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Intrauterine, Early Neonatal, and Postdischarge Growth and Neurodevelopmental Outcome at 5.4 Years in Extremely Preterm Infants After Intensive Neonatal Nutritional Support

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What's Known on This Subject

In comparison with intrauterine growth charts, extremely preterm infants frequently sustain intrauterine and early neonatal growth failure. Furthermore, extremely preterm infants frequently experience impaired neurodevelopment, and poor growth is associated with impaired neurodevelopment.

What This Study Adds

This study enables the comparison of the effects of intrauterine, early neonatal, and postdischarge growth on neurodevelopment at 5.4 years after intensive early neonatal nutrition. The results stress the importance of growth during the early neonatal period.

ABSTRACT

OBJECTIVE. Extremely preterm infants are at risk for poor growth and impaired neurodevelopment. The objective of this study was to determine whether intrauterine, early neonatal, or postdischarge growth is associated with neurocognitive and motor-developmental outcome in extremely preterm infants.

METHODS. Surviving children who were born between July 1996 and June 1999 at <30 weeks' gestation and with a birth weight <1500 g were evaluated at the age of school entry by application of (1) a standardized neurologic evaluation, (2) the Kaufmann Assessment Battery for Children, and (3) the Gross Motor Function Classification Scale. Growth was assessed on the basis of SD scores of weight and head circumference measured at birth, at discharge, and at the time of the follow-up examination. All infants had received intensive early nutritional support.

RESULTS. A total of 219 (83%) of 263 long-term survivors were evaluated at a median corrected age of 5.4 years. Increasing SD scores for weight and head circumference from birth to discharge were associated with a reduced risk for an abnormal neurologic examination. Catch-up growth of head circumference from birth to discharge was also associated with a reduced risk for impaired mobility. Weight SD score at birth, an increase of weight SD score from birth to discharge, and an increase of head circumference SD score from discharge to follow-up had an effect on the mental processing composite score. The effects of growth on neurodevelopment were by far exceeded by the consequences of intraventricular and periventricular hemorrhage.

CONCLUSIONS. Growth from birth to discharge seemed to be associated with long-term motor development. Cognitive development was associated with intrauterine growth measured as weight at birth, early neonatal weight gain, and postdischarge head circumference growth. Improving particularly early neonatal growth may improve long-term outcome in extremely preterm infants, but the effects of improved growth may only be small. *Pediatrics* 2009;123:e101–e109

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Key Words
neurology, neurocognitive outcome, mobility, preterm infant, very low birth weight, growth

Abbreviations
HC— head circumference
SDS—SD score
GMFCS—Gross Motor Function Classification Scale
KABC—Kaufmann Assessment Battery for Children
IVH/PVH—intraventricular or periventricular hemorrhage
ELBW— extremely low birth weight
VLBW—very low birth weight

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In comparison with intrauterine growth charts, extremely preterm infants frequently sustain intrauterine and early neonatal growth failure.[1–5] Furthermore, extremely preterm infants frequently experience impaired neurodevelopment,[6–10] and poor growth is associated with impaired neurodevelopment.[11–15]

Most studies on growth and neurodevelopment of extremely preterm infants are based on evaluations at the age of 18 to 24 months[12–14] (which may not necessarily be predictive of performance at school age[16]), and longer term outcomes are rarely reported.[11,15] Furthermore, most studies do not report on nutritional policies.

Although intensive early neonatal nutritional support[17–20] has been recommended repeatedly, long-term growth and neurodevelopment after such intensive nutritional support have rarely been reported. Furthermore, little is known about the effects of postdischarge growth on long-term development. The aim of this study, therefore, was to determine the contribution of intrauterine, early neonatal, and postdischarge growth until 5 years of age to long-term neurocognitive and motor-developmental outcome in extremely preterm infants after intensive early neonatal nutritional support.

METHODS

Study Subjects

This follow-up study was approved by the institutional review board of the University of Ulm, and written parental consent was obtained. Eligible were all inborn infants who had a gestational age of <30 weeks and a birth weight <1500 g and were admitted to Ulm University level 3 NICU between July 1996 and June 1999. The only exclusion criterion was missing written parental consent.

