral visual impairment (CVI) and if CVI was suspected or diagnosed, this was recorded.

Refraction was measured after cycloplegia. The spherical equivalent (SE) was calculated. Refractive errors were defined as hyperopia or myopia if the error was >3 Diopters (D) SE or if astigmatism was >2 D in the best eye. Anisometropia was defined as >2 D difference between the eyes. Spectacle prescription before or at the 2.5-year examination was recorded. Strabismus (manifest and intermittent) and nystagmus were recorded.

Statistical analysis

Because this was an exploratory study, no a priori formal statistical analysis plan was written. Numbers and percentages were given for categorical variables, and medians and ranges were applied for continuous variables. Mann–Whitney U test was used for testing two groups with respect to a continuous variable. Between-group tests were performed by using Pearson's chi-square test, Fisher's exact test, and Mantel-Haenszel chi-square trend test for non-ordered, dichotomous, and ordered categorical variables, respectively. A p-value <0.05 was considered statistically significant (two-sided tests).

The primary variable was favorable VA (defined as VA ≥20/63) at 2.5 years of corrected age. A high rate of loss to follow-up was noted, and therefore multiple imputation (MI) was performed for the primary variable. Infants' characteristics, clinical and comorbidity data, mothers' ages, comorbidity, and pregnancy data were considered for inclusion. The following variables associated with VA at 2.5 years and/or its missingness at $p < 0.20$ were included in the MI model: treatment, study center, mother's age, preeclampsia, way of delivery, parity, plurality, standardized head circumference at birth, serum AA and DHA levels at birth, intraventricular hemorrhage, bronchopulmonary dysplasia, ROP treatment, duration of treatment exposure, and age at 2.5-year visit. Fifty multiple imputation studies were performed using multivariate normal distribution before pooling the results. Unadjusted and adjusted logistic regression analyses were used to evaluate the impact of AA/DHA supplementation on favourable VA ≥20/63 in the whole cohort (n = 178) and in the complete cases (n = 103). Adjustments were made for GA, center, plurality, and age at the follow-up visit. An additional adjustment analysis was made, including ROP severity as a mediator. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for favourable VA ≥20/63. Secondary outcomes were overall ophthalmological results such as visual testing details, strabismus, nystagmus, and refractive errors, and were only studied in the complete cases cohort without adjustments.

All analyses were done with IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY, IBM Corp.) and SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the Mega Donna Mega study, 178 infants had completed ROP screening and were eligible for this follow-up study. In 115 of the 178 children, an ophthalmological examination had been conducted according to the study protocol at 2.5 years of corrected age or due to clinical indication ≥2 years but <4 years of corrected age. One center did not routinely schedule EPT infants for the 2.5-year follow-up. However, 28 children were referred to the center, and 16 were ophthalmologically examined between the ages of 2 and <4 years and included in the study, Fig. 1. Of the 115 children ophthalmologically examined, 103 had been visually assessed at the examination. In 12 children, VA results were missing, and failure to cooperate was described in five of them (three controls and two AA/DHA supplemented). The other seven missing VA outcomes had been referred and examined at the center which did not schedule children for follow-up, and no visual examination had been performed. Thus, in total 42.1% (75/178) of infants did not have evaluable data for VA, 41.7% (35/84) of the AA/DHA supplemented infants, and 42.6% (40/94) of the control infants.

Table 1 presents characteristics of the children in the whole cohort (n = 178), complete cases (n = 115), complete cases stratified by study arm (controls, n = 62, and AA/DHA supplemented, n = 53), and infants not examined (n = 63). There were no significant differences

