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ORIGINAL ARTICLE

Associations between neonatal nutrition and visual outcomes in 7-year-old children born very preterm

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Abstract

Purpose: There is uncertainty about the effect of increased neonatal protein intake on neurodevelopmental outcomes following preterm birth. The aim of this study was to assess the effect of a change in neonatal nutrition protocol at a major tertiary neonatal intensive care unit intended to increase protein intake on ophthalmic and visual development in school-age children born very preterm.

Methods: The study cohort comprised children ($n = 128$) with birthweight <1500 g or gestational age < 30 weeks born at Auckland City Hospital before (OldPro group, $n = 55$) and after (NewPro group, $n = 73$) a reformulation of parenteral nutrition that resulted in increased total protein intake during the first postnatal week and decreased carbohydrate, total parenteral fluid and sodium intake. Clinical and psychophysical vision assessments were completed at 7 years' corrected age, including visual acuity, global motion perception (a measure of dorsal stream function), stereoacuity, ocular motility and ocular health. Composite measures of favourable overall visual, binocular and functional visual outcomes along with individual vision measures were compared between the groups using logistic and linear regression models.

Results: Favourable overall visual outcome did not differ between the two groups. However, global motion perception was better in the NewPro group ($p = 0.04$), whereas the OldPro group were more likely to have favourable binocular visual outcomes (60% vs. 36%, $p = 0.02$) and passing stereoacuity ($p = 0.02$).

Conclusions: These results indicate subtle but complex associations between early neonatal nutrition after very preterm birth and visual development at school age.

KEYWORDS
binocular vision, motion perception, premature birth, protein

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INTRODUCTION

Children born preterm are at an increased risk of visual impairment.[1] Retinopathy of prematurity (ROP) is a serious concern for children born preterm and requires prompt treatment.[2–6] However, the effects of preterm birth on vision extend beyond the eye to affect cortical visual processing and neuropsychological development.[7]

Within the brain, visual information is processed in two interconnected parallel pathways.[8,9] The dorsal cortical stream projects from the parvocellular layers of the lateral geniculate nucleus (LGN), through the primary visual cortex (V1) and the motion-sensitive middle temporal area (area V5), to the parietal lobes[10] and supports visuo-motor control.[11] The ventral cortical stream projects from the parvocellular layers of the LGN to V1 and the form-sensitive areas of the temporal lobe (V4),[10] and underpins conscious visual awareness and object recognition.[11] Dorsal stream function can be measured indirectly using a psychophysical stimulus called a random dot kinematogram (RDK) to assess motion integration. Performance on this psychophysical task, quantified as a motion coherence threshold,[12] is associated with visuo-motor performance and anatomical features of the parietal lobe.[13–15] Ventral stream function can be measured similarly using a psychophysical task that requires the integration of local form cues.[16,17] Children born preterm have poorer performance on these psychophysical tasks than non-preterm controls, and the performance deficit is greater for motion than for form integration, suggesting a greater impact of preterm birth on dorsal stream function.[18–21]

Parenteral and/or enteral postnatal nutrition may modulate the impact of preterm birth on neurodevelopment.[22] For example, in children born extremely preterm, higher protein intake during the first postnatal month was associated with stronger structural and intrinsic functional connectivity in the prefrontal cortices in mid-childhood.[23] High protein and energy intake for 12 months were also associated with increased head circumference and corticospinal conductivity in both preterm and full-term babies with brain injury.[24] Later studies also observed an association between greater nutritional intake in the first 2 weeks of life and enhanced brain growth and white matter maturation.[25,26] Increased energy and protein intake is also associated with a higher Mental Development Index[27] and better full-scale IQ[28] and verbal IQ[29] scores in later childhood for children born preterm. However, potential adverse effects of early higher intake of parenteral protein on neurodevelopmental outcomes also have been reported.[30] Thus, the optimal combinations and volumes of macromolecular nutrients for preterm babies remain unclear.[22,31]