Policy of Nutrition

During the study period, all infants were started on intravenous dextrose 10% on day 1 of life at a rate of 5.5 mg/kg per minute. Parenteral amino acids (2 g/kg per day) and lipids (1 g/kg per day) were added the next morning (ie, usually within 24 hours) and increased to 3 g/kg per day and 3 to 4 g/kg per day, respectively. Intravenous dextrose was increased to a maximum total intake of carbohydrates of 13 mg/kg per minute. Parenteral nutrition complemented enteral nutrition as long as nutritional goals were not achieved on enteral nutrition alone. Insulin was not administered unless blood glucose levels exceeded 200 mg/dL despite reduction of total carbohydrate intake to 5.0 to 5.5 mg/kg per minute.

Enteral nutrition was started with maltodextrin 15% on day 1 and was advanced to milk feeds aiming at ~16-mL/kg per day increments in enteral nutrition provided that gastric residuals before each feed were <5 mL/kg and the abdominal examination was unremarkable.[21] Infants received either supplemented expressed breast milk of their own mother or a standard preterm infant formula, aiming to achieve a protein intake of 3.5 to 4.0 g/kg per day and an energy intake of 500 to 550 kJ/kg per day (as previously described[22]). An enteral feeding volume of 100 mL/kg per day was achieved on day 13 (median)[22] and full feeds on day 16.[21] After discharge, parents were advised to feed either supplemented breast milk or the preterm infant formula until a weight of 3.5 kg was reached. This regimen was similar to feeding regimens that sometimes are classified as "aggressive."[17–20]

Measures of Growth

Weight and head circumference (HC) at birth and at discharge were retrieved from the infants' charts. Weight and HC were prospectively measured at the 5-year follow-up examination.

Early neonatal growth was evaluated as the SD score (SDS) at discharge minus the SDS at birth and postdischarge growth as the SDS at follow-up minus the SDS at discharge. Because the SDS of weight decreased from birth to discharge in 200 of 217 infants, early neonatal growth was considered restricted only when the SDS of weight fell by >1.

SDS for Weight and HC

SDSs were computed on the basis of the physical measurements described already by using the Microsoft Excel add-in LMSgrowth (version 2.14; www.healthforallchildren.co.uk). The reference population is the British 1990 growth reference,[23,24] fitted by maximum penalized likelihood.[24]

Standardized Follow-up Assessment

The neurologic examination was performed by an experienced pediatric neurologist (Dr Steinmacher), who was blinded for the perinatal risk factors and for prenatal and early neonatal growth data. The neurologic examination was rated as normal, mildly abnormal (in the presence of minor neurologic signs such as broad gait, dysdiadochokinesis, or dysmetria), or severely abnormal (in the presence of any paresis with or without spasticity, cerebral nerve palsy, or ataxia).

Multidimensional assessment of mobility was performed by the Gross Motor Functioning Classification Scale (GMFCS).[25] A score of 0 represents normal mobility, and 1 represents mild abnormality (ie, walking, running, and jumping are possible but somewhat reduced in precision and velocity). A score of 2, 3, or 4 represents obviously impaired and severely impaired mobility and the lack of individual mobility, respectively.

Cognitive function was evaluated by the Kaufmann Assessment Battery for Children (KABC). The KABC comprises 2 summative scales: (1) the mental processing composite, a global measure of cognitive ability in 2 subscales, sequential processing and simultaneous processing, and (2) the achievement scale, an assessment of knowledge of facts, language concepts, and school-related skills. The range of possible scores for both scales is 40 to 150. The test was last standardized in 1992 to a mean of 100 and an SD of 15 in a German reference population.[26] The mental processing composite can be interpreted similarly to an IQ. Children whose severe cognitive impairment or disability precluded the use of this assessment tool were assigned a score of 30 when minimal speech and the ability for minimal communication with the parents were present and a score of 20 when no speech was present but at least minimal sensory or motor achievements were elicited.

