



Original article

Early energy and protein intakes and associations with growth, BPD, and ROP in extremely preterm infants



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SUMMARY

Background & aim: Extremely preterm infants face substantial neonatal morbidity. Nutrition is important to promote optimal growth and organ development in order to reduce late neonatal complications. The aim of this study was to examine the associations of early nutritional intakes on growth and risks of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) in a high-risk population.

Methods: This population-based cohort study includes infants born before 27 0/7 weeks of gestational age without severe malformations and surviving ≥ 10 days. Intake of energy and protein on postnatal days 4–6 and association with weight standard deviation score (WSDS) from birth to day 7, as well as intakes of energy and protein on postnatal days 4–6 and 7 to 27, respectively, and association with composite outcome of death and BPD and separate outcomes of BPD and ROP were examined, and adjusted for potential confounders.

Results: The cohort comprised 296 infants with a median gestational age of 25 3/7 weeks. Expressed as daily intakes, every additional 10 kcal/kg/d of energy during days 4–6 was associated with 0.08 higher WSDS on day 7 (95% CI 0.06–0.11; $p < 0.001$). Between days 7 and 27, every 10 kcal/kg/d increase in energy intake was associated with a reduced risk of BPD of 9% (95% CI 1–16; $p = 0.029$) and any grade of ROP with a reduced risk of 6% (95% CI 2–9; $p = 0.005$) in multivariable models. This association was statistically significant in infants with ≤ 10 days of mechanical ventilation. In infants with > 10 days of mechanical ventilation, a combined higher intake of energy and protein was associated with a reduced risk of BPD.

Conclusion: Early provision of energy and protein may reduce postnatal weight loss and risk of morbidity in extremely preterm infants.

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Abbreviations: BPD, bronchopulmonary dysplasia; BWSDS, birth weight standard deviation score; CI, confidence interval; EPT, extremely preterm; GA, gestational age; MOM, mother's own milk; MV, mechanical ventilation; NEC, necrotizing enterocolitis; PCTL, percentile; PE ratio, protein to energy ratio; PMA, post-menstrual age; ROP, retinopathy of prematurity; RR, risk ratio; SNQ, Swedish neonatal quality register; WSDS, weight standard deviation score.

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1. Introduction

During the last decade, optimizing nutrition in extremely preterm (EPT) infants has been a major strategy to improve the quality of neonatal intensive care. Previous studies have demonstrated that initiation of parenteral nutrition immediately after birth is related to reduced postnatal weight loss and time to regain birth weight [1,2]. Higher energy and protein intake has also been related to less drop in weight standard deviation score (WSDS) from birth to 28 and 70 postnatal days [3].

Affecting approximately 50–80% of EPT infants, bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) are diseases originating from impaired development of the lung and retina [4,5]. Both BPD and severe ROP (grade ≥ 3) have been associated with a higher risk of morbidity, including neurocognitive impairment, in adult life [6,7]. Suboptimal growth among EPT infants has been associated with incidence and severity of BPD and ROP [8–11]. Low energy intake in the first month has been associated with increased risk of severe ROP [12,13], but there is a lack of larger studies on EPT infants that examine the association between early energy and protein intake and the development of BPD.

Implemented bundles of nutritional interventions have resulted in higher intake of energy and protein primarily during the first postnatal week [14]. We hypothesized that these changes are associated with improved growth and decreased neonatal morbidity. This study investigates the association of early energy and protein intake with initial weight development in a cohort of EPT infants and examines whether intake of energy and protein in the first week and month were associated with BPD and ROP in a model that also considers days of mechanical ventilation (MV).

2. Subjects and methods

This was a cohort study of all infants born alive and treated in Stockholm before 27 0/7 weeks of gestational age (GA). Included infants were born from April 1, 2004 to March 31, 2007 and from January 1, 2008 to December 31, 2011. Infants, who were born from 2004 to 2007, were also included in the Extremely Preterm Infants in Sweden Study (EXPRESS) [15]. The period from April 2007 to December 2007 was not included due to inaccessible data. Infants were excluded if they died before 10 days of age, had chromosomal or severe malformations, or had missing data in hospital records. Infants were also excluded if abdominal surgery or transfer outside

Stockholm occurred before the first outcome, i.e., before 7 days of postnatal age (Fig. 1).

