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Published in:
Early Human Development

DOI:
[10.1016/j.earlhumdev.2020.105091](https://doi.org/10.1016/j.earlhumdev.2020.105091)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Kuik, S. J., den Heijer, A. E., Mebius, M. J., Hulscher, J. B. F., Bos, A. F., & Kooi, E. M. W. (2020). Time to full enteral feeding after necrotizing enterocolitis in preterm-born children is related to neurodevelopment at 2-3 years of age. *Early Human Development*, 147, [105091].
<https://doi.org/10.1016/j.earlhumdev.2020.105091>

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Time to full enteral feeding after necrotizing enterocolitis in preterm-born children is related to neurodevelopment at 2–3 years of age

S.J. Kuik^{a,*}, A.E. den Heijer^a, M.J. Mebius^a, J.B.F. Hulscher^b, A.F. Bos^a, E.M.W. Kooi^a

^a University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Division of Neonatology, Groningen, the Netherlands

^b University of Groningen, University Medical Center Groningen, Department of Surgery, Division of Pediatric Surgery, Groningen, the Netherlands

ARTICLE INFO

Keywords:

Behavioral outcome
Cognitive outcome
Motor outcome
Necrotizing enterocolitis
Post-NEC complications
Time to full enteral feeding

ABSTRACT

Background: Necrotizing enterocolitis (NEC) is associated with poorer neurodevelopment. It is, however, unclear which factors besides surgery affect neurodevelopment in preterm-born children surviving NEC.

Aims: We determined whether time to full enteral feeding (FEFt) and post-NEC complications after NEC were associated with neurodevelopment.

Study design: Prospective observational cohort study.

Subjects: Two to three year old preterm-born children who survived NEC (Bells stage ≥ 2). We categorized children in two groups, one group shorter and equal and one group longer than the group's median FEFt. Post-NEC complications included recurrent NEC and/or post-NEC stricture.

Outcome measures: Bayley Scales of Infants and Toddler Development III (Bayley-III) and Child Behavior Checklist (CBCL). Associations between Bayley-III and CBCL scores with FEFt and Post-NEC complications were determined using linear regression analyses, adjusted for severity of illness and potential confounders.

Results: We included 44 children, median gestational age of 27.9 [IQR: 26.7–29.3] weeks, birth weight 1148 [IQR: 810–1461] grams. Median FEFt after NEC was 20 [IQR: 16–30] days. Median follow-up age was 25.7 [IQR: 24.8–33.5] months. FEFt > 20 days was associated with lower cognitive and lower motor composite scores of the Bayley-III (B: -8.6 , 95% CI -16.7 to -0.4 , and B: -9.0 , 95% CI, -16.7 to -1.4). FEFt was not associated with CBCL scores. Post-NEC complications ($n = 11$) were not associated with Bayley-III scores nor with CBCL scores.

Conclusions: Prolonged FEFt after NEC in preterm-born children surviving NEC is associated with lower cognitive and lower motor composite scores at the age of 2–3 years. These results show the importance of limiting the duration of the nil per mouth regimen if and when possible.

1. Introduction

Necrotizing enterocolitis (NEC) is a devastating intestinal inflammatory disease mainly affecting preterm-born children [1–5]. Mortality rates and the burden of morbidity in NEC survivors remain high [1–5]. Major neurodevelopmental impairment was reported in 15% of the children with mild to moderate NEC, while this rate increases up to 50% in children with severe NEC [7,8]. This holds true for cognitive functioning, motor skills, as well as behavior [6–12].

The underlying mechanism leading to a poorer neurodevelopmental outcome in preterm-born children who developed NEC is not yet fully

understood, but two important contributing factors seem to be excessive inflammation and surgical intervention [6,7,9–11,13]. Previously, our group and others demonstrated that preterm-born children who developed NEC requiring surgery showed poorer cognitive and motor functioning than children who were treated conservatively [7,9–11].

One of the main components of NEC treatment is a nil per mouth (NPO) regimen for several days [1,14,15]. Alimentation will be provided by parenteral nutrition (PN). As prolonged PN is associated with cholestatic liver disease and supposedly less efficient than enteral feeding to maintain growth [16–18], another possible contributing

Abbreviations: Bayley-III, Bayley Scales of Infants and Toddler Development, third edition; BW, birth weight; CBCL, Child Behavior Checklist; CP, cerebral palsy; FEF, full enteral feeding; FEFt, time to full enteral feeding; GA, gestational age; GMFCS, gross motor functioning classification system; HC, head circumference; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; NPO, nil per mouth; PN, parenteral nutrition

* Corresponding author at: University of Groningen, University Medical Center Groningen, Department of Pediatrics, Division of Neonatology, Hanzeplein 1, 9713 GZ Groningen, the Netherlands.