Statistical Analyses

In multiple logistic and multiple linear regression analyses, gestational age, gender, multiple birth, severe intraventricular or periventricular hemorrhage (IVH/PVH; ≥3°), periventricular leukomalacia, severe retinopathy of prematurity (≥3°), need for mechanical ventilation, duration of mechanical ventilation (≥7 days), language,

TABLE 1 **Demographic and Neonatal Morbidity Data**

Parameter	Follow-up ($n = 219$)	Lost to Follow-up ($n = 44$)	Died ($n = 34$)
Gestational age, wk			
Mean ± SD	27.0 ± 1.7	27.9 ± 1.3	25.6 ± 1.9
Median (minimum–maximum)	27.1 (22.9–29.9)	28.4 (24.9–29.9)	25.1 (22.9–29.9)
<23⁶⁄₇, *n* (%)	1 (0.4)	0 (0.0)	2 (6.0)
23⁶⁄₇ to 25⁶⁄₇, *n* (%)	66 (30.0)	3 (7.0)	19 (56.0)
26⁶⁄₇ to 27⁶⁄₇, *n* (%)	78 (36.0)	17 (39.0)	8 (24.0)
28⁶⁄₇ to 29⁶⁄₇, *n* (%)	74 (34.0)	24 (55.0)	5 (15.0)
Birth weight, *n* (%), g			
Mean ± SD	867 ± 234	1022 ± 235	605 ± 180
Median (minimum–maximum)	850 (320–1460)	1070 (490–1480)	580 (300–1000)
Female gender, *n* (%)	119/219 (54)	21/44 (48)	22/34 (65)
Any antenatal steroids, *n* (%)	190/208 (91)	37/42 (88)	29/33 (88)
CRIB score			
Mean ± SD	5.3 ± 3.7	3.7 ± 2.2	9.0 ± 3.4
Median (minimum–maximum)	5 (0–16)	3.5 (1–8)	9 (2–15)
<3, *n* (%)	60/187 (32)	13/32 (30)	1/16 (3)
3–7, *n* (%)	74/187 (40)	18/32 (41)	3/16 (9)
8–12, *n* (%)	46/187 (25)	1/32 (2)	8/16 (24)
>12, *n* (%)	7/187 (4)	0/32 (0)	4/16 (12)
Not documented, *n* (%)	32/219 (15)	12/44 (27)	18/34 (53)
IVH/PVH > 2°, *n* (%)	18/218 (8)	4/44 (9)	12/31 (39)
PVL, *n* (%)	6/212 (3)	3/41 (7)	6/32 (19)
ROP >2°, *n* (%)	30/219 (14)	3/44 (7)	2/34 (6)
NEC ≥Bell stage 2, *n* (%)	13/217 (6)	3/44 (7)	4/34 (12)
CLD (FIO_2 >0.21 at 36 wk), *n* (%)	64/213 (30)	9/44 (20)	11/14 (79)
Duration of hospital stay, d			
Mean ± SD	93 ± 40	81 ± 38	67 ± 86
Median (minimum–maximum)	85 (29–361)	77 (34–231)	20 (0–326)
<51, *n* (%)	20/219 (9)	10/44 (23)	21/34 (62)
51–100, *n* (%)	122/219 (56)	23/44 (52)	1/34 (3)
>100, *n* (%)	77/219 (35)	11/44 (25)	12/34 (35)

Percentages shown are column percentages. CRIB indicates Clinical Risk Index for Babies[27]; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; CLD, chronic lung disease, defined as a minimum fraction of inspired oxygen (FIO_2) >0.21 to achieve a SpO_2 ≥90% at 36 weeks' postmenstrual age.

and maternal education were considered as perinatal risk factors.

Multiple logistic regression with forward selection (selection level 5%) was performed to identify important perinatal risk factors for prediction of poor neurodevelopment. After selection of important perinatal risk factors from the aforementioned set, measures of intrauterine, early neonatal, and postdischarge growth were entered into all models to evaluate whether any of these had an additional value for prediction of poor neurodevelopment beyond the predictive value of the perinatal risk factors. Odds ratios with 95% confidence intervals and *P* values were calculated. The value for prediction of outcome of the important risk factors identified was assessed by the area under the receiver operating characteristic curve.

