Outcomes 8 years after preterm birth

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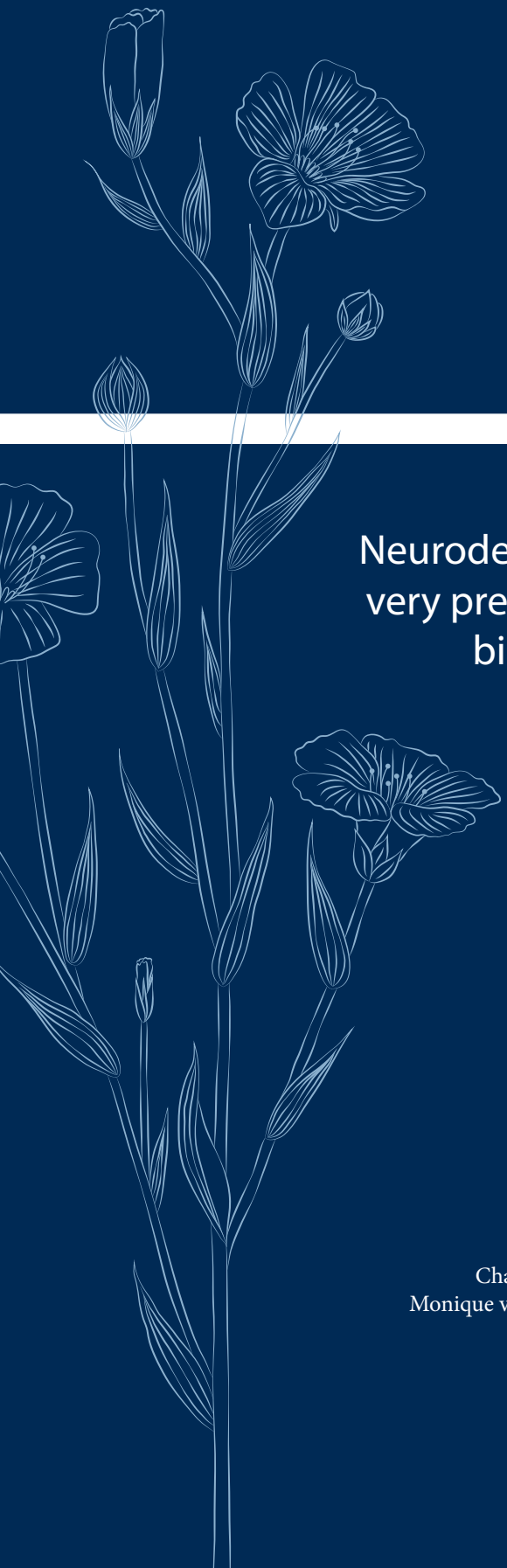

Chapter 4

Neurodevelopment of children born very preterm and/or with a very low birth weight: 8-year follow-up of a nutritional RCT

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ABSTRACT

Background Children born very preterm are at risk for cognitive deficits and motor impairment. Enhanced protein intake immediately after very preterm birth has been associated with favorable growth and improved neurodevelopment. It is unknown whether increased protein intake after discharge from the hospital affects long-term neurodevelopment.

Objective The primary objective was to assess neurodevelopment from infancy to 8 years in preterm-born children who received either protein-enriched formula (PDF), standard term formula (TF), or human milk (HM) after discharge. The secondary objective was to assess the correlation between outcomes obtained at 24 months corrected age (CA) and at 8 years.

Methods This RCT included 152 children born very preterm (gestational age ≤ 32 weeks) and/or with a very low birth weight (≤ 1500 g) of whom 102 were randomly assigned to receive PDF (n = 54) or TF (n = 48) from term age to 6 months CA. A control group of infants fed HM (n = 50) was also included. Neurodevelopmental outcomes were assessed at 24 months CA (cognitive and motor functioning; n = 123) and at 8 years (estimated Full Scale Intelligence Quotient, visual-motor skills, verbal memory, attention, and motor functioning; n = 76).

Results The PDF and TF groups were not significantly different in neurodevelopmental outcomes. The HM group had a better cognitive score compared with the PDF group: at 24 months CA 92.9 ± 12.5 vs. 105.2 ± 18.6, $P < 0.001$ and at 8 years 98.1 ± 11.3 vs. 105.8 ± 9.1, $P = 0.017$ ($P = 0.002$ and $P = 0.080$, respectively, after adjustment for parental educational level). Correlations between outcomes at 24 months CA and 8 years were weak: $r = 0.35$ and $r = 0.37$ for cognitive and motor outcomes, respectively.

Conclusions PDF did not improve long-term neurodevelopmental outcomes as compared with TF. However, these results should be interpreted with caution considering the substantial attrition at follow-up. Furthermore, the correlation between outcomes at different ages was weak, emphasizing the need for long-term follow-up of nutritional intervention studies in preterm-born children.

INTRODUCTION

Children born very preterm are at risk for impairments in cognitive and motor domains.[1,2] A number of risk factors have been identified, including lower gestational age, lower birth weight, and neonatal morbidities including intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD).[3-5] One of the largest preventable risk factors for poor neurodevelopmental outcome is postnatal growth restriction.[4]

Adequate postnatal growth after preterm birth, i.e., growth mimicking intrauterine growth, has been associated with better neurodevelopmental outcomes.[6] For preterm infants, there is sufficient evidence demonstrating that the supply of carbohydrate, protein and fat (often through parenteral nutrition) should be rapidly increased as soon as possible after birth to meet their high nutritional demands and to prevent postnatal growth restriction.[7] Neonatal nutrition has therefore become one of the cornerstones in improving long-term outcomes of preterm infants.[8,9]