E-mail address: s.j.kuik@umcg.nl (S.J. Kuik).

<https://doi.org/10.1016/j.earlhumdev.2020.105091>

Received 14 November 2019; Received in revised form 14 April 2020; Accepted 22 May 2020

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factor to a poorer neurodevelopment in NEC children might be a temporarily less adequate nutritional state. Although it has been reported that adequate nutrition is prerequisite for neurodevelopment and growth [16,19–21], evidence is limited regarding the relation between neurodevelopmental outcome and the duration from NPO until full enteral feeding (FEF) is tolerated again after NEC onset. Additionally, it remains unclear whether post-NEC complications, such as recurrent NEC and post-NEC strictures are associated with poorer neurodevelopmental outcomes.

Therefore, we aimed to determine whether the time to full enteral feeding (FEFt) after NEC onset and the presence of post-NEC complications were associated with neurodevelopmental outcome in preterm-born children with NEC.

2. Material and methods

2.1. Study design and patient population

We performed a prospective observational follow-up (FU) study in our tertiary university hospital with NEC expertise. All children born before 37 weeks of gestation, who were admitted to the neonatal intensive care unit (NICU) of the University Medical Center Groningen and born between August 2010 and January 2017, were eligible for inclusion. Further inclusion criteria were the development of NEC Bell's stage ≥ 2 and available FU data. All children born with a gestational age (GA) < 30 weeks or a birth weight (BW) < 1200 g or preterm-born children with a GA between 30 and 36 weeks who participated in one of our studies during their stay in our NICU, were invited for FU. Exclusion criteria were congenital and/or genetic disorders, and congenital heart disease with the exception of a patent ductus arteriosus (PDA). The study was approved by the ethical review board of University Medical Center Groningen.

2.2. NEC treatment and feeding protocols

All infants were treated according to the local NEC protocol [22]. Conservative treatment consisted of bowel rest (NPO approximately 5 days), antibiotics (7–10 days), and respiratory and/or cardiovascular support if needed. Laparotomy was performed in case of signs of an intestinal perforation and/or a deteriorating clinical condition despite maximal conservative treatment. Reintroduction of enteral feeding started with 20 mL/kg/day on day 6 after NEC onset on the condition that abdominal distension and tenderness had disappeared, bloody stools were absent, and pneumatosis intestinalis had disappeared for at least 24 h on abdominal radiographs, irrespective of Bell's stage. Feeding volumes were subsequently increased daily by 20 mL/kg/day when tolerated. The enteral feeding consisted of mother's own milk and of preterm formula or a combination of both when mother's milk was unavailable or of insufficient quantity.

2.3. Time to FEF and post-NEC complications

FEFt was defined as the time in days from start NPO after primary NEC onset until an amount of enteral feeding of 150 mL/kg/day for at least 24 h was tolerated. Because of the small sample size, we categorized the children based on the group's median FEFt, i.e. shorter/equal to group's median FEFt or longer than group's median FEFt. We evaluated two post-NEC complications, i.e. recurrent NEC and post-NEC strictures, both within the first 6 months after NEC onset. As only one child survived with a short-bowel syndrome after surgery, we refrained from any statistical analysis for this severe post-NEC complication.

2.4. Assessment of neurodevelopmental outcome

Neurodevelopmental outcome was determined at 23 to 44 months of age, corrected for prematurity. We used the Bayley Scales of Infants

and Toddler Development, third edition (Bayley-III), to assess cognitive and motor outcomes [23]. The Bayley-III was conducted in all children by a pediatric neuropsychologist (AEdH). Cognitive and motor outcomes were reported as composite scores. Motor outcome consisted of the scaled subscores fine- and gross motor [23]. All scores were corrected for prematurity. We defined (mildly) abnormal composite and scaled scores as ≤ -1 SD. Cerebral palsy (CP) was defined according to the gross motor functioning classification system (GMFCS). Children with a GMFCS > 2 were not approached for the Bayley-III. Furthermore, we evaluated behavioral and emotional outcome using the Child Behavior Checklist ages 1.5–5 years (CBCL) [24]. The CBCL is a questionnaire which is filled in by the parents. We reported internalizing T-scores, externalizing T-scores and total T-scores. According to the manual (standards of ASEBA), children were classified as normal in case of a T-score < 60 , mildly abnormal in case of a T-score between 60 and 63 points, and abnormal in case of a T-score > 63 [24].