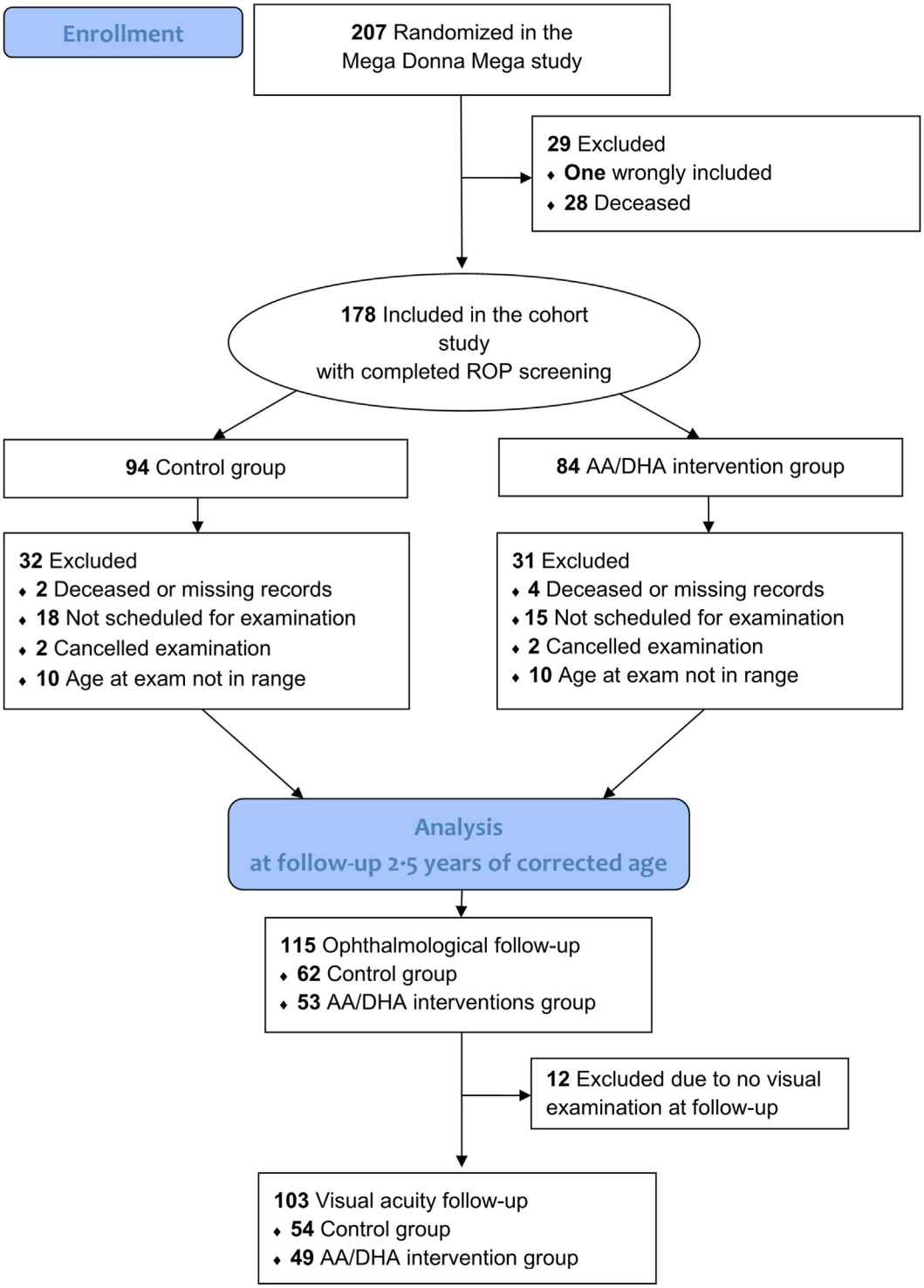

Fig. 1: Flowchart of the study population. "Ophthalmological examination available" is defined as an examination available at ≥ 2 years but <4 years of corrected age.

in any of the presented variables in Table 1 between the complete cases and infants not examined (variables in italics).

In complete cases, the median age at ophthalmological (n = 115) and at visual examination (n = 103) was 2.7 years corrected age (range 2.0–3.9 years).

AA/DHA supplementation and visual acuity ≥20/63

Following MI to account for missing data, we found a significant beneficial impact of AA/DHA supplementation on VA ≥20/63 in the unadjusted logistic regression (OR 2.39, 95% CI 1.13–5.05, p = 0.022), but the results did not persist in the adjusted logistic regression (OR 2.16, 95% CI 0.99–4.69, p = 0.053). Study center, DHA at birth, and AA at birth were the variables most responsible for the change between the primary analysis of the complete cohort (n = 178) and sensitivity analysis of the complete cases visually examined (n = 103). Additional adjustment for ROP severity did not alter the results for VA outcome, Table 2.