Multiple linear regression with forward selection (selection level 5%) was used to identify important factors for continuous outcomes. After selection of important perinatal risk factors from the aforementioned set, measures of intrauterine, early neonatal, and postdischarge growth were entered into the models to evaluate whether any of these had an additional value for prediction of poor neurodevelopment beyond the predictive value of the perinatal risk factors. Parameter estimates with 95% confidence intervals and *P* values were calculated: The goodness of fit of the model and the importance of a factor were assessed by R^2 and partial R^2. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

A total of 297 infants with a gestational age <30 weeks and a birth weight <1500 g were admitted; 28 died during their initial hospitalization (91% NICU survival) and 6 after discharge. A total of 219 infants (83% of the survivors) completed the follow-up assessment at a median corrected age of 5.4 years (range: 4.6–7.0 years).

The clinical characteristics are summarized in Table 1. Infants who were lost to follow-up had higher birth weight, higher gestational age, and shorter hospital stay than infants with complete follow-up.

Measures of intrauterine, early neonatal, and postdischarge growth are depicted in Figs 1 and 2. Early neonatal growth failure was most common in the most premature infants and occurred in ~50% of the infants who were born at <26 weeks' gestation. The median SDS for weight decreased from −0.7 at birth to −1.8 at

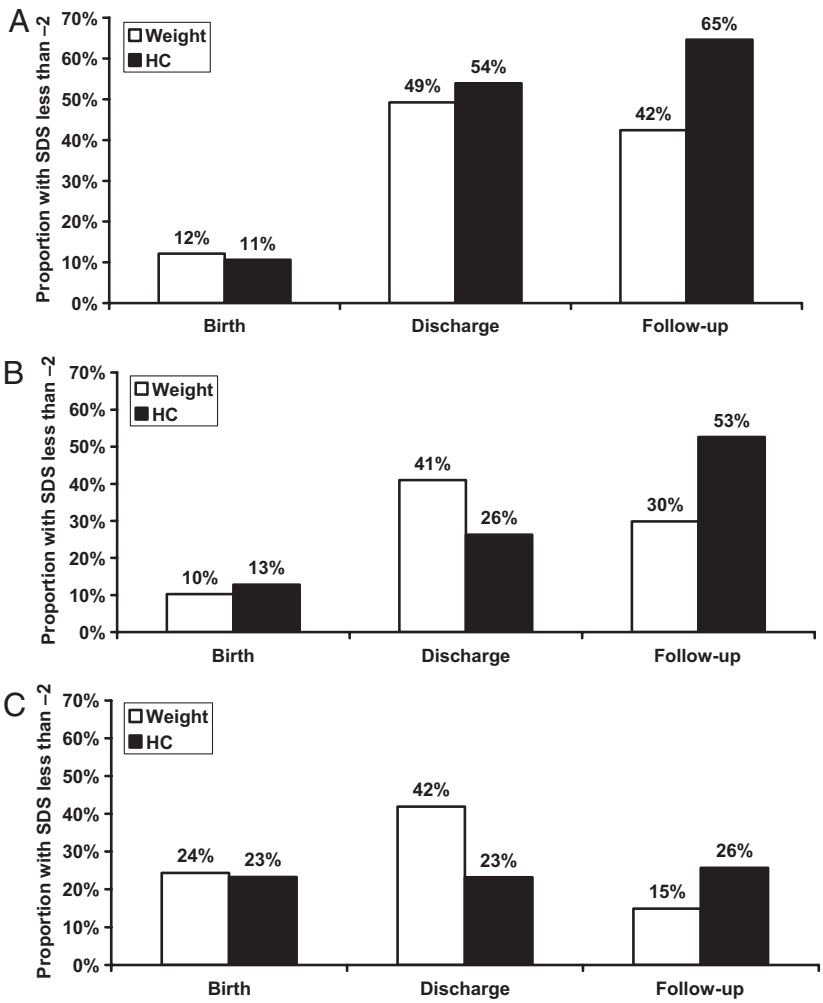

FIGURE 1
Intrauterine, early neonatal, and postdischarge growth after intensive early neonatal nutritional support depicted as proportion of infants with weight or HC SDS less than −2. A, Gestational age 23⅐ to 25⅐ weeks; B, gestational age 26⅐ to 27⅐; C, gestational age 28⅐ to 29⅐ weeks.

discharge and increased again to −1.1 at follow-up. The median SDS for HC decreased from −1.1 at birth to −1.4 at discharge and to −1.9 at follow-up.