2.5. Clinical, demographical and growth variables

We retrospectively collected data on postnatal characteristics and comorbidities, data regarding the development of NEC (including clinical and biochemical variables regarding the severity of illness), and growth variables from patients' medical charts. Variables concerning the severity of illness included laboratory findings, duration of endotracheal intubation, the fraction of inspired oxygen (FiO_2), administration of inotropes, and urine output during the first 24 h after NEC onset. Growth variables included BW, head circumference (HC) at birth, body weight and HC both at one year post term, since catch-up growth occurs for the largest part during the first postnatal year [25]. For all these growth variables we calculated Z-scores, using Niklasson's growth reference tables [26]. We also collected data on the socio-economic status, which was based on the years of education of the mothers of the children. Furthermore we collected data on the cranial ultrasounds performed during NICU admission, including the ultrasounds performed during NEC.

2.6. Statistical analysis

For statistical analyses we used SPSS 23.0 (IBM Corp., Armonk, NY, USA). Patient characteristics were reported as median [interquartile range (IQR)]. Distribution of data was checked with Q-Q plots and the Kolmogorov-Smirnov test. Differences in patient characteristics and FU data were determined by the Man Whitney *U* test, the independent-samples *t*-test, or the Chi-square test. First, we determined whether FEFt in days and post-NEC complications (categorized into recurrent NEC and post-NEC stricture) were associated with cognitive and motor composite scores, fine and gross motor scores, and CBCL T-scores, using univariate linear regression analyses. In addition, we determined which other clinical factors might influence FEFt and/or neurodevelopment. To determine which clinical factors should be included in the univariate analyses we chose for 1) clinical variables concerning the severity of illness that were significantly different between FEFt groups, as these variables might influence FEFt, 2) clinical variables that are reported to influence neurodevelopmental outcome in preterm infants, and 3) other patient characteristics that differed between FEFt groups. Clinical variables that are reported to influence neurodevelopmental outcome in preterm infants included GA, BW, late onset sepsis, intracranial hemorrhage grade III-IV, and bronchopulmonary dysplasia [27–30]. As surgical intervention indicates a more severe disease but is also described as variable influencing neurodevelopmental outcome [7,9–11], surgery was included in the univariate analyses. Next, we included all variables from the univariate analyses that were statistically significant in a multiple linear regression model, after checking for multicollinearity. We built three multiple models, consisting of a model with FEFt adjusted for the severity of illness, a model with FEFt adjusted for variables that might influence neurodevelopmental outcome, and a

Fig. 1. Flow diagram of the study population.

model with FEft adjusted for all clinical variables. A p -value < 0.05 was considered statistically significant. We only included variables with a p -value < 0.05 to prevent over adjustment in a small study population. Because of the explorative nature of our study we chose not to correct for multiple testing.

3. Results

3.1. Patient characteristics

Overall, the incidence of NEC (Bell's stage ≥ 2) between 2010 and 2017 was 3.2% regarding all gestational ages that were admitted to our NICU, including infants who were referred from another NICU without pediatric surgery services and eleven other medical centers of the northern half of the Netherlands. The incidence of NEC (Bell's stage ≥ 2) among preterm infants with a GA below the 30 weeks and/or a BW below 1000 g during this period was 13%. Out of the 120

preterm-born children with proven NEC (Bell's stage ≥ 2) 39 children (33%) died, five children (4%) were excluded, of whom two children were diagnosed with severe CP (GMFCS > 2). Thirty-two children (27%) were not included because of absent Bayley-III scores (Fig. 1). Therefore we enrolled 44 children, born at a median GA of 27.9 [IQR 26.7–29.3] weeks with a median BW of 1148 [IQR 810–1461] g. NEC developed on median postnatal day 11 [IQR 8–24]. Sixteen children (36%) needed surgical intervention. Median age at FU was 25.7 months [IQR 24.8–33.5]. One child had a ventriculoperitoneal shunt and subsequently developed epilepsy. Two children were diagnosed with mild CP (GMFCS ≤ 2). Two children were diagnosed with deafness. Two children were diagnosed with a visual deficit, but none were blind. Table 1 provides a complete overview of the patient characteristics. Only the FU data are depicted in Table 2. Differences of the patient characteristics between included infants and infants who were lost to FU or were invited for FU without Bayley assessment are demonstrated in Table 3. GA and BW were higher in the children in whom the Bayley-

Table 1
Patient characteristics during NICU admission and NEC development.