Human milk (HM) is the preferred type of nutrition for preterm infants, carrying numerous health benefits, including lower risks of necrotizing enterocolitis and late-onset sepsis.[10] Furthermore, a dose-dependent association between Neonatal Intensive Care Unit (NICU)-HM intake and cognitive scores at 20 months corrected age (CA)[11] and both cognitive and motor scores at 30 months CA[12] have been reported. If HM is not sufficiently available, various types of preterm formula can be used during hospital admission, and it has been suggested that a nutrient enriched formula during NICU admission may improve early growth and neurodevelopment.[13] Protein in particular has been suggested to contribute to improving neurodevelopmental outcomes, possibly through enhancing early-postnatal growth[4,14] and increasing lean mass accretion.[15] However, long-term data on neurodevelopmental outcomes after various in-hospital feeding regimes are scarce. To our knowledge, only one study, which was performed 20 years ago, found that boys fed preterm formula had a higher verbal-IQ at age 7.5–8 years as compared to boys fed term formula.[16]

Effects of different types of nutrition after hospital discharge are even less clear. In a systematic review about postdischarge formula feeding, a small beneficial effect of enriched formula on neurodevelopment of preterm infants up to 24 months CA was suggested. However, firm conclusions could not be drawn due to the small sample sizes and heterogeneity of the included studies.[17] Moreover, none of the studies provided follow-up beyond 24 months CA. Neurodevelopmental outcomes measured in infancy have shown poor predictive value for cognitive and motor functioning later in childhood or adolescence.[18,19] Therefore, long-term follow-up is necessary to gain insight in the long-term effects of different types of infant nutrition given to preterm infants after discharge.

The primary aim of this study was to assess whether neurodevelopmental outcomes at 24 months CA and 8 years differ between preterm-born children fed standard or protein-enriched formula during the first 6 months after discharge. The secondary aims were 1) to compare neurodevelopmental outcomes between formula and HM fed infants, 2) to test the correlation between neurodevelopmental outcomes obtained at 24 months CA and estimated Full Scale Intelligence Quotient (eFSIQ) and motor functioning at age 8 years, and 3) to assess which clinical characteristics predict these outcomes.

SUBJECTS AND METHODS

Subjects

Originally, 152 infants born very preterm (gestational age ≤ 32 weeks) and/or with a very low birth weight (≤ 1500 g) were included in a nutritional RCT (Study Towards the Effects of Postdischarge nutrition, STEP) between January 2003 and March 2006. Between birth and term age, the infants were fed 150 mL/kg/day preterm formula (composition per 100 mL: 80 kcal, 2.2 g protein, 4.3 g fat, 7.6 g carbohydrates) or fortified HM depending on availability and preference of parents. The gestational age at discharge from the hospital was median 37.0 (range 35.0 to 42.3) weeks. A total of 102 formula fed infants were randomly assigned at term age (i.e., 40 weeks gestation) to receive either an isocaloric protein- and mineral-enriched postdischarge formula (PDF, $n = 54$) or standard term formula (TF, $n = 48$) and continued this diet until 6 months corrected age (CA, i.e., calculated from term age). The composition of the formulas per 100 mL was as follows (PDF/TF, respectively): 67/67 kcal, 1.70/1.47 g protein, 3.50/3.55 g fat, 7.00/7.23 g carbohydrates. Infants fed predominantly (> 80%) HM at term age were included as a control group (HM, $n = 50$).[20] After term age HM was no longer fortified. In case HM was insufficiently available, which was the case in about 50% of HM fed infants after 3 months CA, TF was given instead. Data on intake between birth and discharge were collected from medical records. After discharge, parents recorded their child's intake in a nutritional diary: until term age daily, from term age until 6 months CA one day per week. The exact intake from breast-fed children was unknown. Protein intake in the PDF group between term age and 6 months CA was significantly higher compared with the TF group, while intake volumes were comparable.[20]

Exclusion criteria were severe physical impairment or conditions that might affect growth or body composition. Subjects visited the outpatient clinic at term age and at 3, 6, 12, and 24 months CA, and for the follow-up study (STEP-2) at chronological age 8 years. Further details of the follow-up study protocol as well as the primary outcomes of this RCT were

described previously.[21] The study protocol was approved by the Ethics Committee of VU University Medical Center, Amsterdam, The Netherlands. All parents of participants gave written informed consent.

Data collection

Gestational age and disease severity (represented in the Neonatal Therapeutic Intervention Scoring System (NTISS)) were extracted from medical charts. Weight, length/height and head circumference were measured using standard procedures and values were converted to standard deviation scores (SDS) using the appropriate reference curves.[22,23] Small-for-gestational-age (SGA) was defined as a weight and/or length at birth ≤ -2 SDS.

In addition, parents reported their education level (dichotomized as 0 or ≥ 1 highly educated parent, i.e., who had finished higher vocational or university) and ethnicity (dichotomized as 'white' or 'non-white').

Parents and investigators of neurodevelopmental outcomes were unaware of the treatment allocation in the neonatal period. Neurodevelopmental performance at 24 months CA and cognitive functioning at 8 years was assessed by a single certified child psychologist and a trained research assistant.

Neurodevelopmental tests at 24 months CA

At 24 months CA, neurodevelopmental performance was assessed by using the Bayley Scales of Infant Development, Dutch second version (BSID-II-NL).[24] This measure consists of a series of developmental play tasks. It provides indices for cognitive development (Mental Development Index (MDI)) and motor development (Psychomotor Development Index (PDI)), reported as a standardized score with a mean (SD) of 100 (15).