The aim of this study was to explore the association between nutrition following preterm birth and ocular and vision development at school age. We analysed clinical and psychophysical vision data collected from a cohort of 7-year-old children who were born very preterm at Auckland City Hospital before and after a reformulation of parenteral nutrition solutions in the Neonatal Intensive Care Unit (NICU) that increased total protein intake and reduced fluid intake in the first weeks after birth. Because of the reduced fluid intake, the change in nutrition also reduced carbohydrate intake. Paediatric, neurodevelopmental and neuroimaging outcomes in these children have been reported previously.[23,32–34]

Key points

- Neonatal nutrition following preterm birth was associated with visual neurodevelopment.
- Increased neonatal protein and reduced carbohydrate intake after preterm birth were associated with improved global motion perception but decreased stereopsis in school-age children.
- Vision measures should be included in future follow-up studies of neonatal nutrition interventions for children born preterm.

METHODS

We analysed data from a cross-sectional, matched cohort study conducted at the Liggins Institute, University of Auckland (New Zealand) that recruited 536 babies with birth weight <1500 g or gestational age <30 weeks cared for in the NICU at Auckland City Hospital from July 2005 to October 2008 (Figure 1). To align with changes to recommended nutritional intake for preterm babies, the parenteral nutrition solution was reformulated in January 2007.[35] Babies born before 2007 were given the original parenteral formulation containing amino acids, minerals and electrolytes, made up in 10% dextrose solution, henceforth referred to as the old protocol (OldPro) group. Those born from 2007 onwards were given a new parenteral solution with increased total protein concentration and decreased carbohydrate, total fluid and sodium (the NewPro group; see Tables S1–S3).

Families were traced and all surviving participants were invited to attend an assessment at 7 years ± 6 months corrected age between December 2012 and March 2016. Detailed descriptions of the full study protocol have been published previously.[23,32–34,36] Of the 201 participants available for follow-up, 128 underwent the visual assessment.

Visual assessment

Composite visual functions including overall visual, binocular and functional visual outcomes were evaluated as well as visual acuity (VA), global motion perception, and morphological and refractive data. We used composite outcomes to reduce the risk of a type 1 error. We also analysed