Multiple logistic regression with forward selection of perinatal risk factors and entering measures of growth into these models revealed that early neonatal HC growth defined as the HC SDS at discharge minus the HC SDS at birth was an important predictor of neurologic outcome and gross motor development at 5.4 years of age (Table 2). Furthermore, early neonatal weight gain, defined as the weight SDS at discharge minus the weight SDS at birth was an important predictor of neurologic outcome. Additional important risk factors in these models were IVH/PVH, duration of mechanical ventilation, retinopathy, and the education of the mother.

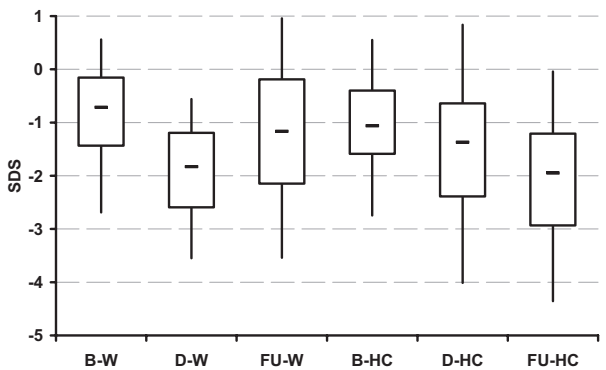

FIGURE 2
Intrauterine, early neonatal, and postdischarge growth depicted as median, interquartile range, and 5th and 95th percentiles of SDS of weight (W) and HC at birth (B), discharge (D), and follow-up (FU).

Multiple linear regression revealed that intrauterine growth measured as SDS of weight at birth was an important predictor of the mental processing composite score at the age of 5.4 years (Table 3). In addition, in-hospital weight gain, defined as the weight SDS at discharge minus the weight SDS at birth, was another important predictor of the mental processing composite. An increase in the weight SDS from birth to discharge by 1 results in an increase in the mental processing composite score by 3.3. HC growth but not weight gain from discharge to follow-up was also an important predictor of the mental processing composite. The analysis of partial R^2 revealed that the combined contribution of growth until follow-up for the mental processing composite score was exceeded only by the effect of severe

TABLE 2 **Odds Ratios of Perinatal Risk Factors for Abnormal Neurologic Examination or Abnormal Mobility From Multiple Logistic Regressions With Forward Selection After Entering Measures of Intrauterine, Early Neonatal, and Postdischarge Growth Into the Preselected Models**

Parameter	Growth Measured as Weight ($n = 203$)				Growth Measured as HC ($n = 188$)			
	Mildly or Severely Abnormal Neurologic Examination		Abnormal Mobility (GMFCS ≥1)		Mildly or Severely Abnormal Neurologic Examination		Abnormal Mobility (GMFCS ≥1)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Perinatal risk factor								
GA, wk	[a]				[a]		[a]	
Gender, male vs female	[a]		[a]		[a]		[a]	
Multiple birth, yes vs no	[a]		[a]		[a]		[a]	
IVH/PVH, ≥3° vs <3°	9.17 (2.23–37.70)	.002	13.00 (3.37–50.00)	.002	15.00 (2.69–84.10)	.002	14.70 (3.44–62.50)	.003
PVL, yes vs no	[a]		[a]		[a]		[a]	
ROP, ≥3° vs <3°	2.90 (1.01–8.35)	.049	3.55 (1.09–11.60)	.035	3.63 (1.20–11.00)	.023	4.43 (1.31–15.00)	.017
MV, yes vs no	[a]		[a]		[a]		[a]	
Duration of MV, ≥7 vs <7 d	2.23 (0.98–5.03)	.055	2.49 (0.79–7.87)	.119	2.02 (0.83–4.96)	.124	2.12 (0.62–7.22)	.229
Language, other vs German	[a]		[a]		[a]		[a]	
Highest academic degree of mother, none or lowest school degree vs higher degrees[b]	2.74 (1.30–5.75)	.008	3.30 (1.16–9.37)	.025	2.93 (1.32–6.53)	.008	3.17 (1.13–8.88)	.028
Measure of growth								
SDS at birth[c]	0.80 (0.52–1.24)	.315	1.33 (0.74–2.39)	.346	1.10 (0.71–1.71)	.662	1.36 (0.79–2.33)	.265
SDS difference (discharge − birth)[c]	0.55 (0.30–0.99)	.049	0.54 (0.25–1.18)	.125	0.59 (0.39–0.89)	.012	0.61 (0.38–0.97)	.037
SDS difference (follow-up − discharge)[c]	0.84 (0.63–1.14)	.265	0.72 (0.49–1.06)	.095	0.96 (0.64–1.43)	.813	0.81 (0.50–1.32)	.406
Area under the ROC curve (c)	0.788		0.860		0.809		0.841	