Neurodevelopmental tests at 8 years

At 8 years, cognitive functioning was assessed by using the following individually administered norm-referenced tests:

1. A four-subtest short form (including the subtests Similarities, Vocabulary, Picture Arrangement, and Block Design) of the Dutch Wechsler Intelligence Scales for Children – third version (WISC-III-NL), measuring an eFSIQ,[25,26] reported as a standardized score with a mean (SD) of 100 (15). eFSIQ as measured by this short form has a high reliability (r = 0.93) and correlates strongly with FSIQ (r = 0.92);[26]
2. The Beery-Buktenica Test of Visual-Motor Integration (VMI) assessing visual-motor skills, including visual-spatial perceptive abilities, fine motor abilities and motor

planning.[27] The sum of points was transformed into a 6-month interval age-adjusted standardized score with a mean (SD) of 100 (15);

3. The Dutch version (15 Word Test) of the Rey Auditory Verbal Learning Test[28] assessing verbal memory including immediate recall, delayed recall, and recognition.[29,30] According to Dutch normative data, raw scores on immediate and delayed recall were converted into decile scores (1 to 10), adjusted for age and sex;
4. The Test of Everyday Attention for Children (TEA-Ch) assessing selective, sustained, and divided attention, and attentional control, including the subtests 'Sky Search', 'Score!', 'Sky search Dual Task', and 'Creature Counting'.[31] According to Dutch normative data, raw scores were converted to scaled scores with a mean (SD) of 10 (3), adjusted for age and sex.

For all tests mentioned above, higher scores indicate better performance.

At 8 years, motor functioning was assessed by a trained physiotherapist by using the Movement Assessment Battery for Children – second edition (M-ABC-2).[32] The total score consists of scores derived on the following skills: hand function, catching and throwing a ball, and static and dynamic balance. Results are reported as scaled scores with a mean (SD) of 10 (3).

Statistical analyses

Normally distributed data were presented as means ± SDs and skewed data as medians [interquartile ranges, IQRs]. Participants and nonparticipants of the follow-up study were compared using independent sample T-tests or Mann-Whitney U tests as appropriate.

The feeding groups (i.e., PDF, TF, HM) were compared on baseline characteristics using Chi-square tests for categorical and one-way ANOVA for continuous variables. Neurodevelopmental outcomes were compared using linear regression analyses, with the feeding groups represented in dummy variables as independent variables. Next, the analyses were adjusted for parental educational level.

Linear regression analysis was used to assess associations between neurodevelopmental outcomes obtained at 24 months CA and 8 years. For the association of MDI with eFSIQ and of PDI with M-ABC (total score) an intraclass correlation coefficient (ICC-*r*) was calculated from linear mixed model analyses. This method takes into account the intra-individual correlation between the outcomes at 24 months CA and 8 years. Analyses were repeated with adjustment for parental educational level and feeding group.

To assess which clinical characteristics were predictive of neurodevelopmental outcomes at 24 months CA (BSID-II-NL MDI and PDI) and 8 years (eFSIQ and M-ABC total

score), we used a linear regression backward-selection procedure with the pre-selected characteristics sex, gestational age, NTISS, SGA, head circumference SDS at term age, feeding group (formula groups vs. HM), and parental education. For the outcomes at 8 years we also added the appropriate outcomes from the BSID-II-NL to the model: MDI as possible predictor for eFSIQ and PDI for M-ABC. All variables were put into the model together and subsequently the 'predictor' with the highest *P* value was removed from the model. This procedure was repeated until there were no longer variables with a *P* value > 0.20. A cut-off *P* value of 0.20 was chosen because of the relatively small sample size, in particular at age 8 years. The percentage of the variance in outcome variables explained by the predictors in the model was represented as the adjusted R^2 (R^2_{adj}). In addition, we assessed which of the preselected characteristics were associated with a higher score on cognitive and motor outcomes at 8 years as compared with 24 months CA using logistic regression analyses (outcome: increase vs. decrease in test score, MDI minus eFSIQ and PDI minus M-ABC total score, respectively).

All analyses were performed using IBM SPSS statistics version 22.0 and a *P* value of < 0.05 was considered significant.

RESULTS

Study population

A total of 139 (91%) children had assessments up to and including 24 months CA and 13 children were lost to follow-up or excluded from the analyses (4 withdrawal of consent, 1 feeding protocol deviation, 2 renal insufficiency, 6 unknown reason).[21] Of the 139 children that completed the study until 24 months CA, BSID-II results were available for 123 (81%) of them (16 non-available: 3 unable to complete test, 1 hearing problems, 1 cerebral palsy, 3 no show, 8 unknown reason). A total of 76 (50%) children participated in the follow-up study at 8 years: cognitive outcomes were available for 63 children (13 non-available: 1 deaf, 12 too much burden of participating in the assessments) and motor outcomes for 76 children (**Figure 4.1**).

Characteristics of the study population are shown in **Table 4.1**. Participants and nonparticipants of the follow-up study from whom BSID-II results were available were comparable on baseline characteristics (**Supplemental Table S4.1**).