Perinatal and neonatal care data were prospectively registered in the Swedish Neonatal Quality (SNQ) register. Outcome variables BPD and ROP as well as covariates necrotizing enterocolitis (NEC) and sepsis were validated using hospital records. Information regarding anthropometric measurements and nutrition data were retrospectively collected from hospital records and registered in nutrition calculating software (www.nutrium.se, Nutrium AB, Umeå, Sweden). Amino acids were counted as protein. Nutrition calculations used Atwater's factors for both enteral and parenteral intakes (4 kcal/g protein, 9 kcal/g fat and 4 kcal/g carbohydrates). Feeding guidelines were described in a previous publication [14]. Standard practice during the entire study period was to use mother's own milk (MOM) if available; if not, infants were fed with donor milk (DM). Minimal enteral feeding was initiated from day of birth. From 2004 to 2009, initiation of target fortification was recommended when parenteral nutritional supply was terminated. From 2010, target fortification was recommended when enteral nutrition contributed 75% of total fluid intake. Recorded intake of all parenteral and enteral nutrition and other fluids was registered daily from birth to postnatal day 27 and thereafter once a week until unaccountable amounts of enteral feeds due to breast feeding occurred or due to transfer to a hospital outside the Stockholm region, discharge or death. Both MOM and DM macronutrient content was analyzed using mid-infrared spectrophotometry (MilkoScan 4000, FOSS Hillerød, Denmark) at Eurofins Steins Laboratory AB, Jönköping, Sweden [16]. After analyses, all DM was routinely heat-treated using Holder pasteurization. MOM was not pasteurized. The local guidelines recommended analysis of MOM every other week with a first analysis at postnatal day 7–14. When analyses of MOM were not available during the first 28 postnatal days, nutritional calculations were based on the average content of

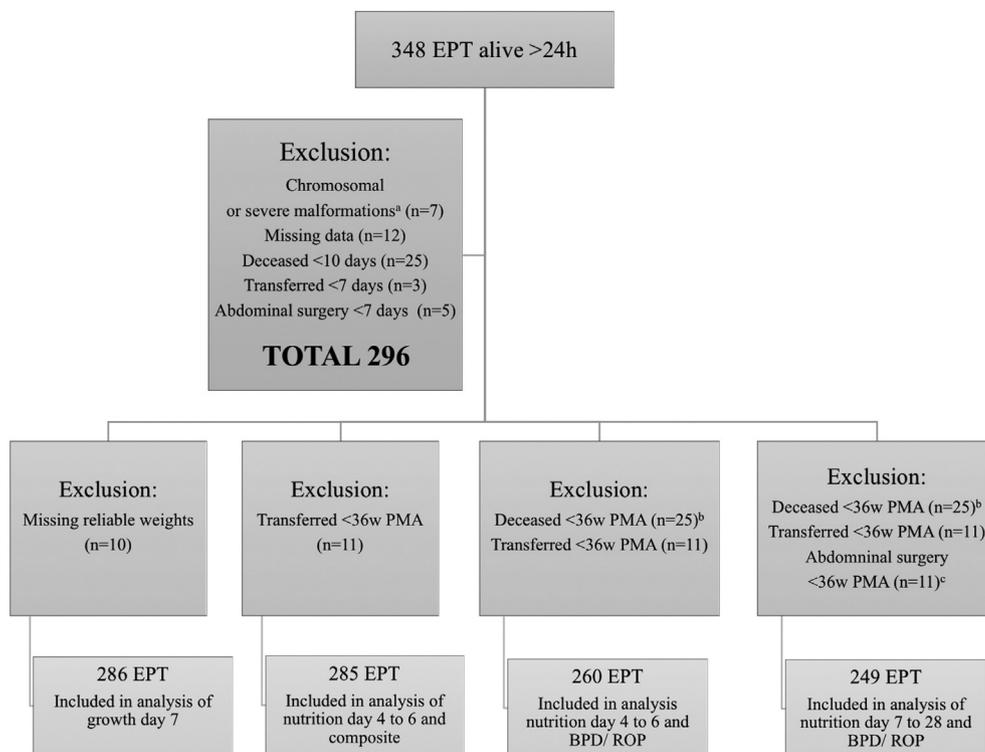


Fig. 1. Flowchart of included infants. Abbreviations: extremely preterm infant (EPT), postmenstrual age (PMA), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP). ^a Malformations excluded: Hypoplasia of the lungs, Intestinal malformation and Beckwith Wiedemann. ^b Death between postnatal day 10 and 36 weeks PMA. ^c Sixteen infants had abdominal surgery before 36 weeks PMA. Five infants were excluded as deceased before 36 weeks PMA.

breast milk samples from mothers of EPT infants who expressed milk up to 28 days after delivery. When MOM analyses after 28 postnatal days were lacking, nutritional calculations were based on the average content of breast milk samples from mothers of EPT infants who expressed milk later than 28 days after delivery [16]. Nutrient content of blood products was included in nutrient calculations. Estimated contents of energy and protein were 18 kcal and 4.1 g per 100 ml erythrocytes and 28 kcal and 6.9 g per 100 ml plasma or thrombocytes [17,18].