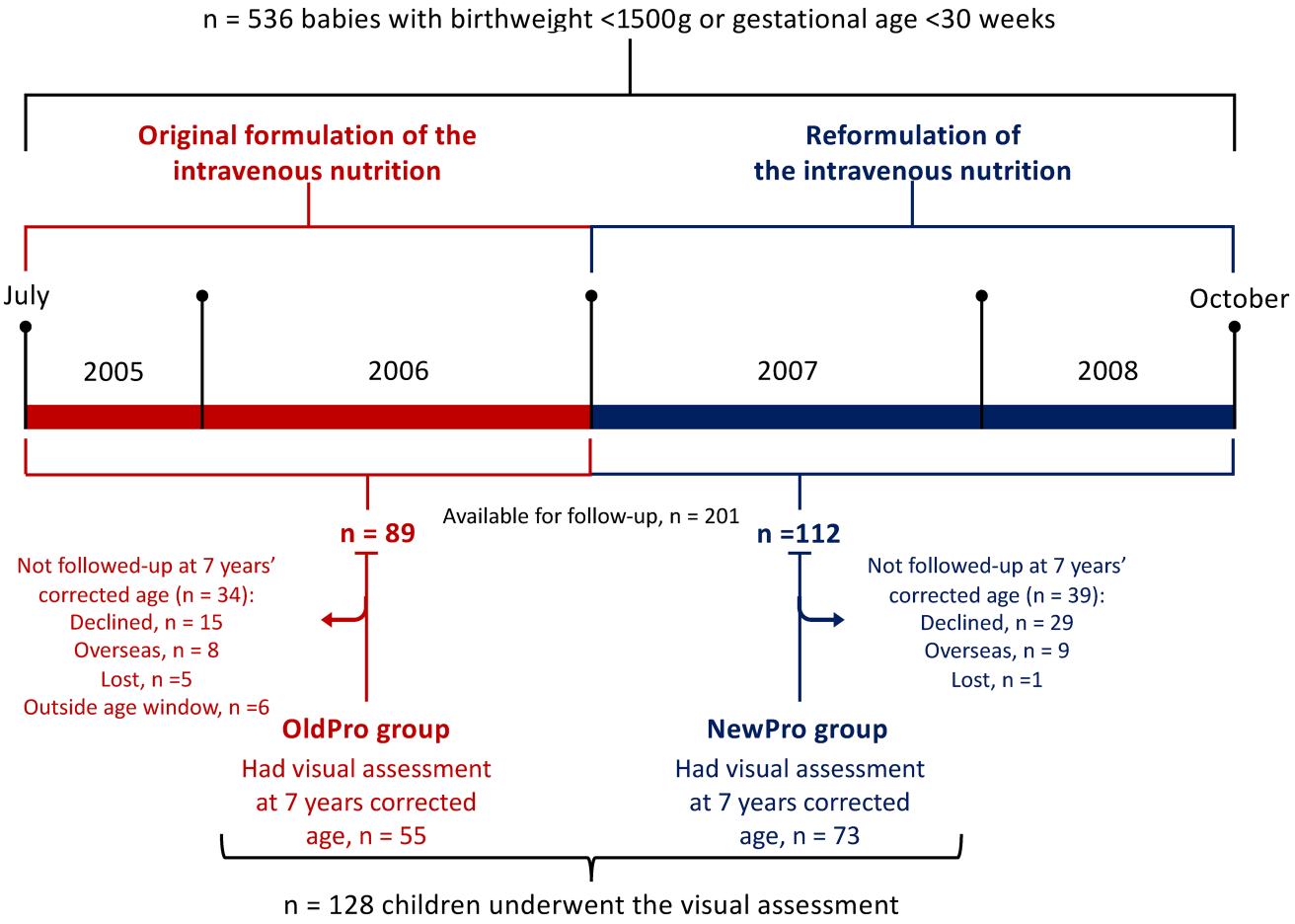

FIGURE 1 Recruitment of study participants for the follow-up visual assessment.

all components of the composite measures separately as secondary outcomes. For all measurements that involved separate eyes, a better and poorer eye were identified depending on the level of VA. If VA was the same between the eyes, then the eye with less refractive error was labelled the better eye. For children who wore spectacles, tests were performed with refractive correction. Details of VA measurement, ocular alignment and motility, binocular motor fusion, examination for nystagmus and palpebral aperture abnormalities, TNO stereoacuity (lameris-group.nl/producten/lameris-tno-stereotest/), RDKs[14] for the global motion perception, ocular biometry, autorefraction and keratometry were provided in our previous report[36] and are presented in Appendix S1.

Favourable overall visual outcome was defined if a participant had good distance VA (equal or better than 6/12 vision in the better eye), no strabismus, passed TNO stereoacuity (≤240 arc second) and did not require spectacles for refractive error in either eye (spherical equivalent refraction >−0.50 to <+2.00 D and cylinder <1.00 DC). Favourable binocular visual outcome was defined as no strabismus, no nystagmus, normal ocular motility (full unrestricted movement in all gazes) and convergence (to ≤10 cm from the eyes), the presence of motor fusion (able to overcome 20Δ base out prism) and passing TNO stereoacuity. Favourable functional visual outcome was defined as good distance VA (can be wearing spectacles), no strabismus and passing TNO stereoacuity.

Data on birth weight, sex, gestational age and nutritional intake were obtained from the electronic neonatal medical record. Ethical approval was obtained from the Northern Y Regional Ethics Committee (NTY/12/05/035) of the New Zealand Ministry of Health. Written informed consent was obtained from the parents or legal guardians, and the child gave verbal assent.