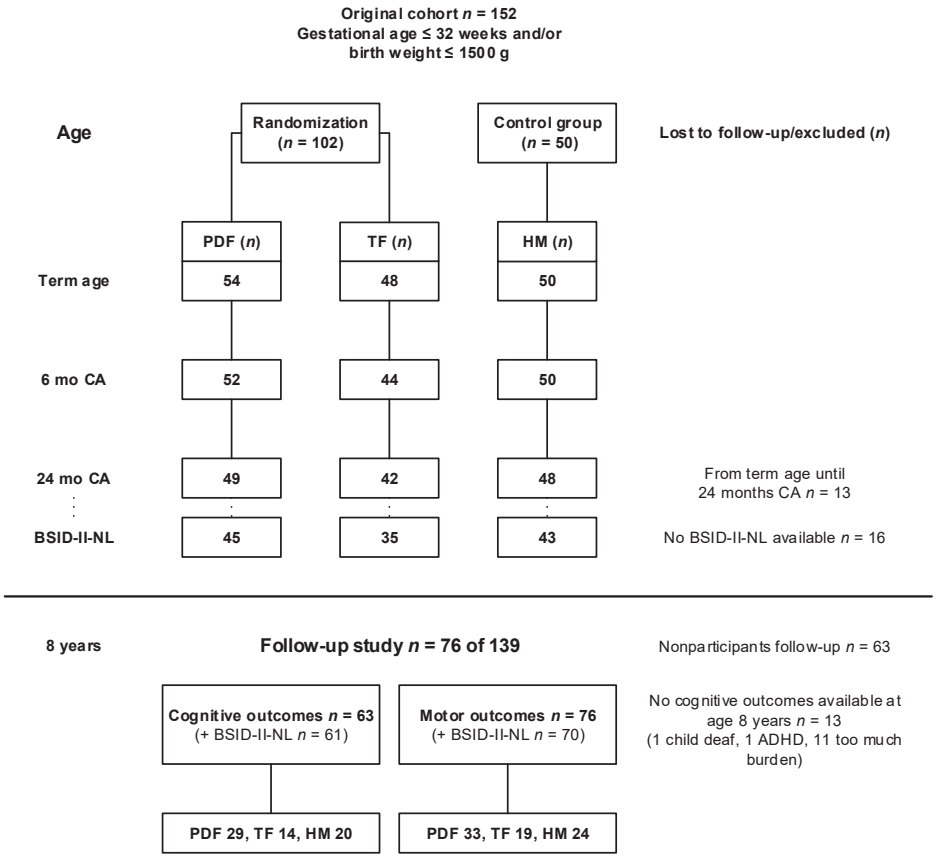

Figure 4.1. Flow-chart of study population.
BSID-II-NL, Bayley Scales of Infant Development – Dutch second edition; CA, corrected age; HM, human milk; PDF, postdischarge formula; TF, term formula.

Feeding groups

The feeding groups were compared on the characteristics shown in Table 4.1, both at 24 months CA and at 8 years. No differences were found, with the exception of a higher parental educational level of the HM group as compared with both formula groups. Parents with a higher educational level were distributed as follows: at 24 months CA PDF 33.3%, TF 48.6%, HM 74.4% ($P < 0.001$ and $P = 0.012$, for PDF and TF vs. HM, respectively), and at 8 years PDF 33.3%, TF 42.1%, HM 75.0% ($P = 0.003$ and $P = 0.028$, for PDF and TF vs. HM, respectively). **Table 4.2** shows the results of the neurodevelopmental tests per feeding group (*P* values can be found in **Supplemental Table S4.2**).

Table 4.1. Characteristics of the study population at 24 months CA and 8 years

	24 months CA	8 years
n	123	76
Male	59 (48.0)	37 (48.7)
Gestational age, wk	30.3 ± 1.5	30.2 ± 1.7
Birth weight, g	1329 ± 291	1325 ± 301
SDS	-0.4 ± 1.0	-0.4 ± 1.0
Birth length, cm	38.0 ± 2.9	38.2 ± 3.0
SDS	-0.9 ± 1.2	-0.7 ± 1.3
Birth head circumference, cm	27.7 ± 1.9	27.6 ± 1.9
SDS	-0.2 ± 1.1	-0.2 ± 1.1
SGA	29 (23.6)	16 (21.1)
NTISS	21.3 ± 7.2	21.6 ± 7.7
Intracranial hemorrhage	14 (11.4)	9 (11.8)
Head circumference term age	35.8 ± 1.4	35.7 ± 1.4
SDS	0.7 ± 1.0	0.6 ± 0.9
Feeding group term age – 6 mo. CA		
PDF	45 (36.6)	33 (43.4)
TF	35 (28.5)	19 (25.0)
HM	43 (35.0)	24 (31.6)
Parents		
Ethnicity white	95 (77.2)	61 (80.3)
Parental education high (1 or 2 parents university/ higher vocational)	64 (52.0)	37 (48.6)

Values are means ± SDs or *n* (%). CA, corrected age; HM, human milk; NTISS, Neonatal Therapeutic Intervention Scoring System; PDF, postdischarge formula; SDS, standard deviation score; SGA, small-for-gestational-age (weight and/or length at birth ≤ -2 SDS); TF, term formula

Neurodevelopmental outcomes at 24 months CA

Performances below -1 SD of the normative mean (corrected for preterm birth) were found for 20 (16.3%) and 26 (21.1%) children on the MDI and PDI, respectively. At 24 months CA, the HM group had a higher score on the MDI compared with the PDF group (**Table 4.2**). After adjustment for parental educational level the association remained significant (**Supplemental Table S4.2**).

Neurodevelopmental outcomes at 8 years

Performances below -1 SD of the normative mean (= mild-moderate impairment) were found in 4 (6.3%) children for eFSIQ, and 14 (18.4%) children for VMI and verbal memory. For selective, sustained and divided attention, and attention switch, the numbers were 8 (10.5%), 28 (36.8%), 22 (28.9%), and 22 (28.9%), respectively. Performances below -1 SD

Table 4.2. Neurodevelopmental outcomes at 24 months CA and 8 years according to type of infant feeding, compared using linear regression analyses