For infants not weighed on the precise day (7), weight was calculated assuming an exponential growth pattern between measurements within two weeks [19]. The revised Fenton growth chart was used to calculate WSDS [20]. BPD was defined as a need for supplemental oxygen at 36 weeks postmenstrual age (PMA). ROP was classified according to international guidelines [21], and graded as no ROP (stage 0), mild ROP (stage 1–2), or severe ROP (stage ≥ 3). Sepsis was defined as a positive blood culture or clinical symptoms in association with elevated c-reactive protein (>20 mg/L) or leukocyte count ($>20 \times 10^9/L$). NEC was defined as Bell stage II or more according to modified Bell's stage criteria [22]. Exposure was total parenteral and enteral intake of energy (kcal/kg/d) and protein (g/kg/d) on postnatal days 4–6 and 7 to 27, expressed as mean intake/kg/day calculated from daily intakes. The period of postnatal days 4–6 was pre-specified as exposure in order to examine more stable nutritional intakes after initial escalation, while still reflecting early nutrition. Results regarding postnatal days 0–3 are also shown. If intake of energy was significantly associated with the outcomes, protein intake was evaluated as a protein to energy ratio (PE ratio), calculated as the fraction of protein intake (g/kg/d) per 100 kcal of energy intake (kcal/kg/d). Our primary outcome of interest was change in WSDS (Δ WSDS) from birth to postnatal day 7. Secondary outcomes were a composite of death or BPD and separate outcomes of BPD and ROP.

2.1. Statistical methods

All analyses were performed using Stata/IC 14.2 software (StataCorp LP, College Station, Texas, USA). Linear regression with robust standard errors was used to examine the continuous outcome of growth and Poisson regression with robust standard errors [23] was used to calculate differences in relative risk of the composite outcome, BPD, and ROP, expressed as risk ratios (RR). The association with ROP was examined as no ROP vs. any ROP (mild and severe) and no/mild ROP vs. severe ROP. Linearity of continuous outcomes was tested using splines [24]. The following covariates were considered potential confounders: antenatal corticosteroids, exact GA in days, birth weight standard deviation score (BWSDS), sex, fluid intake, transfusions of erythrocytes and plasma, and days on MV. Directed acyclic graphs and backward selection was used. Covariates not included in the final models did not contribute significantly to outcome estimates, neither in univariate nor multivariate models. Interactions were tested between energy intake and MV, fluid and protein intake. If the interaction term was significant, analyses were supplemented with stratified analyses. The level of significance was set at 5%. We did not have reliable data regarding the dates of the episodes of sepsis and NEC, or dates of given postnatal steroids in the entire cohort, and therefore these variables were only included in sensitivity analyses. Supplemental analyses, including adjustment for time period (2004–2007 or 2008–2011) were also performed, and differences in association between time-periods examined using an interaction term between energy intake and time-period.

Regional ethical review boards approved this study (Lund 2004-42, amendments 2006-201 and 2008-138; Stockholm 2007/1613-31, amendment 2013/265-32).

3. Results

A total of 296 infants born at GA ranging from 22 4/7 to 26 6/7 weeks were included in this study (Fig. 1). Characteristics of the included infants and nutritional intakes are demonstrated in Tables 1 and 2. Mean intakes of protein without blood products were 1.8 g/kg/d on days 0–3, 2.9 g/kg/d on days 4–6, and 3.1 g/kg/d on days 7–27. Weight development in the entire cohort is illustrated in the supplement (eFig. 1). There was no statistically significant difference in Δ WSDS between infants with measured and extrapolated weights.