Visual acuity in complete cases

Results from VA testing were available in 89.6% (103/115) of the children ophthalmologically examined, and monocular VA was available in 72.5% (74/103). About two-thirds of the children had been tested with optotypes. VA acuity was ≥20/63 in 73.8% (76/103) of the children, Table 3. Seven untreated control children and one supplemented child were categorized as having a VA <20/63 as they could not complete or participate in VA testing but could fixate and follow a flashlight or a toy at a 30 cm distance. One child in the control group could not fixate or follow a target even when tested and was also classified as having VA <20/63.

Overall ophthalmological outcome in complete cases

In the complete cases (n = 115), hyperopia (16.8%) was more prevalent than myopia (4.0%). Myopia was exclusively found in the untreated control group. Three of the four myopic children had received ROP treatment. Spectacles were prescribed in 18.3% of the children, and strabismus was diagnosed in 18.9%. Esotropia was more commonly found (55.0%) than exotropia, (30.0%). Nystagmus was recorded in three children, 2.6%, Table 3.

Visual impairment in complete cases

Four children (4.2%) in the complete case cohort had been referred to a low-vision clinic, of whom three were in the untreated control group. CVI had not been diagnosed in any child.

Discussion

In this exploratory follow-up of the Mega Donna Mega study of children born EPT, we report visual outcomes at 2.5 years corrected age after postnatal enteral AA/DHA supplementation. When approaching the low follow-up rate statistically with MI, we found a positive impact of AA/DHA supplementation in the unadjusted analysis. However, our result was no longer significant (p = 0.053) when adjusting for GA, center, plurality, and age at the visual examination, indicating that additional studies are needed. Study center was identified as most responsible for the change between results in the primary analysis (whole cohort) and sensitivity analysis (complete cases). We hypothesize that the study center's impact may partly be because data from one center was derived from children exclusively examined by clinical indication and not by the study protocol.

The importance of AA and DHA as major structural and functional components in the developing central nervous system (i.e, retina and brain) is well established.[10–12] It has been suggested that AA and DHA promote membrane integrity and prevent oxidative stress damage in the central nervous system and in the vasculature.[10] The complex visual system comprises several neural structures; the photoreceptors in the retina convert the visual stimulus into electrical signals,

Birth characteristics	Whole cohort (n = 178)	Complete cases (n = 115)	Complete cases control group (n = 62)	Complete cases AA/DHA group (n = 53)	Infants not examined (n = 63)
Gestational age (weeks + days)	25 + 4/7 (22 + 4/7–27 + 6/7)	*25 + 4/7*[a] *(22 + 4/7–27 + 6/7)*	25 + 4/7 (23 + 0/7–27 + 6/7)	25 + 4/7 (22 + 4/7–27 + 6/7)	*25 + 6/7*[a] *(22 + 6/7–27 + 5/7)*
Birth weight (grams)	787 (425–1345)	*790*[a] *(425–1330)*	787 (425–1330)	790 (470–1220)	*775*[a] *(455–1345)*
Sex (boys)	56.7% (101/178)	*58.3%*[b] *(67/115)*	54.8% (34/62)	62.3% (33/53)	*54.0%*[b] *(34/63)*
ROP outcome					
No ROP	40.4% (72/178)	*44.3%*[c] *(51/115)*	45.2% (28/62)	43.4% (23/53)	*33.3%*[c] *(21/63)*
Mild ROP (stages 1 and 2)	30.9% (55/178)	*30.4%*[c] *(35/115)*	19.4% (12/62)	43.4% (23/53)	*31.7%*[c] *(20/63)*
Severe ROP (stages ≥3)	28.7% (51/178)	*25.2%*[c] *(29/115)*	35.5% (22/62)	13.2% (7/53)	*34.9%*[c] *(22/63)*
ROP treatment	20.2% (36/178)	*21.7%*[b] *(25/115)*	30.6% (19/62)	11.3% (6/53)	*17.5%*[b] *(11/63)*

Values are presented as median (min–max) or as % (n). Abbreviation: ROP, retinopathy of prematurity. [a]Mann–Whitney U test. [b]Pearson's chi-square test. [c]Mantel-Haenszel Chi-square trend test. When analysing differences between the complete cases and the infants not examined according to [a], [b] and [c], no significant differences were detected (variables in italics).