24 months CA	Total	PDF	TF	HM
n	123	45	35	43
Age, months				
Corrected age (CA)	24.1 [23.9; 24.4]	24.0 [23.7; 24.3]	24.2 [23.9; 24.7]	24.1 [23.8; 24.4]
Chronological age (chron.)	26.4 [26.0; 26.7]	26.4 [25.9; 26.5]	26.4 [25.9; 27.2]	26.5 [26.1; 26.7]
BSID-II-NL, standardized score (100 ± 15)				
MDI, CA[1]	99.5 ± 16.6	92.9 ± 12.5	101.1 ± 16.1	105.2 ± 18.6
MDI, chron.[2]	92.8 ± 14.8	87.4 ± 11.6	94.3 ± 14.7	97.3 ± 16.2
PDI, CA	95.5 ± 14.1	93.1 ± 12.3	95.8 ± 11.1	97.8 ± 11.8
PDI, chron.	85.7 ± 13.6	83.6 ± 12.4	85.3 ± 11.6	88.5 ± 16.0
8 years				
Age, years	7.9 ± 0.4	7.9 ± 0.4	8.0 ± 0.4	7.9 ± 0.4
Cognitive functioning (n)	63	29	14	20
eFSIQ standardized score (100 ± 15)[3]	100.8 ± 11.1	98.1 ± 11.3	99.1 ± 11.6	105.8 ± 9.1
Visual-motor skills standardized score (100 ± 15)	93.8 ± 10.3	93.6 ± 12.4	92.5 ± 10.4	95.1 ± 6.5
Attention, scaled score (10 ± 3)				
Selective attention	10.1 ± 2.4	9.7±2.5	10.5±2.4	10.5±2.1
Sustained attention[4]	8.3 ± 3.2	7.2 ± 2.9	7.8 ± 1.6	10.1 ± 3.7
Divided attention	8.1 ± 3.6	7.6 ± 4.4	8.2 ± 3.1	8.6 ± 2.9
Attention switch	9.0 ± 2.9	9.0 ± 3.0	8.4 ± 2.8	9.4 ± 3.0
Verbal memory				
Total score, decile score (1–10)	5.5 ± 2.9	5.8 ± 2.7	4.8 ± 3.1	5.6 ± 3.2
Delayed recall, decile score (1–10)	6.6 ± 2.6	7.0 ± 2.4	5.6 ± 2.3	6.8 ± 3.0
Motor functioning (n)	76	33	19	24
M-ABC-2, scaled score (10 ± 3)				
Total test score	9.8 ± 3.3	9.5 ± 3.6	10.5 ± 3.6	9.5 ± 2.6
Manual dexterity	9.6 ± 3.0	9.3 ± 3.3	10.2 ± 3.3	9.7 ± 2.3
Aiming and catching	8.9 ± 2.6	8.6 ± 2.5	9.9 ± 2.9	8.6 ± 2.4
Balance	10.7 ± 3.7	10.7 ± 3.9	10.8 ± 4.0	10.6 ± 3.5

Values are means ± SDs or medians [25th, 75th IQRs]. BSID-II-NL, Bayley Scales of Infant Development – Dutch second edition; CA, corrected age; eFSIQ, estimated Full Scale Intelligence Quotient; HM, human milk; M-ABC-2, Movement Assessment Battery for Children – second edition; MDI, mental developmental index; PDF, postdischarge formula; PDI, psychomotor developmental index; TF, term formula. [1]PDF vs. HM $P < 0.001$, [2]PDF vs. HM $P = 0.007$ [3]PDF vs. HM $P = 0.017$ [4]PDF vs. HM $P = 0.002$, TF vs. HM $P = 0.033$ (unadjusted linear regression)

of the normative mean were found in 9 (11.8%) children for the M-ABC total score. At 8 years, the HM group had a higher eFSIQ compared with the PDF group. After adjustment for parental educational level the association was no longer significant (**Supplemental Table**

S4.2). Scores on other cognitive measures and motor functioning were not significantly different between the feeding groups, with the exception of 'sustained attention'.

Association between neurodevelopmental outcomes at 24 months CA and 8 years

The individual scores (expressed as percentile) on cognitive (MDI and eFSIQ) and motor (PDI and M-ABC total score) outcomes at 24 months CA and 8 years are plotted in **Figure 4.2**.

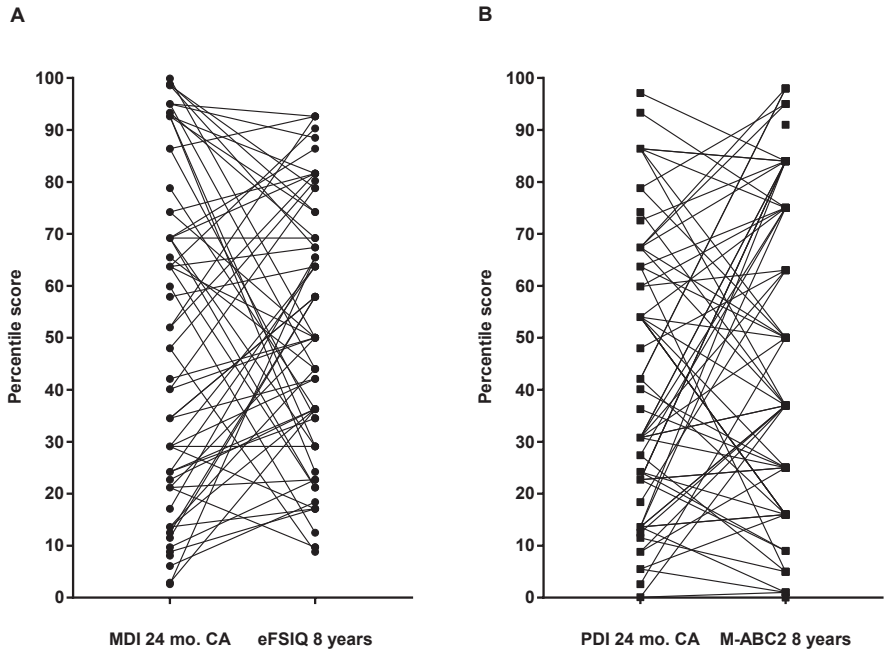

Figure 4.2. Individual scores on the MDI and eFSIQ (A) and on the PDI and M-ABC-2 (B) at 24 months CA and at 8 years, expressed as percentile.
CA, corrected age; eFSIQ, estimated Full Scale Intelligence Quotient; M-ABC-2, Movement Assessment Battery for Children – second edition; MDI, mental developmental index; PDI, psychomotor developmental index.