Statistical analysis

Statistical calculations were performed using SPSS Statistics 22 (ibm.com). Potential confounders likely to be strongly associated with outcomes included sex, gestational age, birth weight *z*-score, socio-economic status (New Zealand deprivation index at birth),[37] multiple births and Clinical Risk Index for Babies (CRIB) score.[38] These were compared between the OldPro and NewPro groups for children who were assessed at 7 years of age. Only sex and birth weight *z*-score differed by more than 10% between the two groups and were included as covariates when comparing the outcomes of the two groups.

Descriptive data are presented as number (%), mean (standard deviation, SD) or median (interquartile range, IQR). All outcomes were compared between the NewPro and OldPro groups using unadjusted and adjusted logistic and linear regression models and are presented as odds ratios (OR) or the mean difference between groups, with a 95% confidence interval (CI) and *p*-value.

RESULTS

Infants in the NewPro group had a significantly higher intake of protein in the first week after birth, lower intake of carbohydrates in the first week and month after birth and tended to have lower fat intake in the first month after birth than babies in the OldPro group (Table 1). Although the NewPro group had a lower energy intake than the OldPro group in the first week and month after birth, they received a greater proportion of their energy from parenteral protein.

Maternal and perinatal baseline characteristics of all participants have been published elsewhere.[34] For participants with vision outcome measures, there were no statistically significant differences between the OldPro versus NewPro groups for maternal characteristics, neonatal baseline demographics and complications (Table S4); and weight, height and head circumference *z*-scores at birth, 28 days after birth and at 36–40 gestational weeks.

At the time of assessment, the mean corrected age of all participants was 7.2 (±0.1) years and there was a similar proportion of boys and girls (Table 2). Children in the OldPro group tended to have higher socio-economic status at 7 years of age, but there were no statistically significant between-group differences in anthropometric measurements (Table 2). Thirteen children wore spectacles (OldPro = 5, NewPro = 8).

Favourable overall visual outcome occurred in 61%–65% of participants and did not differ significantly between the two groups (Table 3). However, favourable binocular visual outcomes were more common in the OldPro group (60% vs. 36%, adjusted OR [aOR]: 2.55, 95% CI: 1.16–5.61, $p = 0.02$) along with passing stereoacuity (Figure 2). In contrast, global motion perception was significantly better in the NewPro group (adjusted mean difference in threshold 8.95, CI: 0.55–17.35, $p = 0.04$). Because a previous study of this cohort indicated an increased risk of cerebral palsy in the NewPro group,[34] the analysis was repeated with cases of cerebral palsy excluded ($n = 10$ total, $n = 8$ who could be assessed Table 3, Figure 3). The group difference in favourable binocular visual outcome remained significant. There was little change in the ORs or mean difference, but the CIs were wider and no longer met statistical significance for passing TNO stereoacuity ($p = 0.10$) and motion coherence thresholds ($p = 0.06$). To assess whether this was due to reduced statistical power or a particular characteristic of the children with cerebral palsy, we compared the motion coherence thresholds between children with and without cerebral palsy. The thresholds did not differ significantly, and the distribution of thresholds for the cerebral palsy group covered the full range of thresholds from the non-cerebral palsy group (Figure 3). In addition, of the seven children with cerebral palsy who completed stereopsis testing, five had measurable stereopsis and two did not.

Components of the composite visual outcomes (including VA, ocular motility and convergence, retinal findings, the presence of strabismus, nystagmus and motor fusion, refractive error and ocular morphological measurements) were similar or did not show a clinically significant difference between the OldPro and NewPro groups (Table S5). The proportion of children with ocular abnormalities requiring further follow-up or referral was the same for both groups. These included macula ectopia or macula scarring due to severe ROP (five children), blood vessel straightening (two children) and dot haemorrhages in the retina (two children).