Table 1: **Characteristics of children and ROP outcome in the whole cohort, complete cases cohort stratified by study arm and in infants not examined.**

Analysis of VA ≥20/63 at 2.5 years corrected age	AA/DHA versus control	
	OR (95% CI)	p-value
Primary analysis		
Whole cohort including MI (n = 178), unadjusted	2.39 (1.13–5.05)	0.022
Whole cohort including MI (n = 178), adjusted for GA, center, plurality, and corrected age at visual exam	2.16 (0.99–4.69)	0.053
Whole cohort including MI (n = 178), adjusted for GA, center, plurality, corrected age at visual exam, and ROP severity	2.11 (0.95–4.67)	0.066
Sensitivity analysis		
Complete cases visually assessed (n = 103), unadjusted	3.53 (1.34–9.33)	0.011
Complete cases visually assessed (n = 103), adjusted for GA, center, plurality, and corrected age at visual exam	3.39 (1.17–9.86)	0.025
Complete cases visually assessed (n = 103), adjusted for GA, center, plurality, corrected age at visual exam, and ROP severity	3.91 (1.20–12.79)	0.024

Abbreviations: AA, arachidonic acid; CI, confidence interval; DHA, docosahexaenoic acid; GA, gestational age; MI, multiple imputations; OR, odds ratio; VA, visual acuity; ROP, retinopathy of prematurity. ROP severity in the second adjustment primary and sensitivity analysis should be seen as a mediator rather than a confounder.

Table 2: **Unadjusted and adjusted logistic regression evaluating AA/DHA versus control group and favourable VA ≥20/63 at 2.5 years corrected age.**

and the optic nerve and visual pathway transfer the signals to the occipital cortex and the temporal and parietal lobes of the brain for processing and interpretation. Besides affecting retinal maturation, we suggest that fatty acid supplementation affects all neural components in the visual system, and previous ROP thus is of impact but not solely for visual outcome. We did not identify ROP severity to have any impact on VA outcome in this study. Future preclinical studies should aim to clarify the exact mechanism of how AA and DHA affect retinal maturation, ROP development, and visual outcome.

Prior studies are inconsistent regarding visual outcomes after LC-PUFA supplementation in preterms. Moon et al. found in their Cochrane review that there was no support for improved visual outcomes after LC-PUFA supplementation (DHA and AA) via formula milk to preterm infants (GA <37 weeks), while Shulkin et al. reported positive effects of supplementation (various combinations of DHA, AA and eicosapentaenoic acid).[23,24] The evidence in many publications is difficult to compare due to varying supplementation regimes and assessment methods prohibiting meta-analysis.[24]