N = 44	FEFt ≤ 20 days n = 24	FEFt > 20 days n = 20
<i>Baseline characteristics</i>		
Gestational age, weeks	28.1 [27.1–29.4]	27.3 [26.2–29.1]
Birth weight, grams	1200 [943–1514]	1025 [750–1369]
Head circumference at birth, centimeters	26.0 [23.8–28.0]	24.7 [23.2–27.4]
Small for gestational age ¹	3 (13%)	4 (20%)
Gender, male	14 (58%)	13 (65%)
Multiple birth	5 (21%)	5 (25%)
Delivered by C-Section	9 (38%)	11 (55%)
Apgar score 5th min	8 [6–9]	7 [6–8]
Surfactant therapy	13 (54%)	13 (65%)
Treated Patent ductus arteriosus	9 (38%)	10 (50%)
Late onset sepsis (blood culture proven) ²	7 (29%)*	14 (70%)*
NICU admission, days	43 [28–58]*	65 [45–95]*
<i>NEC development and severity of illness</i>		
Postnatal age NEC onset	11 [8–24]	12 [8–25]
NEC Bell's classification		
Bell's stage 2A	11 (46%)	6 (30%)
Bell's stage 2B	4 (17%)	6 (30%)
Bell's stage 3A	1 (4%)	4 (20%)
Bell's stage 3B	8 (33%)	4 (20%)
Laparotomy	9 (38%)	7 (35%)
Relaparotomy	–	2 (10%)
NEC complications		
Recurrent NEC	2 (8%)	1 (5%)
Post-NEC stricture	2 (8%)	5 (25%)
Recurrent NEC and post-NEC stricture	–	1 (5%)
Short bowel ³	1 (4%)	–
Thrombocytes (10 ⁹ /L) (0–72 h after NEC onset, lowest value)	193 [108–305]	170 [90–299]
Leucocytes (10 ⁹ /L) (0–72 h after NEC onset)	10.1 [5.5–17.4]	7.7 [3.7–18.2]
C-reactive protein (mg/L) (0–72 h after NEC onset)	77 [17–157]	134 [25–178]
pH (0–72 h after NEC onset, lowest value)	7.23 [7.18–7.32]	7.22 [7.13–7.30]
pCO ₂ (kPa) (0–72 h after NEC onset)	6.8 [6.2–7.6] [#]	7.6 [6.5–7.6] [#]
Lactate (mmol/L) (0–72 h after NEC onset)	1.6 [0.7–2.8]	1.5 [1.2–3.5]
Endotracheal intubation	14 (58%)	16 (80%)
Days of mechanical ventilation from NEC onset	6 [0–8]*	10 [3–21]*
Fraction of inspired oxygen (Max % 0–72 h after NEC onset)	25 [21–30] [#]	30 [21–56] [#]
Administration of inotropes (0–72 h after NEC onset)	6 (25%)	5 (25%)
Urine output (ml/kg/h) (0–24 h after NEC onset)	5.0 [3.8–5.8]	5.0 [3.3–5.7]
<i>Other characteristics</i>		
Cerebral ultrasound		
Intracranial hemorrhage grade I–II	4 (17%)	7 (35%)
Intracranial hemorrhage grade III–IV	2 (8%)	1 (5%)
Posthemorrhagic ventricular dilatation	2 (8%)	1 (5%)
Bronchopulmonary dysplasia	4 (17%)	6 (30%)
Retinopathy of prematurity		
Grade I–II	–	8 (40%)*
Grade ≥ III	2 (8%)	–
Socio-economic status (mothers)	21 (87%)	14 (70%)
14 years of education or less	–	3 (15%) [#]
14–18 years of education	11 (45%)	6 (30%)
18 years of education or more	10 (42)	5 (25%)

Data are expressed as numbers (percentages) or median [interquartile range] unless otherwise specified.

Abbreviations: FEFt – time to full enteral feeding; NEC – necrotizing enterocolitis; NICU – neonatal intensive care unit; pCO₂ – partial carbon dioxide.

* $p < 0.05$.

[#] $p < 0.10$.

¹ Based on Niklasson's growth reference tables [26].

² Late onset sepsis in the period before and/or after NEC.

³ Based on local hospital protocol [45].

III assessment was missing.

3.2. The association between time to full enteral feeding and neurodevelopmental outcomes

Median FEFt after primary NEC onset was 20 [IQR 16–30] days. Mean (SD) scores of the Bayley-III and the CBCL of infants with FEFt ≤ 20 days and infants with FEFt > 20 days are shown in Table 2. First, we found a significant association between lower cognitive composite scores and FEFt of > 20 days with a reduction of the cognitive composite score of 8.6 (95% CI –16.7 to –0.4) (Table 4). We also found a significant association between lower motor composite

scores and FEFt of > 20 days with a reduction of the motor composite score of 9.0 points (95% CI –16.7 to –1.4) (Table 4). This was mainly due to a reduction of gross motor scaled scores, but not fine motor scaled score (Table 4). FEFt was not associated with the total, internalizing, or externalizing CBCL T-scores (Table 4).