OR indicates odds ratio; CI, confidence interval; GA, gestational age; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; MV, mechanical ventilation; ROC, receiver operating characteristic.

[a] Evaluated but not selected for this model.

[b] Lowest level of the 3-level German school system qualifying for nonacademic professional education.

[c] Measures of growth were entered into each model as continuous variables after perinatal risk factors had been selected (entering these measures of growth reduced the contribution of preselected perinatal risk factors, particularly that of the duration of MV).

IVH/PVH and the effect of prolonged mechanical ventilation, despite that parameters of growth were entered into the model after all other perinatal risk factors (Table 3). The combined contribution of severe IVH/PVH and of prolonged mechanical ventilation was >9 times greater than the combined contribution of growth.

DISCUSSION

Preterm infants are at risk for impaired neurodevelopment,[6,9,10] and additional efforts to identify effective interventions to improve outcomes for these vulnerable children are required. Our study adds to the growing body of evidence that growth is associated with neurodevelopment in extremely preterm infants. This study addresses several important aspects. First, it enables the comparison of 3 periods of growth: intrauterine growth, early neonatal (ie, in hospital) growth, and postdischarge growth. Second, this study enables the comparison of growth measured as HC and growth measured as weight and the differential associations of weight and HC with motor development and cognitive development. Third, the study provides detailed outcome data of growth and neurodevelopment in infants who were uniformly supported in keeping with current recommendations for intensive early neonatal nutrition.[17–19]

The results stress the importance of weight gain and HC growth during the early neonatal period (ie, the initial stay in the NICU) for long-term neurodevelopment. Poor early neonatal HC growth was associated with abnormal neurologic examination and abnormal mobility at the age of 5.4 years, and poor early neonatal weight gain was associated with abnormal neurologic examination and with lower mental processing composite scores in multiple regression models accounting for perinatal risk factors and socioeconomic status. Very similar to our findings, Cooke[15] reported that motor development at 8 years of age correlated most strongly with HC growth from birth to discharge. Ehrenkranz et al[14] reported that a higher rate of HC growth and weight gain from birth to discharge was associated with a lower incidence of cerebral palsy, subnormal mental developmental index, and neurodevelopmental impairment. These previous reports and this study leave unanswered whether poor nutritional intake is the major determinant of both poor growth and poor neurodevelopment and, consequently, whether improving growth by intensifying nutrition would result in better neurodevelopment.