DISCUSSION

Increased protein and decreased carbohydrate intake following very preterm birth were not associated with a difference in the composite measure of overall visual outcome or secondary outcomes relating to ocular structure and refractive development. However, secondary outcomes relating to binocular vision and global motion perception (an indirect measure of dorsal stream function) revealed a complex effect of neonatal nutrition on visual development. In the NewPro group, binocular visual outcomes were decreased relative to the OldPro group, primarily due to decreased stereopsis in the NewPro group, whereas global motion perception was better in the NewPro group. Differences in motion coherence threshold and passing stereopsis no longer reached statistical significance when children with cerebral palsy were excluded from the analysis. For motion coherence thresholds, a post-hoc comparison of children with and without cerebral palsy suggested that this effect was due to reduced statistical power rather than cerebral palsy. Similarly, five of the seven children with cerebral palsy who completed the Randot stereo test had measurable stereopsis, also suggesting that reduced statistical power caused the loss of statistical significance, not cerebral palsy itself. Together, the current results and the results from our previous analyses[34] suggest that the change in nutrition was associated with altered global motion, stereopsis and risk for cerebral palsy. It is possible that these changes fall along the same causal pathway.

Although these group differences were small from a clinical perspective, reduced stereopsis in the NewPro group is of concern due to the growing interest in even higher neonatal protein intake.[39] In a recent study by Bloomfield et al.,[30] higher parenteral amino acid intake (1 g/day for 5 days after birth) in babies with birthweight <1000 g did not increase the survival rate free from neurodisability at

TABLE 1 Neonatal nutritional intake of children exposed to original IVN formulation and IVN reformulation who were and were not assessed for visual outcomes at 7 years' corrected age.

	OldPro group ($n = 89$)			NewPro group ($n = 112$)			p-Value OldPro vs. NewPro assessed for visual outcomes
	Assessed for visual outcomes ($n = 55$)	Not assessed for visual outcomes ($n = 34$)	p-Value	Assessed for visual outcomes ($n = 73$)	Not assessed for visual outcomes ($n = 39$)	p-Value	
P:E ratio (g/kcal): Days 0–7	2.77 ± 0.23	2.84 ± 0.22	0.18	3.68 ± 0.43	3.69 ± 0.40	0.90	0.0001
P:E ratio (g/kcal): Days 0–14	2.70 ± 0.12	2.75 ± 0.15	0.09	3.18 ± 0.35	3.19 ± 0.28	0.88	<0.0001
The percentage of total protein received parenterally: Days 0–7, mean ± SD [%]	73 ± 18	72 ± 22	0.81	83 ± 15	84 ± 13	0.73	<0.0001
The percentage of total protein received parenterally: Days 0–14, mean ± SD [%]	40 ± 21	44 ± 27	0.43	55 ± 22	53 ± 21	0.66	<0.0001
Nutritional intake (mean ± SD)							
Protein (g/kg/day)							
Week 1	2.34 ± 0.32	2.36 ± 0.40	0.74	2.92 ± 0.36	2.90 ± 0.42	0.78	< 0.0001
Month 1	3.32 ± 0.33	3.32 ± 0.34	0.97	3.41 ± 0.25	3.45 ± 0.31	0.53	0.06
Carbohydrate (g/kg/day)							
Week 1	11.70 ± 1.42	11.70 ± 1.61	0.99	10.07 ± 1.38	10.10 ± 1.33	0.92	< 0.0001
Month 1	15.11 ± 1.47	15.29 ± 1.31	0.56	14.24 ± 1.30	14.27 ± 1.45	0.92	0.001
Fat (g/kg/day)							
Week 1	3.60 ± 0.76	3.51 ± 1.04	0.68	3.48 ± 0.76	3.36 ± 0.64	0.39	0.39
Month 1	6.12 ± 0.83	6.12 ± 0.72	0.98	5.82 ± 0.91	5.95 ± 0.86	0.49	0.06
Energy (kcal/kg/day)							
Week 1	84.39 ± 9.92	83.70 ± 15.47	0.82	80.08 ± 9.61	78.86 ± 8.98	0.51	0.01
Month 1	127.10 ± 13.90	127.90 ± 12.32	0.80	121.30 ± 14.08	122.90 ± 14.34	0.60	0.02

Note: Data are mean ± SD.