For the entire group, the MDI was associated with the eFSIQ at 8 years (**Table 4.3**). After adjustment for feeding group and parental educational level the association was no longer significant (β 0.18, 95% CI -0.01; 0.36, $P = 0.061$). The intraclass correlation between results of the MDI and eFSIQ (taking into account the intra-individual correlation) was poor with $r = 0.35$ unadjusted and $r = 0.23$ when adjusted for parental educational level and feeding group. There was no statistically significant association between MDI and other cognitive skills, with the exception of 'selective attention' (**Table 4.3**). Adjustment for feeding group and parental educational level did not change the results (data not shown).

Table 4.3. Associations between neurodevelopmental outcomes at 24 months CA and 8 years, assessed by using linear regression analyses

	Neurodevelopmental outcomes 24 months CA	
	MDI	
Cognitive functioning 8 years (*n* = 61)	β (95% CI)	*P* value
eFSIQ	0.25 (0.09; 0.41)	0.003[1]
Visual-motor skills	0.09 (-0.05; 0.25)	0.222
Attention		
Selective	0.05 (0.02; 0.08)	0.005
Sustained	0.02 (-0.04; 0.07)	0.545
Divided	0.05 (-0.01; 0.11)	0.087
Switch	0.04 (0.00; 0.09)	0.076
Verbal memory		
Total score, decile	0.02 (-0.03; 0.07)	0.363
Delayed recall, decile	0.01 (-0.03; 0.05)	0.584
	PDI	
Motor functioning 8 years (*n* = 70)	β (95% CI)	*P* value
M-ABC-2		
Total test score	0.10 (0.05; 0.15)	< 0.001
Manual dexterity	0.06 (0.01; 0.11)	0.012
Aiming and catching	0.06 (0.02; 0.10)	0.004
Balance	0.10 (0.04; 0.15)	0.001

Results of unadjusted linear regression analyses, represented as beta with 95% confidence interval (CI). CA, corrected age; eFSIQ, estimated Full Scale Intelligence Quotient; M-ABC-2, Movement Assessment Battery for Children – second edition; MDI, mental developmental index; PDI, psychomotor developmental index.
[1]After adjustment for feeding group and parental educational level the association was no longer significant (*P* = 0.061).

For the entire group, the PDI was associated with the M-ABC total score and all subtest scores (**Table 4.3**) and adjustment for feeding group and parental educational level did not change these results (data not shown). The intraclass correlation between results of the PDI and M-ABC (total score) was poor with $r = 0.37$ unadjusted and moderate with $r = 0.42$ when adjusted for parental educational level and feeding group.

Predictive factors of neurodevelopmental outcomes

24 months CA

The combination of characteristics that best predicted the MDI consisted of feeding group, parental education and NTISS ($R^2_{adj} = 0.159$): HM and higher parental education were positively associated with MDI. The characteristics that best predicted the PDI consisted of feeding group and sex ($R^2_{adj} = 0.030$): HM and male sex were positively associated with PDI.

8 years

The combination of characteristics that best predicted the eFSIQ at 8 years consisted of the MDI, feeding group, parental education, sex, and SGA ($R^2_{adj} = 0.181$): a higher MDI, HM, higher parental education, and male sex were positively associated and being born SGA was negatively associated with eFSIQ. The characteristics that best predicted the M-ABC total scaled score consisted of the PDI, sex and gestational age ($R^2_{adj} = 0.317$): a higher PDI and gestational age were positively associated and male sex was negatively associated with the M-ABC total scaled score.

Characteristics associated with a higher score on outcomes at 8 years as compared with 24 months CA

Characteristics that were associated with a higher score on cognitive functioning at 8 years included higher head circumference SDS at term age (OR 2.03, 95% CI 1.06; 3.88, $P = 0.032$) and female sex (OR 3.60, 95% CI 1.20; 10.77, $P = 0.022$); and a trend was seen for PDF feeding and increased gestational age at birth ($P = 0.094$ and $P = 0.082$, respectively). None of the characteristics assessed were significantly associated with a higher score on motor functioning at 8 years as compared with 24 months CA (data not shown).

DISCUSSION

No significant differences in neurodevelopmental outcomes were found between preterm-born children fed protein-enriched formula or standard formula during the first 6 months after discharge. Children predominantly fed HM had better cognitive outcomes at both time points compared with formula fed children, although at age 8 years the association was no longer significant after adjustment for parental educational level. Cognitive and motor scores at 24 months CA were associated with the corresponding cognitive and motor outcomes at 8 years, however, when taking into account the intra-individual dependency between results, the correlations were weak.

Previous studies on the optimal nutritional composition for preterm infants mostly concern interventions before discharge from the hospital, with considerable heterogeneity in the composition of studied formulas and the duration of follow-up. In general, the studies demonstrated that increased protein and energy intake during the first weeks of life are associated with improved neurodevelopmental outcome up to adolescence.[33] However, a recent study showed that optimizing protein intake in the first week after birth according to current recommendations does not improve cognitive or motor outcomes at 2 years, in spite of an improvement in early growth.[34]

In our study, feeding preterm infants PDF during the first 6 months after discharge did not lead to more favorable cognitive (or motor) functioning when compared with TF. Remarkably, the PDF group had a lower MDI-score compared with the TF group at 24 months CA, albeit not significantly lower. Lower parental education in the PDF group, despite randomization, may partly explain this, whereas possible confounding factors such as SGA, disease severity, and intracranial hemorrhage were all equally distributed among the feeding groups.