3.1. Energy and protein intake and growth

A higher intake of energy on postnatal days 4–6 was associated with a significantly smaller decrease in WSDS from birth to day 7: A 10 kcal/kg/d increase of energy intake corresponded to +0.08 Δ WSDS (95% CI 0.06–0.11; $p < 0.001$), adjusted for GA, BWSDS, days of MV, and transfusions. A higher PE ratio on postnatal days 4–6 was also significantly associated with initial weight development. Every one-gram increase in PE ratio corresponded to +0.13 Δ WSDS (95% CI 0.07–0.18; $p < 0.001$), adjusted for GA, BWSDS, days of MV, and transfusions. The fluid intake was tested as a covariate in the model of energy and protein intakes on days 4–6, but it did not alter the estimates, and was not included in the final model. Figure 2 illustrates association between protein intake and Δ WSDS from birth to postnatal day 7 at different levels of energy intake on postnatal days 4–6. At a mean energy intake of 100 kcal/kg/d, every additional one-gram increase in protein intake corresponded to an increase of 0.15 in Δ WSDS (95% CI 0.08–0.22; $p < 0.001$). Higher energy and protein intakes on postnatal days 0–3 were also positively associated with Δ WSDS to day 7 (eTable1).

3.2. Early energy and protein intake and morbidity

In the multivariable regression model, there was no statistically significant association between energy intake on days 4–6 and the composite outcome of BPD or death (RR 0.95 95% CI 0.88–1.02; $p = 0.164$) or components of the composite, adjusted for GA, BWSDS, transfusions, MV and antenatal steroids. The association between energy intake on days 4–6 and severe ROP did not reach statistical significance (RR 0.90 95% CI 0.81–1.00; $p = 0.056$), adjusted for GA, BWSDS, transfusions, and MV. Neither the composite outcome of BPD or death nor components of the composite nor ROP were associated with protein intake on postnatal days 4–6 in analyses adjusted for GA, BWSDS, transfusions, MV and antenatal steroids. Moreover, Δ WSDS from birth to day 7 was not significantly associated with the composite outcome of BPD and death, components of the composite, or ROP in adjusted analyses.

3.3. Energy and protein intake on days 7–27 and morbidity

Twenty-five infants died before 36 weeks PMA. Seventeen of these infants died before 28 days of postnatal age, and were excluded from all analyses of energy and protein intakes on days 7–27. The results regarding energy intake and the composite outcome of BPD and death are presented in supplement (eTable2a) and do not differ from the results regarding BPD. Higher energy intake on postnatal days 7–27 was associated with a lower risk of BPD and ROP of any stage (Table 3), but not with a risk of severe ROP in adjusted analyses (eTable2b). PE ratio on days 7–27 was not associated with risk of BPD or ROP in analyses including adjustment for transfusions on days 0–28. Lower growth rate, expressed as Δ WSDS from birth to day 28, was associated with an increased risk of severe ROP, but not with BPD in a multivariable adjusted analysis.

Table 1
Characteristics and morbidity of included infants (n = 296).

	Median	25 th – 75 th centiles	min – max
GA, weeks + days	25 + 3	24 + 4–26 + 2	22 + 4–26 + 6
BW, grams	762	670–916	416–1189
BW, SDS ^a	0.21	–0.35–0.79	–2.30–2.53
Weight at postnatal day 7, SDS ^b	–0.51	–0.90 to –0.10	–2.1–1.1
Mechanical ventilation day 0–3, days	4	2–4	0–4
Mechanical ventilation day 4–6, days	2.5	0–3	0–3
Mechanical ventilation day 7–27, days ^c	6	0–16	0–21
	n	%	
Antenatal corticosteroids	257	86.8	
Cesarean section	146	49.3	
Sex, female	135	45.6	
Postnatal corticosteroids (systemic)	53	17.9	
BPD, O ₂ at PMA 36 weeks ^d	134	51.5	
BPD severe, >30% O ₂ at PMA 36 weeks ^d	40	15.4	
ROP no ^d	42	16.2	
ROP mild, stage 1–2 ^d	117	45.0	
ROP severe, stage ≥3 ^d	101	38.8	
IVH severe, grade ≥3	35	11.8	
Sepsis ^e	194	65.5	
NEC	26	8.8	
Death between postnatal day 10 and 36 weeks PMA ^f	25	8.8	

Abbreviations: percentile (PCTL), bronchopulmonary dysplasia (BPD), postmenstrual age (PMA), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), gestational age (GA), birth weight (BW), standard deviation score (SDS), postmenstrual age (PMA).

^a Weight standard deviation score (WSDS) according to the 2013 preterm growth chart by Fenton et al.¹⁷.