Abbreviations: IVN, intravenous nutrition; P:E, protein to energy ratio; SD, standard deviation.

TABLE 2 Characteristics of children ($n = 128$) at the time of assessment in the OldPro and NewPro groups.

Characteristics	OldPro group ($n = 55$)	NewPro group ($n = 73$)	OldPro vs. NewPro p-value
Age at assessment, years	7.2 ± 0.1	7.2 ± 0.1	0.81
Boys	26 (47%)	42 (58%)	0.25
Year at school	3 (1, 3)	3 (2, 4)	0.71
Cerebral palsy	1 (2%)	9 (12%)	0.06
Deprivation index			
Most deprived decile	4 (7%)	15 (21%)	0.06
Least deprived decile	11 (20%)	4 (5%)	
Anthropometry			
Weight, kg	23.2 (19.4, 25.4)	24.6 (22.1, 27.4)	0.18
Height, cm	122.2 (118.1, 127.2)	124.4 (119.9, 129.0)	0.13
Head circumference, cm	51.4 (50.5, 53.0)	51.6 (50.4, 53.0)	0.59

Note: Data are *n* (%), mean ± standard deviation, median (interquartile range).

TABLE 3 Composite visual outcomes, stereopsis and global motion perception in the whole cohort and after excluding those with cerebral palsy.

Outcomes	OldPro group ($n = 55$)	NewPro group ($n = 73$)	Unadjusted OR		Adjusted[a] OR	
			95% CI	p-Value	95% CI	p-Value
Favourable overall visual outcomes	24/37 (65%)	39/64 (61%)	1.18 (0.51, 2.75)	0.70	1.15 (0.49, 2.68)	0.76
Favourable binocular visual outcomes	27/45 (60%)	24/66 (36%)	2.63 (1.20, 5.72)	0.02	2.55 (1.16, 5.61)	0.02
Favourable functional visual outcomes	41/50 (82%)	47/70 (67%)	2.23 (0.93, 5.36)	0.07	2.34 (0.96, 5.72)	0.06
Pass stereoacuity (TNO)	43/50 (86%)	48/71 (68%)	2.94 (1.15, 7.54)	0.03	2.98 (1.15, 7.72)	0.02
Mean global motion perception threshold	54.16 ± 23.50	45.06 ± 22.34	9.10 (0.73, 17.47)[b]	0.03	8.95 (0.55, 17.35)[b]	0.04
Visual outcomes when cerebral palsy excluded in the OldPro ($n = 54$) and NewPro ($n = 64$) groups						
Favourable overall visual outcome	24/37 (65%)	39/58 (67%)	0.90 (0.38, 2.15)	0.81	0.86 (0.36, 2.08)	0.74
Favourable binocular visual outcome	27/45 (60%)	23/60 (38%)	2.41 (1.09, 5.33)	0.03	2.34 (1.05, 5.19)	0.04
Favourable functional visual outcome	41/50 (82%)	46/63 (73%)	1.68 (0.68, 4.19)	0.26	1.73 (0.69, 4.36)	0.25
Pass stereoacuity (TNO)	43/50 (86%)	46/63 (73%)	2.27 (0.86, 6.01)	0.10	2.32 (0.87, 6.20)	0.10
Mean global motion perception threshold	53.26 ± 22.82	44.92 ± 22.22	8.34 (−0.08, 16.76)[b]	0.05	8.07 (−0.46, −16.61)[b]	0.06

Note: Data are *n* (%), mean ± standard deviation.

Abbreviations: CI, confidence interval; OR, odds ratio; TNO, Toegepast Natuurkundig Onderzoek (test for stereoscopic vision).