3.3. The association between post-NEC complications and neurodevelopmental outcomes

Three children (7%) had recurrent NEC with a median FEFt of sixteen (range: 16–26) days ($p = 0.45$). Seven children (16%) developed a post-NEC stricture and had a median FEFt of 30 [IQR: 18–50] days

Table 2
Patient characteristics during follow-up.

N = 44	FEFt ≤ 20 days n = 24	FEFt > 20 days n = 20
Age (corrected for GA) at Bayley-III performance, months	26.4 [25.1–41.8]	25.4 [24.5–26.5]
Development of cerebral palsy (GMFCS I–II)	–	2 (10%)
Visual impairments		
Blindness	–	–
Visual deficit of one eye	–	2 (10%)
Hearing impairments (deafness)	2 (8%)	–
Bayley-III		
Cognitive outcome, n	20 (83%)	16 (80%)
Abnormal (–1SD)	–	4 (20%)*
Composite score, mean (SD)	103 (11)*	95 (13)*
Motor outcome, n	18 (75%)	17 (85%)
Abnormal (–1SD)	3 (13%)	5 (25%)
Motor composite score, mean (SD)	98 (11)*	89 (11)*
Fine motor score (scaled), mean (SD)	11 (2)	10 (2)
Gross motor score (scaled), mean (SD)	8 (3)*	6 (2)*
CBCL, n	21 (88%)	15 (75%)
Subclinical/clinical	2 (8%)	–
Total T-score, mean (SD)	45 (10)	47 (6)
Internalizing T-score, mean (SD)	45 (8)	42 (8)
Externalizing T-score, mean (SD)	47 (10)	51 (7)
Growth 1 year post term, n	20 (83%)	19 (95%)
ΔWeight, kilograms	8.2 [7.5–8.6]	7.6 [7.2–8.3]
ΔWeight, Z-score ¹	–0.4 [–1.6 to –0.02] #	–1.0 [–2.1 to –0.3] #
ΔHead circumference, centimeters	21.6 [20.2–22.1]	20.9 [18.8–22.3]
ΔHead circumference, Z-score ¹	0.2 [–0.4–1.1]	–0.3 [–0.9–0.5]

Data are expressed as numbers (percentages) or median [interquartile range] unless otherwise specified.

Abbreviations: Bayley-III – Bayley Scales of Infants and Toddler Development, third edition; CBCL – Child Behavior Checklist, ages 1.5–5 years; FEFt – time to full enteral feeding; GMFCS – gross motor functioning classification system; SD – standard deviation.

* $p < 0.05$.

$p < 0.10$.

¹ Based on Niklasson's growth reference tables [26].

Table 3
Patient characteristics of the included and non-included infants.

	Study population n = 44	Not included (missing Bayley-III) n = 32
Gestational age, weeks	27.9 [26.7–29.3]*	30.1 [28.7–33.3]*
Birth weight, g	1148 [810–1461]*	1275 [981–1680]*
Male	27 (61%)	22 (69%)
NEC onset, postnatal day	11 [8–24]	10 [7–20]
Laparotomy	16 (36%)	11 (34%)
Post-NEC complications		
Recurrent NEC	3 (7%)	–
Post-NEC stricture	8 (18%)	8 (25%)

Data are expressed as numbers (percentages) or median [interquartile range] unless otherwise specified.

Abbreviations: Bayley-III – Bayley Scales of Infants and Toddler Development, third edition.

* $p < 0.05$.

($p = 0.05$). We did not find an association between the development of post-NEC complications and cognitive or motor composite scores, or CBCL T-scores (Table 4). One infant developed both, recurrent NEC and a post-NEC stricture. This infant had a FEFt of 101 days and scored an abnormal CBCL externalizing T-score of 67.

3.4. The relation between FEFt, the severity of illness, clinical variables and neurodevelopmental outcomes

We presented the results of all univariate analyses in Table 4 and the results of the multiple analyses in Table 5. Only FEFt, surgery, GA, BW, and late onset sepsis were significantly associated with neurodevelopmental outcomes in the univariate analyses. As GA and BW were significantly correlated ($\rho = 0.9$, $p < 0.01$) we chose to only include GA in the multiple model and not BW. Adjusted for surgery, FEFt >

20 days remained significantly associated with lower cognitive composite (B = –8.4, 95% CI –16.5 to –0.3) and lower motor composite scores (B = –8.9, 95% CI –17.2 to –0.5). Adjusted for GA and late onset sepsis, FEFt > 20 days remained significantly associated with lower cognitive motor composite scores (B = –9.3, 95% CI –18.6 to –0.1). Adjusted for surgery, GA, and late onset sepsis FEFt > 20 days remained significantly associated with lower motor composite scores (B = –8.7, 95% CI –17.2 to –0.5). When we adjusted not just for the surgical intervention for NEC as presented in Table 4, but also for any other surgery at a later stage during NICU admission, we found similar associations (Supplemental Table 1).