^b Out of 286 infants (10 infants had missing reliable weight measurements).

^c Out of 269 infants (17 infants died, 8 had abdominal surgery and 2 were transferred between postnatal day 7 and 28).

^d Out of 260 infants (25 infants died and 11 were transferred before 36 weeks PMA).

^e Positive blood culture or clinical symptoms in association with elevated c-reactive protein or leukocyte count.

^f Out of 285 infants (11 were transferred before 36 weeks PMA).

Table 2

Nutritional intakes in included infants (n = 296).

	Mean (SD)	Median	25 th – 75 th PCTL
Energy day 0–3, kcal/kg/day	62 (12)	62	54–71
Energy day 4–6, kcal/kg/day	91 (13)	92	83–100
Energy day 7–27, kcal/kg/day ^a	109 (14)	110	100–119
Protein day 0–3, g/kg/day	2.9 (1.1)	2.9	2.1–3.7
Protein day 4–6, g/kg/day	3.4 (1.0)	3.3	2.7–4.1
Protein day 7–27, g/kg/day ^a	3.4 (0.4)	3.4	3.1–3.6
Protein to energy ratio day 0–3, g/100 kcal	4.6 (1.3)	4.6	3.8–5.5
Protein to energy ratio day 4–6, g/100 kcal	3.8 (0.8)	3.7	3.2–4.3
Protein to energy ratio day 7–27, g/100 kcal ^a	3.1 (0.5)	3.1	2.7–3.5
Fluids day 0–3, ml/kg/day	133 (23)	130	116–146
Fluids day 4–6, ml/kg/day	153 (20)	151	138–164
Fluids day 7–27, ml/kg/day ^a	161 (12)	162	154–169
Transfusions day 0–3, ml/kg/day ^b	16.6 (8.5)	15.4	11.2–22.1
Transfusions day 4–6, ml/kg/day ^b	9.1 (8.0)	7.7	3.6–14.2
Transfusions day 7–27, ml/kg/day ^{a,b}	3.9 (2.8)	3.4	1.8–5.7

Abbreviation: percentile (PCTL).

^a Out of 269 infants (17 infants died, 8 had abdominal surgery and 2 were transferred within 28 days).

^b Transfusions include erythrocytes, plasma and thrombocytes.

An increase in WSDS of 0.1 from birth to day 28 was associated with 8% (95% CI 3–12; p = 0.001) reduction in the risk of severe ROP.

3.4. Interaction of energy and protein intake and mechanical ventilation

Energy intake differed depending on number on days of MV. Mean energy intake on postnatal days 7–27 was 12 kcal/kg/d (95% CI 9–15; p < 0.001) lower in infants who received MV >10 days compared to ≤10 days during the first 28 days of life. The interaction term of energy intake on days 7–27 and MV was significant in analyses of BPD and ROP. In infants with ≤10 days on MV, higher energy intake on days 7–27 was associated with reduced risk of BPD (RR 0.79 95% CI 0.65–0.95; p = 0.011) and ROP (RR 0.87 95% CI 0.80–0.95; p = 0.003). In infants with >10 days of MV the association between energy intake and outcome was not significant for

BPD (RR 0.96 95% CI 0.89–1.05; p = 0.402) or ROP (RR 0.99 95% CI 0.96–1.03; p = 0.724) in the adjusted analyses.

In infants with >10 days on MV, higher intakes of both energy and protein on postnatal days 7–27 reduced the risk of BPD (eFig. 2) in analyses adjusted for GA, BWSDS, antenatal corticosteroids, MV and transfusions on days 0–28. At a mean energy intake of 100 kcal/kg/d, increased protein intake was not associated with a significant reduction of BPD risk. At a mean energy intake of 120 kcal/kg/d on days 7–27, every 0.5 g/kg/d increase in protein intake reduced the risk of BPD by 25% (95% CI 2–42; p = 0.034).

3.5. Sensitivity analysis

Adjusting for any episode of sepsis or NEC, or any dose of postnatal steroids did not alter any of the results.