With regard to nutritional interventions after discharge, a recent systematic review suggests that an increased protein-energy ratio may lead to improved growth in weight, length and head circumference. However, only a few of the included studies reported neurodevelopmental outcomes, and benefits of enriched formulas are only reported in 2 of the 10 studies.[17] Moreover, the longest follow-up period is until 24 months CA. In our cohort at 8 years, eFSIQ was comparable between the formula groups, suggesting that, particularly in the PDF group, an 'improvement' in neurocognitive functioning might have occurred between 24 months CA and 8 years. This was supported by the observation that MDI-scores were not significantly different between participants and nonparticipants of the follow-up. In other words, the suggested 'catch-up' cannot be explained by the follow-up of children with better MDI-scores.

As mentioned previously, in term-born as well as preterm-born children HM feeding is beneficial for cognitive and motor functioning,[35,36] even though weight gain in the neonatal period is usually lower than in formula fed infants.[37] Preterm infants who received HM in the first weeks of life were found to have a higher IQ at age 7.5–8 years compared to those who did not receive HM, also after adjustment for confounding factors.[38] This is consistent with our results, showing that eFSIQ at 8 years was higher in the HM group as compared with both formula groups : HM versus PDF by 8 points and HM versus TF by 7 points, which equals 0.5 SD. However, after adjustment for parental educational level, the impact of feeding was no longer significant at 8 years. In addition to parental educational level, this might in part be explained by the relatively small sample size per feeding group at follow-up.

The exact reason why HM may improve neurodevelopment is unknown. Its unique composition, including anti-inflammatory components, growth factors, and long-chain polyunsaturated fatty acids may stimulate brain growth.[36] In addition, a reduction in neonatal illnesses, such as necrotizing enterocolitis and bronchopulmonary dysplasia, has been described and is likely to contribute to improved neurodevelopment.[11] Compared with (protein-enriched) formulas, HM has a relatively low protein and high fat content, which is why a protein-rich human milk fortifier is added to meet the needs of preterm infants.

In our study, the lack of association between protein-enriched formula and improvement of neurodevelopment might in part be explained by the small sample size. Nevertheless, the suggested positive effect of increased protein on growth and lean mass accretion in particular,[17] which have been associated with improved neurodevelopment,[39,40] may support the choice for a protein-enriched formula.

Studies on the predictive value of early cognitive measures are inconclusive. Previously, it has been shown that cognitive test scores are stable from infancy to adolescence[19] and that adult IQ can be predicted from 20 months onward with fair certainty ($r > 0.50$) in very preterm/very low birth weight individuals.[41] However, a meta-analysis concluded that the predictive value of the BSID for neurodevelopment into childhood is limited, with a large proportion of explained variance remaining undetermined.[42] Our results also suggest a poor predictive value from neurocognitive outcome at 24 months CA towards 8 years. Although we found that higher MDI-scores were associated with better performance on different domains of attention at 8 years, these results should be interpreted with caution because the effect sizes were very small. For motor functioning we found a poor predictive value of the BSID. In contrast, when the same test is used to assess motor functioning (M-ABC) in preterm-born children at ages 4 and 8 years, a strong association and a large explained variance were found.[43] This may suggest that follow-up of preterm infants should be continued after 24 months CA, but also that the comparison of outcomes of different tests (i.e., BSID-PDI with M-ABC) is limited.

Worldwide, around 24% of very preterm-born children show moderate to severe cognitive, motor and/or behavioral impairments and these problems increase with lower gestational age.[44] These impairments can, at least partly, be explained by white-matter abnormalities related to very preterm birth.[45,46] Identification of more specific risk groups for neurodevelopmental impairment could be useful as early interventions may result in better outcomes. In our study, SGA was negatively associated with cognitive functioning at 8 years, which may contradict with the conclusion of Linsell et al.[47] that suggests that the influence of perinatal characteristics on cognitive development decreases over time. Furthermore, male sex has been associated with poorer cognitive skills into adulthood[19] as well as worse motor skills in infancy and childhood.[43,48,49] In our study male sex was only negatively associated with motor functioning at 8 years.

Strengths and limitations

The most important strength of this study is that it included the long-term follow-up of an RCT with an early nutritional intervention in preterm infants in whom neurodevelopment

was assessed both in infancy and at school age, which allowed us to test whether associations persisted over time. In addition, various perinatal characteristics were recorded which enabled us to study the relative contribution of factors other than nutrition. An important limitation of our study was the lack of a term-born control group. In addition, substantial attrition at follow-up, a common problem of nutritional intervention studies, reduced the sample size at 8 years, making it impossible to study sub groups such as children that scored below -1 SD of the normative mean. For the same reason, our results concerning the prediction of outcomes should be interpreted with caution. They should be seen as a cluster of variables that has an association with the outcomes rather than as independent predictive variables. Furthermore, we did not correct for multiple testing. Nevertheless, we believe reporting these results is essential as supported by the recent statement of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition early nutrition research working group: despite the almost inevitable cohort attrition, long-term follow-up of early-nutrition RCTs is necessary.[50] The poor predictive value of neurodevelopmental assessment in infancy or early childhood further emphasizes the need for a longer follow-up after preterm birth. Furthermore, because a direct comparison between the methods used to assess neurodevelopment at 24 months CA and 8 years cannot be made we have to be careful as to call a better score at 8 years an 'improvement' in cognitive or motor functioning. Still, results at 8 years may be considered reassuring, specifically for the PDF group. Another limitation may be generalizability to preterm infants in a broader context for reasons related to selection bias. First, due to strict inclusion criteria, the subjects in our sample were relatively healthy. Second, as with any trial, the parents of our study population were more often highly educated. This might have influenced the cognitive outcomes, although they were still variable enough to demonstrate associations with nutritional composition.