4. Discussion

We demonstrated that a longer FEFt after NEC onset in preterm-born children was associated with lower cognitive and lower motor scores at the corrected age of 2–3 years. These findings were irrespective of a difference in overall severity of illness or NEC requiring surgical intervention. Our results therefore indicate that withdrawal of enteral feeding for a prolonged period of time because of NEC may contribute to a poorer neurodevelopment in preterm-born children. Furthermore, we found that, contrary to the association with neurodevelopmental outcomes, FEFt was not associated with behavior reported at 2–3 years post term. In this study, there was no evidence that post-NEC complications were associated with poor neurodevelopment or behavior.

During the third trimester, the brain undergoes rapid growth and differentiation [31,32]. As a result, the brain of preterm-born children which is very vulnerable to disturbances, including malnutrition [32]. Our results confirm that adequate nutrition is prerequisite for brain development [31,32], and that PN does not seem to be equally efficient as enteral feeding for maintaining adequate nutrition. A recent animal model supports our results by demonstrating that malnutrition during a vulnerable period of brain development lead to a reduction in brain

Table 4

The relation of time to full enteral feeding and post-NEC complications with Bayley-III and CBCL outcomes, using univariate linear regression analyses.

	Bayley-III scores				CBCL T-scores		
	Cognitive B (95% CI)	Motor B (95% CI)	Fine motor B (95% CI)	Gross motor B (95% CI)	Total B (95% CI)	Internalizing B (95% CI)	Externalizing B (95% CI)
<i>Primary independent variables</i>							
FEFt > 20 days	-8.6 (-16.7 to -0.4)*	-9.0 (-16.7 to -1.4)*	-1.0 (-2.3-0.3)	-1.8 (-3.5 to -0.02)*	1.4 (-4.6-7.5)	-2.6 (-8.1-2.9)	4.4 (-1.8-10.7)
NEC complications	-1.1 (-12.0-9.8)	-1.2 (-11.5-9.2)	0.7 (-0.9-2.3)	-1.0 (-3.2-1.3)	2.3 (-4.3-8.9)	2.2 (-3.9-8.2)	4.1 (-2.8-11.0)
<i>Severity of illness</i>							
Surgical intervention	4.6 (-4.4-13.6)	-9.4 (-17.3 to -1.5)*	-0.4 (-1.7-0.9)	-2.5 (-4.2 to -0.8)*	-1.1 (-7.3-5.1)	0.7 (-5.0-6.4)	-0.6 (-7.2-6.0)
Days of endotracheal intubation from NEC onset	-0.2 (-0.4-0.1)	-0.1 (-0.3-0.1)	-0.01 (-0.04-0.02)	-0.02 (-0.06-0.03)	-0.1 (-0.2-0.1)	-0.1 (-0.2-0.1)	-0.1 (-0.2-0.1)
<i>Other variables that might influence neurodevelopment</i>							
Gestational age	0.5 (-1.3-2.4)	1.0 (-0.7-2.8)	-0.1 (-0.4-0.2)	0.4 (0.1-0.8)*	0.6 (-0.6-1.8)	1.2 (0.1-2.2)*	-0.1 (-1.4-1.2)
Birth weight (per 100 g)	0.1 (-1.0-1.4)	0.4 (-0.6-1.4)	-0.1 (-0.2-0.1)	0.2 (0.001-0.4)*	0.1 (-0.6-0.8)	0.5 (-0.1-1.1)	-0.2 (-1.0-0.5)
Small for gestational age	6.5 (-5.8-18.7)	3.3 (-7.0-13.6)	0.5 (-1.2-2.1)	0.6 (-1.7-2.9)	3.4 (-4.5-11.3)	5.8 (-1.3-12.8)	0.5 (-8.0-9.0)
Late onset sepsis (blood culture proven)	-2.0 (-11.1-7.1)	-2.9 (-11.2-5.4)	-0.3 (-1.6-1.1)	-0.9 (-2.6-0.9)	2.6 (-3.2-8.5)	-3.0 (-8.5-2.5)	6.6 (0.6-12.7)*
IVH grade III-IV	-13.9 (-28.7-0.9)*#	5.6 (-12.2-23.4)	1.6 (-1.2-4.5)	0.3 (-3.7-4.3)	-2.5 (-15.5-10.5)	-9.0 (-20.6-2.5)	-1.9 (-15.7-12.0)
BPD	-1.1 (-12.0-9.8)	0.3 (-9.2-9.8)	0.6 (-0.9-2.1)	-0.4 (-2.5-1.7)	-1.4 (-8.9-6.1)	-3.5 (-10.3-3.3)	-1.3 (-9.3-6.7)
ROP grade III-IV	-0.1 (-0.6-0.4)	4.4 (-13.3-22.2)	2.2 (-0.6-5.0)	-0.7 (-4.6-3.3)	-12.4 (-24.8-0.0)*#	-8.9 (-20.7-2.8)	-11.8 (-25.1-1.6)*#
SES mother (> 18 years of education)	6.4 (-1.2-14.0)*	-0.3 (-8.6-8.1)	0.7 (-0.6-2.1)	-0.7 (-2.6-1.3)	0.6 (-5.9-7.0)	0.7 (-4.7-6.2)	0.1 (-6.6-6.9)