[a]Adjusted for sex and birth weight *z*-score.

[b]Mean difference (95% CI).

2 years but did appear to increase the risk of moderate–severe neurodisability. The potential negative effect of high protein and low carbohydrate intake on binocular vision could be considered in future follow-up studies of neonatal nutrition trials.

In contrast, our observation of better global motion perception in the NewPro group is consistent with a previous study of neonatal nutrition and vision. Blakstad et al.[40] used visual event-related potentials to investigate the neural response to global motion and form stimuli in 31 five-month-old babies with very low birthweight (<1500 g) randomised to enhanced neonatal nutrition, which included increased protein intake, or standard care. Stronger cortical responses to global motion were observed in the intervention group. Together, these results suggest that dorsal visual stream development can be modulated by neonatal nutrition, perhaps with higher protein intake promoting enhanced cortical function.

The clinically meaningful effect size for a difference motion coherence threshold is not known because test parameters are not uniform in the literature.[41] However, the measurement is an index of dorsal stream development that is sensitive to neurodevelopmental differences.[10–15] In our previous work using the same test parameters, 4.5-year-old children exposed prenatally to alcohol had motion coherence thresholds that were 9% worse than those not exposed to alcohol—the same between-group difference observed in the present study.[42]

The opposite effects of higher protein and lower carbohydrate intake on stereopsis and global motion perception are difficult to explain. One possibility is that

higher neonatal protein intake supports visual cortex development (improved global motion perception) but impairs oculomotor control. Reduced oculomotor control would preferentially affect stereoacuity, which requires precise ocular alignment but would not impair global motion perception which is relatively independent of other visual functions.[43] Standard clinical measures of ocular alignment and motility did not differ between the NewPro and OldPro groups. However, subtle changes in fixation stability that are sufficient to influence stereoacuity can often only be detected using specialised eye-tracking techniques.

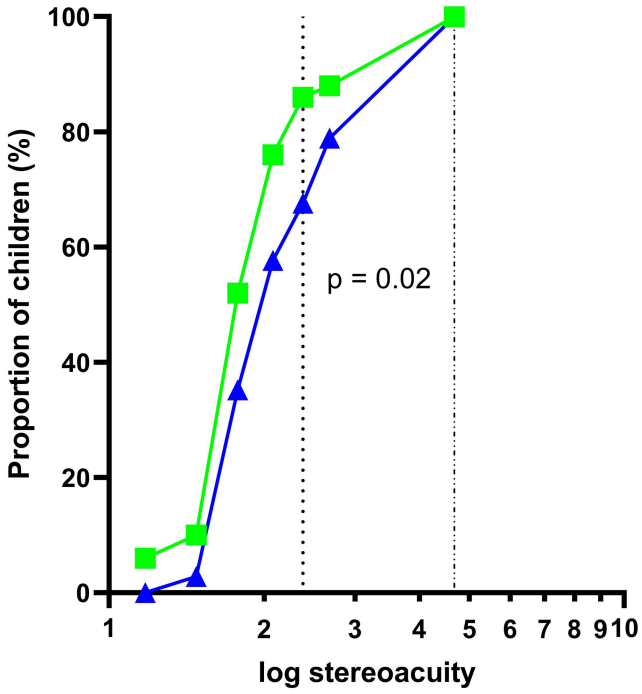

FIGURE 2 Cumulative log stereoacuity distribution in the OldPro (green) and NewPro (blue) groups. The dotted line at $x = 2.38$ denotes the pass mark of the test; the dashed line at $x = 4.68$ denotes no measurable stereoacuity. *p*-Value adjusted for sex and birth weight *z*-score.