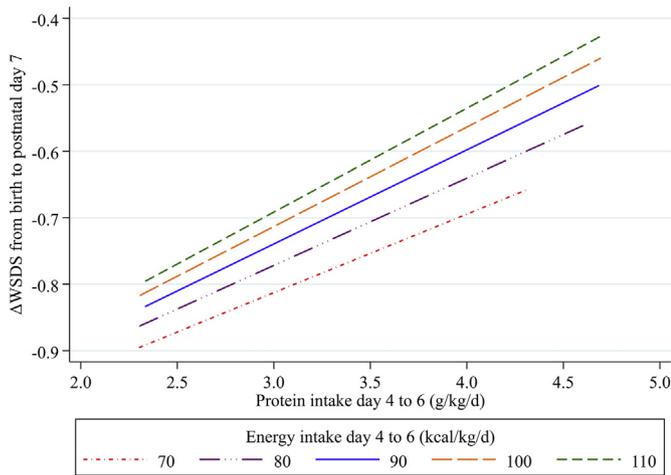


Fig. 2. Illustration of energy and protein intake and association with change in WSDS (Δ WSDS) from birth to postnatal day 7. Association between Δ WSDS and protein intake at given energy intakes. Results from the multivariable regression model including a modified effect of PE ratio depending on energy intake and adjusted for GA, BWSDS, MV and transfusions. Protein intake was calculated from PE ratio. Prediction assumes mean values of the other variables in the regression model: gestational age (25.4 weeks), birth weight standard deviation score (0.2 SDS), days of MV (4.5 days), and transfusions (9.7 ml/d) on days 0–6. Nutritional values used in the regression model included nutrient content in transfusions.

Table 3
Association between energy intake on days 7–27 and risk of BPD and ROP (n = 249).

	CRUDE			ADJUSTED		
	RR	95% CI	p-value	RR	95% CI	p-value
BPD^a						
O2 @ 36 weeks						
Energy day 7–27 (10 kcal/kg/d)	0.83	0.77–0.90	<0.001	0.91	0.84–0.99	0.029
ROP^b						
mild/severe						
Energy day 7–27 (10 kcal/kg/d)	0.92	0.88–0.96	<0.001	0.94	0.91–0.98	0.005

Abbreviations: bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), risk ratio (RR).

^a Adjusted for gestational age (GA), birth weight standard deviation score (BWSDS), antenatal corticosteroids, transfusions of erythrocytes and plasma (mL/d) the first week and number of days on mechanical ventilation (MV) day 0–28.

^b Adjusted for GA, BWSDS, transfusions of erythrocytes and plasma (mL/kg) the first week and days on MV day 0–28.

After adjusting for time period, the associations between energy and protein intake, respectively, and Δ WSDS to day 7 remained, however, the estimated effect size and statistical significance diminished (eTable3). Adding time-period into the models did not change previous findings that early energy and protein intakes on postnatal day 4–6, respectively, had no links to the composite of mortality and BPD, or to ROP.

The association between energy intake on postnatal days 7–27 and BPD differed between the two time-periods, the p-value for the interaction term was 0.03. Modeling GA, BWSDS, transfusions, MV, antenatal steroids and time-period, there was no significant association between energy intake and BPD in the first time period in 2004–2007 (RR 1.04 95% CI 0.93–1.17; p = 0.496), whereas a higher energy intake was associated with a reduced risk of BPD in 2008–2011 (RR 0.86 95% CI 0.74–0.99; p = 0.035). Adding time period to the regression models addressing associations between energy intake on postnatal days 7–27 and ROP did not alter previous findings.

4. Discussion

This study demonstrates the importance of initial nutritional management in the care of EPT infants. Our results show that energy intake in combination with protein intake had a positive impact on initial weight development. Higher energy intake during postnatal days 7–27 was associated with a lower risk of BPD and ROP. This study also indicates an association between higher protein intake and reduced risk of BPD provided there was sufficient energy intake. The findings suggest that energy and protein supply to extremely preterm infants is important despite critical illness. Our results did not demonstrate any statistically significant associations between energy or protein intake during the first postnatal week and subsequent risk of BPD or ROP.