Factors that were associated with poor growth in the early neonatal period (ie, in the NICU) were determined previously: infants with major neonatal morbidities regain birth weight later and thereafter gain weight more slowly.[1] Major neonatal morbidities are associated not only with poor growth: extremely low birth weight (ELBW) infants with nosocomial infection,[28] necrotizing enterocolitis,[13] severe IVH,[2] and bronchopulmonary dys-

TABLE 3 **Effect of Perinatal Risk Factors on Mental Processing Composite by Multiple Linear Regressions With Forward Selection After Entering Measures of Intrauterine, Early Neonatal, and Postdischarge Growth Into the Preselected Models**

Parameter	Growth Measured as Weight (n = 197)			Growth Measured as HC (n = 184)		
	Mental Processing Composite			Mental Processing Composite		
	Parameter Estimate (95% CI)	Partial R^2	P	Parameter Estimate (95% CI)	Partial R^2	P
Perinatal risk factor						
GA, wk	[a]			[a]		
Gender, male vs female	[a]			[a]		
Multiple birth, yes vs no	[a]			[a]		
IVH/PVH, ≥3° vs <3°	−21.60 (−29.60 to 13.70)	0.213	<.001	−20.60 (−29.40 to 11.90)	0.213	<.001
PVL, yes vs no	−13.70 (−26.00 to 1.45)	0.020	.029	−14.80 (−27.30 to 2.42)	0.020	.020
ROP, ≥3° vs <3°	[a]			[a]		
MV, yes vs no	[a]			[a]		
Duration of MV, ≥7 vs <7 d	−9.86 (−14.50 to 5.18)	0.113	<.001	−10.60 (−15.60 to 5.50)	0.113	<.001
Language, other vs German	[a]			[a]		
Highest academic degree of mother, none or lowest school degree vs higher degrees[b]	−5.55 (−9.70 to 1.41)	0.016	.009	−4.25 (−8.68 to 0.17)	0.016	.060
Measure of growth		0.035			0.032	
SDS at birth[c]	3.52 (1.05 to 5.98)		.005	2.32 (−0.10 to 4.74)		.060
SDS difference (discharge − birth)[c]	3.30 (0.04 to 6.57)		.047	1.80 (−0.47 to 4.06)		.120
SDS difference (follow-up − discharge)[c]	0.12 (−1.51 to 1.75)		.884	2.21 (0.02 to 4.41)		.048
Total R^2 of the model		0.396			0.393	

CI, confidence interval; GA, gestational age; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; MV, mechanical ventilation.

[a] Evaluated but not selected for this model.

[b] Lowest level of the 3-level German school system qualifying for nonacademic professional education.

[c] Measures of growth were entered into each model as continuous variables after perinatal risk factors had been selected.

plasia[14] are at greater risk for having both poor growth and poor neurodevelopment. These associations may also be interpreted as indicators for a common pathophysiology of poor growth and impaired outcome that may not be easily corrected by nutritional efforts alone (eg, severe inflammatory response syndromes associated with catabolism and brain injury); however, that measures of growth did contribute to prediction of long-term neurodevelopment after allowing for perinatal risk factors and socioeconomic status in our study supports the hypothesis that the perinatal risk factors alone do not explain the outcome, that growth is not just the consequence of previous neonatal complications, and that nutritional interventions may improve outcome. Nevertheless, the contribution of growth to long-term neurodevelopment was small (partial R^2 = 0.035) in our setting of intensive neonatal nutritional support.

Can we improve early neonatal growth? Intensive early neonatal nutritional support, similar to that provided in our cohort, improved growth and weight gain in very low birth weight (VLBW) infants in a randomized trial.[17] Increased energy supply during the first 10 days of life was associated with improved HC growth in a cohort study of more mature VLBW infants.[29] When compared with a previous cohort of VLBW infants who were born between 1994 and 1995 and for whom mean weight was at the 50th percentile at birth and dropped to far below the 10th percentile (corresponding to a drop of SDS by >1.5) at ~36 weeks' gestation,[1] our cohort lost on average "only" 1.1 SDS after intensive neonatal nutritional support, which is still by far not satisfactory.