Variables	Complete cases (n = 103)	Complete cases control group (n = 54)	Complete cases AA/DHA group (n = 49)	p-value
Corrected age at visual assessment (years)	2.7 (2.0–3.9)	2.7 (2.0–3.3)	2.8 (2.0–3.9)	0.065
	Complete cases (n = 115)	**Complete cases control group (n = 62)**	**Complete cases AA/DHA group (n = 53)**	**p-value**
Corrected age at ophthalmological assessment (years)	2.7 (2.0–3.9)	2.7 (2.0–3.3)	2.8 (2.0–3.9)	0.057
Visual outcome (n = 103)				
Visual acuity ≥20/63	73.8% (76/103)	63.0% (34/54)	85.7% (42/49)	0.009
Optotype test	62.4% (63/101)[a]	58.5% (31/53)[a]	66.7% (32/48)[a]	0.40
Preferential looking test	29.7% (30/101)[a]	28.3% (15/53)[a]	31.3% (15/48)[a]	0.75
Follow and fixate light or toy at 30 cm	7.9% (8/101)[a]	13.2% (7/53)[a]	2.1% (1/48)[a]	0.062
Referred to a low-vision clinic	4.2% (4/96)[b]	6.1% (3/49)[b]	2.1% (1/47)[b]	0.62
Ophthalmological outcome (n = 115)				
Strabismus	18.9% (20/106)[c]	19.3% (11/57)[c]	18.4% (9/49)[c]	0.90
Spectacles at 2.5 years	18.3% (21/115)	17.7% (11/62)	18.9% (10/53)	0.88
Nystagmus	2.6% (3/115)	3.2% (2/62)	1.9% (1/53)	1.00
Refraction (the best eye refraction error) (n = 115)				
Any refractive error	20.8% (21/101)[d]	26.9% (14/52)[d]	14.3% (7/49)[d]	0.12
Hyperopia (>3 D SE)	16.8% (17/101)[d]	19.2% (10/52)[d]	14.3% (7/49)[d]	0.51
Myopia (>3 D SE)	4.0% (4/101)[d]	7.7% (4/52)[d]	0% (0/49)[d]	0.12
Astigmatism (>2 D SE)	3.0% (3/101)[d]	3.8% (2/52)[d]	2.0% (1/49)[d]	1.00
Anisometropia (>2 D SE)	7.9% (8/101)[d]	3.8% (2/52)[d]	12.2% (6/49)[d]	0.15

Values are presented as median (min–max) or as % (n). Abbreviations: D, diopters; SE, spheric equivalent. [a]Data missing in two children, one control and one AA/DHA supplemented. [b]Data missing in seven children, four controls and three AA/DHA supplemented. [c]Data missing in nine children, five controls and four AA/DHA supplemented. [d]Data missing in 14 children, 10 controls and four AA/DHA supplemented.

Table 3: **Visual (n = 103) and ophthalmological outcomes in complete cases (n = 115).**

Most studies evaluating LC-PUFA supplementation do not report subsequent LC-PUFA levels in the children, making it difficult to determine the actual effect of the intervention. In this study cohort, we previously reported higher fractions of both AA and DHA in serum in supplemented infants compared to the controls. The most immature infants had the highest increase in AA and DHA serum fractions in response to the supplementation.[13] To our knowledge, we are the first to report outcomes in EPT with verified higher fractions of AA and DHA after supplementation. Makrides et al. and Uauy et al. reported that DHA levels correlate with visual development in term infants.[25,26] Children fed human milk have higher levels of LC-PUFAs and better VA than those fed formula (even though the formula is LC-PUFA supplemented).[25,27] The LC-PUFA needs of EPT and also of term infants are not well understood, and there is an ongoing discussion regarding AA and DHA fortification of infant formula. The European Food Safety Authority recommends fortification with DHA in infant formula in higher concentrations than that found in human milk, but does not yet suggest a need to include AA.[9] In a position paper, the European Academy of Paediatrics and the Child Health Foundation presented evidence for the importance of AA supplementation during infancy and they strongly recommended supplementation of AA in infant formula at concentrations that are at least equal to that of DHA.[28] In the present study, no group was supplemented with DHA alone, so we cannot evaluate the importance of AA on visual outcome specifically.

In this study, we used the cut-off VA ≥20/63, which is a validated threshold for "normal VA outcome" in children at 30–35 months of age.[22] Some children could not participate in any visual testing, including tracking an object at near. The reason for the inability to participate was sometimes stated in the medical records as suspected neurological deficits. Additional neurological testing in this group should be explored. A recent study evaluating infants born at less than 24 weeks of GA found a clear correlation between visual impairment and neurological deficits.[7] Poor VA found with early testing has been associated with a later diagnosis of cognitive impairment.[29]