Limitations of this study include its observational design, which prevented any firm conclusions regarding causal relationships. Because infants with more severe illness are not weighed as regularly as healthier infants, there is some uncertainty in the interpolated weights, especially when examining the initial growth pattern. Narrowing the window of accepted missing weights did not significantly alter the result of nutritional association with initial weight loss. In Sweden, transfusions of erythrocytes and plasma are given liberally. We do not know to what extent protein from blood products are used in the protein metabolism of EPT infants. The data in this study, which were retrospectively obtained from hospital charts, did not provide complete information regarding blood losses. The time span in this study provided a relatively large cohort of EPT infants with a great variability in energy and protein intakes. We have previously demonstrated that nutrition guidelines during this period, have been revised and nutritional intakes increased [14]. Birth year covaried strongly with the exposure, and the size of the cohort did not allow for a good quality model conditional on birth year. We decided to build the multivariable regression models adjusting for known important confounders and interactions. To minimize the risk of confounding by indication, variables related to severity of illness before the exposure were included in the regression models, interaction between days on MV and nutritional intake were examined, and the effect of adding co-morbidities to the model was analyzed. To examine potential residual confounding, the results were supplemented with analyses including time-period as a factor variable. This study examines total macronutrient intake without regard to how it was provided, so conclusions regarding the benefits of enteral or parenteral nutrition cannot be made. Infants in this study were born in 2004–2011, and the findings may not be generalizable to present neonatal care.

A randomized controlled trial (RCT) of early parenteral amino acid delivery, in very preterm infants with similar energy intakes, did not demonstrate any effect of higher protein intake on weight development [25]. In a RCT by Vlaardingerbroek et al. an increased amino acid and lipid intake, limited to postnatal days one and two, improved nitrogen balance but not growth rate [26]. Previous observational studies have reported associations between nutritional intake the first weeks of life and growth [27,28]. Our study, including more recently born infants, provides evidence that energy and protein intake during the first postnatal week is important in reducing the initial weight loss in EPT infants. The results also emphasize the need to provide adequate intakes of both energy and protein. It has previously been demonstrated that optimal utilization of protein depends on adequate provision of non-protein energy [29]. The importance of energy and protein intake has also been demonstrated in a RCT demonstrating improved head growth by increased energy and protein intake [30], and in a study by Stephens et al. that showed that higher energy and protein intake

the first week of life was associated with higher mental development index scores at 18 months [31].

There is reason to discuss both the risks and benefits of reducing initial weight loss. In preterm infants, there is a known physiological initial weight loss due to the redistribution of fluid, but optimal initial weight development is not known. Rochow et al. examined preterm infants without morbidities and proposed altered growth charts including an initial reduction in WSDS of 0.9 for infants born in gestational week 26 followed by growth parallel to current growth charts [32]. Nutritional intake is not presented in that study, and the magnitude of optimal initial weight loss could still be debated. In our model of growth, an infant born in gestational week 25 who received energy and protein at the lower end of current recommendations in Sweden (energy on days 4–6: 110 kcal/kg/d and protein on days 4–6: 3.5 g/kg/d) had a reduction of 0.6 WSDS the first week of life.

To our knowledge, the association between early nutritional intakes and BPD has not been evaluated in any major studies of EPT infants including updated nutritional regimens and adjusting for respiratory morbidity. In a study of extremely low birth weight infants born between 1999 and 2001, Ehrenkranz et al. found that energy intake during the first postnatal week mediated the association between initial critical illness and later development of BPD, and interacted in the association between initial critical illness and death [33]. In that study, need for MV the first 7 postnatal days defined the degree of critical illness. As with our findings, they also demonstrated that infants with more days on MV had a lower total energy intake during the first three weeks of life, a finding that illustrates persisting difficulties in providing adequate nutrition to infants on MV. In a review from 1988, several animal studies are presented that support an association between undernourishment and pulmonary morbidity, including higher susceptibility to pulmonary damage, a lower ability to repair, and a lower ability to synthesize lung proteins in undernourished animals [34]. Our study proposes a positive effect of providing EPT infants with sufficient energy and protein despite critical illness and need of MV.

Our large cohort study of EPT infants showed associations indicating that adequate amounts of energy and protein have the potential to improve growth and reduce morbidity. Intervention studies are needed to establish the requirements of enteral and parenteral energy and protein during the first days, weeks, and months for EPT infants with and without MV. This study emphasizes the importance of ensuring energy and protein intakes according to recommendations. That is, provision of nutrition is an important priority in the clinical care of EPT infants.

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Statement of authorship

SK contributed in data collection and study design, performed the statistical analyses, and drafted the initial manuscript. VV collected the data and contributed in manuscript writing. ESS collected the data and contributed in manuscript revision. MN and MD contributed to the study concept and design, and revised the manuscript for important intellectual content. AKEB contributed to the study concept and design, assisted in data analysis, and revised the manuscript. BH conceptualized the study, and contributed to

the study design and manuscript revision. All authors approved the final version of the manuscript.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clnu.2018.05.012>

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