Abbreviations: Bayley-III – Bayley Scales of Infants and Toddler Development, third edition; BPD – bronchopulmonary dysplasia; CBCL – Child's Behavior Checklist, ages 1.5–5 years; FEFt – time to full enteral feeding; IVH – intracranial hemorrhage; NEC – necrotizing enterocolitis; ROP – retinopathy of prematurity.

* $p < 0.05$.

$p < 0.10$.

cells, myelin production, and number of synapses [32]. Additionally, enteral nutrition during early life after preterm birth is reported to be the most significant contributor to brain development [33].

The association between lower motor scores and a longer FEFt was predominantly dependent on the gross motor domain, while the fine motor domain was not associated with FEFt. This may be explained by the difference in timing of fine and gross motor development after birth. Gross motor development starts directly after birth as the all-round support from the amniotic fluid is missing and the child is suddenly exposed to the gravity forces requiring postural control to maintain body position [34]. Fine motor development, however, is firstly observed around 10 to 12 weeks postmenstrual age [34,35].

The children with a longer FEFt after NEC may have been more severely ill than the children with a shorter FEFt. Inflammation, which characterizes NEC, is associated with an arrest in oligodendrocyte maturation, followed by myelination failure and neural axons [31]. This in turn results in a reduced neuronal connectivity and brain volume, two important characteristics of the brain necessary for an adequate neurodevelopment [31]. In our study population, however, we did not find different levels of C-reactive protein, as measure for inflammation, between children with a shorter FEFt and longer FEFt. From the other variables indicating illness severity, only the duration of endotracheal intubation was different between the groups, but this was not associated with neurodevelopmental outcomes. The association between FEFt and motor scores was thus not based on differences in illness severity. In addition to the severity of illness, we also demonstrated that FEFt remained strongly associated with neurodevelopmental outcomes when adjusted for GA and late onset sepsis. It may be possible that the effect of a longer FEFt on neurodevelopmental outcome is larger in infants with a lower GA, but this requires further study.

Previously, our group and others demonstrated that preterm-born children who developed NEC requiring surgery had lower cognitive and motor development compared with conservatively treated children

[7,9–11]. We demonstrated that adjusted for surgery, FEFt remains significantly associated with both cognitive and motor scores. This suggests that the duration of FEFt after NEC onset may be even more important for neurodevelopmental outcome in this group of children, than whether surgical intervention was required. This needs to be further investigated in larger prospective studies.

In our study population, we did not find a difference in relative weight gain and head growth one year post term between children with a longer and shorter FEFt. This suggests that although NEC is a risk factor for impaired growth, this might be unrelated to the duration until full enteral feeding is tolerated again. Supposedly, growth after NEC is more likely to be dependent on the severity of NEC [8,9], or differences in growth are too subtle to detect and have been overcome in the months following NEC.

We also determined whether the development of post-NEC complications, including recurrent NEC and post-NEC strictures, resulted in a poorer neurodevelopmental outcome, and demonstrated that this was not the case. A possible explanation may be that FEFt did not differ between children with and without recurrent NEC, and similarly between children with and without post-NEC strictures. It might also be that our sample size was too small to detect any associations.

In the present study, FEFt and the presence of post-NEC complications were not associated with behavioral outcomes. Several studies also did not find associations between nutritional restriction, indirectly measured by growth, and behavior outcomes [36–40]. Nevertheless, behavioral problems may become more obvious at an older age as they have been reported at school age in children who survived NEC [10,12,41]. We tested behavior using a questionnaire that was filled in by the parents at home, which may have underestimated behavioral problems, as has been reported before [42].

Our study population achieved relatively high cognitive and motor composite scores with means between the 0 SD and -1 SD of the reference population. Several studies reported lower cognitive and motor outcomes in preterm-born children who developed NEC than their peers

Table 5
The relation of time to full enteral feeding with Bayley-III and CBCL outcomes adjusted for potential confounders, using multiple linear regression analyses.