In the youngest children that are not able to actively participate in testing, VA can only be assessed with preferential-looking tests, such as Teller acuity cards, Cardiff or Kasper tests, and results must be interpreted with care. In particular, studies evaluating the benefits of supplementation using Teller cards to measure VA have shown inconsistent results.[27,30] However, Carlson et al. reported better VA in preterm infants given omega-3 supplemented formula (up to 2 months post expected term age) using Teller acuity cards at two and four months post-term but not at six, nine, and twelve months potentially indicating some initial benefits.[14,31]

The visual pathway function can be evaluated by visual evoked potential (VEP). VEP exposes the eye to a visual stimulus, then records the brain's electrical response, thus minimizing the need for the child's cooperation. O'Connor et al. reported improved visual development assessed as mean VEP acuity at six months in AA/DHA supplemented (up to 12 months post expected term age) preterm infants. However, no VA differences between supplemented infants and controls were detected using Teller acuity cards at two, four, and six months.[16] Higher VEP acuity and more mature VEP wave latency among preterm children supplemented with DHA have been reported by others.[14,32] Shulkin et al. reported a more powerful effect of LC-PUFAs in children when using VEP compared with behavioral VA measures in their review.[23]

Most studies evaluate infants up to 12 months of age, during which visual testing is challenging. The child's ability to cooperate and normal diversity in visual development may impact the outcome. However, in long-term follow-up, neither Collins et al. nor Molloy et al. reported benefits in visual outcomes in 7 years old preterm-born children after DHA supplementation.[17,33] The mechanism of improved visual outcome in the AA/DHA supplemented children in the present study needs to be explored, and further follow-up of the current cohort is in progress.

Four children in our complete case cohort had been referred to a low-vision clinic (4.2%), of whom three were in the untreated control group. CVI was rarely considered at the 2.5-year follow-up, and information regarding the presence, absence, or attempts to identify symptoms of CVI was missing in most children's medical files. However, visual perceptual problems, a hallmark of CVI may be more evident in older children. Previous studies have indicated that CVI might be underdiagnosed in children born EPT.[6] CVI is caused by malfunction of the higher-order visual cortical tracts, and children born EPT are especially vulnerable to damage of these pathways.[34] DHA is vital for several visual processes, including phototransduction in the retina, and the maturation of the cortical visual pathway. The relationship between LC-PUFA supplementation and its possible role in influencing the cortical visual pathways is a major research gap and warrants further attention.[35]

Our findings on overall ophthalmological outcomes in EPT infants at 2.5 years of age are similar to other studies such as Holmström et al., who reported strabismus in 14.1% and refractive errors in 25.6% of children born less than 27 weeks GA at 2.5 years of age.[2,6,7]

Limitations

Because the study of necessity was exploratory in nature, there was no predetermined statistical analysis plan, which is an inherent limitation. A major limitation is the 42% missing data, primarily from one site that did not follow the study protocol for an ophthalmological

exam at 2.5 years of corrected age. The results may have differed if there was a higher follow-up rate; thus, the statistical power was limited. Another limitation of our study is that nutrition was not controlled beyond the postmenstrual age of 40 weeks.

Conclusions

The current study is, to our knowledge, the first to report a relatively long-term ophthalmological follow-up at 2.5 years of corrected age in a cohort of children born EPT with a documented increase in both AA and DHA after receiving postnatal enteral lipid supplementation. In this exploratory study, we could not conclude if postnatal supplementation with AA/DHA significantly affected VA outcome at 2.5 years of corrected age in EPT infants. As the follow-up rate was low and statistical power was limited, we stress the importance of additional studies.

Contributors

Dr Lundgren and Professor Hellström had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Dr Lundgren and Professor Hellström. Acquisition of data: Dr Lundgren, Professor Hellström, Dr Jacobson, and Dr Gränse. Analysis or interpretation of data: All authors. Drafting of the manuscript: Dr Lundgren and Professor Hellström. Critical revision of the manuscript for important intellectual content: All authors. Approval of the final manuscript: All authors. Statistical analyses: MSc Pivodic and Dr Lundgren. Administrative, technical, or material support: All authors.

Data sharing statement

Due to the nature of the research, supporting data is not available.

Declaration of interests

The authors declare no competing financial interests. DSM Nutritional Products Inc. provided Formulaid.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2023.100696.

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