The incidence of strabismus and refractive error in our cohort was similar to other studies of preterm birth,[44,45] with similar VA but a higher incidence of strabismus and myopia than previously reported in children born at term, and this was independent of neonatal protein intake.[46,47] For the cohort as a whole, motion coherence thresholds were also higher (poorer performance) than those reported in other studies of children born preterm or children with hemiplegic cerebral palsy.[20,48] This may reflect differences in the global motion tasks used in different studies or an effect of very preterm birth.

A limitation of this study was that the NewPro and OldPro groups were non-contemporaneous. However, detailed neonatal information was available for all children within the cohort and the follow-up rate at 7 years of age was high. Our results suggest that future studies might usefully explore the specific nutrients that influence visual development and whether effects would also be seen in children born after 30 weeks' gestation.

These results indicate a subtle but complex association between neonatal nutrition and visual development in school-age children born very preterm. Overall visual outcome was similar between the NewPro and OldPro groups, but secondary outcomes indicated opposing effects of higher protein and lower carbohydrate intake on stereopsis and global motion perception. Whether these group differences persist in late childhood is currently unknown.

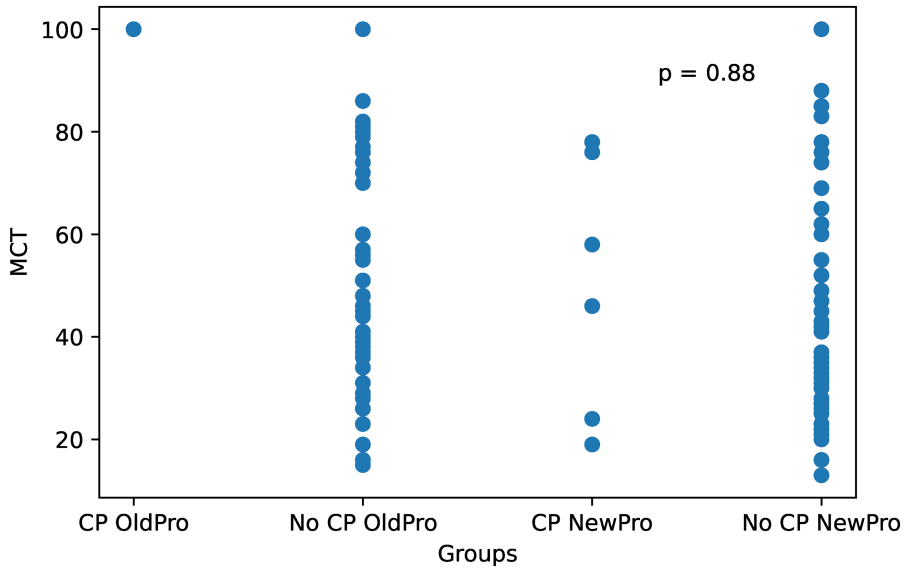

FIGURE 3 Motion coherence thresholds (MCT) for both the OldPro and NewPro groups for children with and without children with cerebral palsy (CP).

AUTHOR CONTRIBUTIONS

Mukhit Kulmaganbetov: Writing – original draft (equal). **Myra Leung:** Conceptualization (equal); investigation (equal); methodology (equal); software (equal); visualization (equal). **Jane M. Alsweiler:** Conceptualization (equal); project administration (equal); resources (equal); supervision (equal); writing – review and editing (equal). **Joanna Black:** Writing – review and editing (equal). **Frank H. Bloomfield:** Writing – review and editing (equal). **Greg D. Gamble:** Writing – review and editing (equal). **Jane E. Harding:** Resources (equal); project administration (equal); writing – review and editing (equal). **Yannan Jiang:** Writing – review and editing (equal). **Tanya Poppe:** Writing – review and editing (equal). **Anna C. Tottman:** Writing – review and editing (equal). **Trecia A. Wouldes:** Writing – review and editing (equal). **Benjamin Thompson:** Conceptualization (equal); project administration (equal); resources (equal); supervision (equal); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PATIENT CONSENT

Written informed consent was obtained from the parents or legal guardians and the child gave verbal assent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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