	FEFT > 20 days univariate B (95% CI)	FEFT > 20 days adjusted for surgery B (95% CI)	FEFT > 20 days adjusted for gestational age and late onset sepsis B (95% CI)	FEFT > 20 days adjusted for surgery, gestational age, and late onset sepsis B (95% CI)
Bayley-III				
Cognitive composite score	-8.6 (-16.7 to -0.4)*	-8.4 (-16.5 to -0.3)*	-9.3 (-18.6 to -0.1)*	-8.7 (-18.0 to 0.7)*
Motor composite score	-9.2 (-16.7 to -1.4)*	-8.9 (-17.2 to -0.5)*	-8.1 (-16.9 to 0.8)*	-8.7 (-17.2 to -0.5)*
Fine motor (standard scores)	-1.0 (-2.3 to 0.3)	-1.0 (-2.3 to 0.3)	-1.0 (-2.5 to 0.4)	-1.0 (-2.5 to 0.4)
Gross motor (standard scores)	-1.8 (-3.5 to -0.0)*	-1.9 (-3.4 to -0.3)*	-1.3 (-3.2 to 0.5)	-1.5 (-3.2 to 0.2)*
CBCL				
Total score (T-scores)	1.4 (-4.6 to 7.5)	1.4 (-4.7 to 7.5)	-2.0 (-4.9 to 8.8)	2.1 (-5.0 to 9.2)
Internal scores (T-scores)	-2.6 (-8.1 to 2.9)	-2.6 (-8.2 to 3.0)	-0.3 (-6.7 to 6.0)	0.4 (-6.0 to 6.8)
External scores (T-scores)	4.4 (-1.8 to 10.7)	4.4 (-1.9 to 10.7)	3.1 (-4.0 to 10.1)	3.0 (-4.3 to 10.4)

Abbreviations: Bayley-III – Bayley Scales of Infants and Toddler Development, third edition; CBCL – Child's Behavior Checklist, ages 1.5–5 years; FEFT – time to full enteral feeding.

* $p < 0.05$.

$p < 0.10$.

[7–9]. The relatively high composite scores in our study population might be explained by the version of the Bayley assessment [43,44]. Additionally, anaesthetic, surgical and neonatal techniques may have improved during the past years.

To the best of our knowledge, we are the first to demonstrate an association between withdrawal of enteral feeding because of NEC and a decrease in cognitive and motor scores at the corrected age of 2–3 years. We do acknowledge several limitations. We realize that although this study was in part prospective, patient data were also collected retrospectively. Because of our small sample size, we were limited in the amount of potential confounders that we could include in our multiple analyses. This small sample size may also have introduced type-II error, leading to insufficient power to detect differences between groups. Furthermore, we found that infants who were excluded because of missing Bayley-III data were older than the included infants. This may have caused bias. Finally, we used the time between NPO after primary NEC onset until FEF was tolerated again and adjusted our analysis for surgical intervention. Some infants, however, needed surgery for several reasons for several times at different ages, including a repetitive postoperative NPO regimen. When adjusting not just for the surgical intervention for NEC in the acute phase of the disease, but also for any other surgery at a later stage during NICU admission, results remain similar. Unfortunately, due to the small sample size, we were also unable to adjust for multiple NPO periods. This study, however, is a first step to address the association between withdrawal of enteral feeding and neurodevelopment.

In conclusion, we demonstrated that FEFT of > 20 days after primary NEC onset in preterm-born children was, independent of illness severity or need for surgery, associated with a considerable reduction of cognitive and motor scores during neurodevelopmental FU at the corrected age of 2–3 years. We did not find an association between FEFT and behavior. Finally, there was no evidence that the presence of post-NEC complications were associated with cognitive, motor, and behavior outcomes. Our findings suggest that the withdrawal of enteral feeding longer than 20 days contributed to a poorer neurodevelopmental outcome in preterm-born children who survived NEC. Although a rapid reintroduction of enteral feeding after NEC onset is not always achievable, these results show the importance of being aware of the effect of withdrawing enteral feeding to limit the duration of this regimen if and when possible. The results of the present study, however, should be confirmed in a prospective study in a larger cohort, addressing also the influence of possible confounders.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.earlhumdev.2020.105091>.

Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Funding

This work was supported by the research programme of the post-graduate school for Behavioral and Cognitive Neurosciences, University of Groningen. S.J. Kuik and M.J. Mebius were financially supported by a grant from the Junior Scientific Master Class of the University of Groningen, Groningen, the Netherlands. This grant was used for a contribution to the PhD fee.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

Acknowledgements

We would like to acknowledge the nurses and medical staff of the neonatal intensive care unit of Beatrix Children's Hospital in Groningen, and the medical students for creating the opportunity to carry out this study. Furthermore, we would like to acknowledge the infants and their parents for participating in the follow-up program.

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