CONCLUSION

Neurodevelopment is undeniably a complex process that can be influenced by numerous prenatal, neonatal, social, as well as later environmental factors. We found no differences with respect to cognitive or motor functioning at 24 months CA or 8 years between preterm-born children fed a protein-enriched formula as compared to standard formula after hospital discharge. Human milk was associated with better cognitive outcomes in infancy as well as at school age, although at age 8 years the association was no longer significant after adjustment for parental educational level. These results should be interpreted with caution considering the substantial attrition at follow-up. Nevertheless, our results support the preference of HM as the primary choice of nutrition for preterm infants. With regard to

type of formula, long-term follow-up of adequately powered nutritional RCT's is necessary. Furthermore, as the correlations between neurodevelopmental outcomes measured in infancy and at school age were weak, long-term follow-up of preterm infants is deemed relevant.

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Supplemental Table S4.1. Characteristics of participants and nonparticipants of the follow-up at age 8 years of whom BSID-II results were available (*n* = 123)

	Participants	Nonparticipants	*P* value
n	70	53	
MDI (CA)	100.7 ± 16.2	98.0 ± 17.2	0.372
PDI (CA)	95.8 ± 14.0	95.0 ± 14.4	0.760
Male	33 (47)	26 (49)	0.833
Gestational age, wk	30.2 ± 1.7	30.4 ± 1.2	0.318
Birth weight, g	1306 ± 302	1358 ± 276	0.330
SDS	-0.4 ± 1.0	-0.3 ± 0.9	0.798
Birth length, cm	38.1 ± 3.0	37.8 ± 2.8	0.579
SDS	-0.8 ± 1.2	-1.1 ± 1.0	0.109
Birth head circumference, cm	27.5 ± 1.9	27.8 ± 1.9	0.433
SDS	-0.2 ± 1.1	-0.2 ± 1.1	0.706
SGA	15 (21)	14 (26)	0.421
NTISS	21.9 ± 7.6	20.6 ± 6.5	0.301
Intracranial hemorrhage	7 (10)	7 (13)	0.579
Head circumference term age	35.6 ± 1.4	35.9 ± 1.4	0.250
SDS	0.6 ± 0.9	0.8 ± 1.0	0.236
Feeding group term age – 6 mo. CA			0.358
PDF	29 (41.4)	16 (30.2)	
TF	17 (24.3)	18 (34.0)	
HM	24 (34.3)	19 (35.8)	
Parents			
Ethnicity white	55 (79)	40 (75)	0.685
Parental education high (1 or 2 parents university/higher vocational)	36 (51)	28 (53)	0.774

Values are means ± SDs or *n* (%). None of the characteristics were significantly different between participants and nonparticipants. CA, corrected age; HM, human milk; MDI, mental developmental index of BSID-II-NL; NTISS, Neonatal Therapeutic Intervention Scoring System; PDF, postdischarge formula; PDI, psychomotor developmental index of the BSID-II-NL; SDS, standard deviation score; SGA, small-for-gestational-age (weight and/or length at birth ≤ -2 SDS); TF, term formula

Supplemental Table S4.2. *P* values from linear regression analyses for comparison of neurodevelopmental outcomes at 24 months CA and 8 years according to type of infant feeding

	Crude *P* values			Adjusted *P* values [1]		
	PDF vs. TF	PDF vs. HM	TF vs. HM	PDF vs. TF	PDF vs. HM	TF vs. HM
24 months CA						
BSID-II-NL, standardized score (100 ± 15)						
MDI, CA	0.023	< 0.001	0.263	0.036	0.002	0.329
MDI, chron.	0.034	0.001	0.358	0.056	0.009	0.462
PDI, CA	0.396	0.126	0.543	0.419	0.164	0.551
PDI, chron.	0.592	0.098	0.301	0.627	0.130	0.304
8 years						
Cognitive functioning (n)						
eFSIQ standardized score (100 ± 15)	0.792	0.017	0.076	0.925	0.080	0.105
Visual-motor skills standardized score (100 ± 15)	0.757	0.621	0.484	0.489	0.872	0.608
Attention, scaled score (10 ± 3)						
Selective attention	0.331	0.264	0.989	0.554	0.633	0.884
Sustained attention	0.576	0.002	0.033	0.504	0.002	0.031
Divided attention	0.636	0.403	0.809	0.949	0.834	0.906
Attention switch	0.535	0.643	0.338	0.387	0.949	0.377
Verbal memory						
Total score, decile score (1–10)	0.298	0.778	0.460	0.280	0.705	0.487
Delayed recall, decile score (1–10)	0.100	0.704	0.220	0.094	0.627	0.241
Motor functioning (n)						
M-ABC-2, scaled score (10 ± 3)						
Total test score	0.321	0.976	0.365	-	-	-
Manual dexterity	0.315	0.595	0.631	-	-	-
Aiming and catching	0.072	0.956	0.101	-	-	-
Balance	0.872	0.935	0.824	-	-	-

BSID-II-NL, Bayley Scales of Infant Development – Dutch second edition; CA, corrected age; eFSIQ, estimated Full Scale Intelligence Quotient; HM, human milk; M-ABC-2, Movement Assessment Battery for Children – second edition; MDI, mental developmental index; PDF, postdischarge formula; PDI, psychomotor developmental index; TF, term formula.

[1] adjusted for parental educational level.