Whether additional nutritional efforts will be able to correct growth failure remains unknown. Nevertheless, additional intensification of nutritional support (eg, starting 3 g/kg per day parenteral amino acids as soon as possible after birth) was recently recommended[20] and may further improve growth and outcome, although another study suggested that increased amino acid supplementation (3.5 g/kg per day instead of 2.5 g/kg per day) alone may not be sufficient to improve growth.[30] Furthermore, although intensifying parenteral nutrition (aiming for 16.5 g/kg per day glucose, 4 g/kg per day amino acids, and 4 g/kg per day lipids, including the administration of insulin to correct hyperglycemia) reduced days to regain birth weight and improved cumulative energy and protein intake, it did not improve HC growth at 36 weeks' postmenstrual age in a recent report.[31] Despite intensified parenteral nutrition, 80% of these infants were still in a cumulative protein and energy deficit after 4 weeks, and energy and protein deficits correlated with growth.[31] Given the unsatisfactory growth outcome in that cohort as well as in our cohort, additional efforts to improve growth are mandatory but may not be realized easily.

Whether additional nutritional efforts will not only prevent growth failure but also improve neurodevelopment remains even more uncertain. At least, higher energy intake in the first 10 days of life was associated not only with improved HC growth but also with improved neurodevelopment until 6 years of life in a cohort of more mature VLBW infants.[29] Again, in more mature infants, feeding a nutrient-enriched formula resulted in improved cognitive development at 8 years of age.[32] Furthermore, total brain volume at term and

physical and mental developmental indices at 3 months' corrected age correlated with the cumulative energy deficit at 28 days of life[33]; however, intensified parenteral nutrition did not result in improved total brain volume or higher developmental indices,[33] and early administration of parenteral amino acids in ELBW infants, although associated with improved weight gain, was not associated with improved neurodevelopment in a secondary analysis of a randomized trial.[34]

In addition to early neonatal growth, intrauterine growth measured as weight at birth was associated with the mental processing composite at 5.4 years of age. Similarly, Cooke[15] reported that cognitive development at 8 years of age was associated with intrauterine growth. A birth weight <10th percentile was previously associated with poor growth, developmental delay, and language problems at 56 months of age[35]; however, taking into account numerous risk factors for poor neurodevelopment, Vohr et al[36] did not find a strong association of being small versus appropriate for gestational age and neurodevelopment at 22 months of age.

Finally, postdischarge growth measured as weight was not associated with neurodevelopment at 5.4 years after adjustment for perinatal risk factors in our cohort, who were fed preterm infant formula or fortified breast milk until reaching a weight of 3.5 kg. Similarly, poor postdischarge growth measured as HC, which was very common in our cohort, was not associated with either abnormal neurologic examination or abnormal mobility at the age of 5.4 years and was only weakly associated with lower mental processing composite scores. This seems to be in contrast to previous reports of an association of low weight or low HC in infancy or childhood and poor neurodevelopment[11,12,15]; however, postdischarge growth was determined differently in this study: because low weight and low HC for gestational age at birth and at discharge were associated with low weight and low HC at follow-up in our and other cohorts,[4,14,35] we decided to measure postdischarge growth as the SDS at follow-up minus the SDS at discharge. Similar to our results, Cooke[15] reported that HC measured at 4 years was associated with poor outcome, whereas the difference of HC SDS at 4 years and at discharge was not. Similarly, also in infants who were born at term, HC growth in utero and until the first year of life was found to be associated with neurodevelopment, whereas HC growth from 1 to 4 years of age was not.[37]

Most longitudinal studies of VLBW and ELBW infants show catch-up of weight during childhood,[4,38,39] and our results are in agreement with these findings. This catch-up in weight may suggest that nutrition in this period after discharge from the NICU is adequate in most patients and that neither HC growth nor neurodevelopment may be further improved by nutritional supplementation beyond the NICU. This is in keeping with a recent review that suggested that there is little evidence that nutritional supplementation of preterm infants after discharge will improve growth and outcome.[40]

Nevertheless, it is a disturbing finding of our study that the median SDS for HC decreased further after discharge, despite an overall improvement in weight, and that postdischarge HC growth was at least weakly associated with the mental processing composite at 5.4 years. In the light of a recent report of improved brain and corticospinal tract growth in a small number of term and preterm infants with perinatal brain injury after an energy- and protein-supplemented postdischarge diet,[41] we cannot rule out that there are subgroups of preterm infants for whom outcome may be improved with additional intensification of postdischarge diet.

Our finding of a consistent association of early neonatal growth measured both as weight and as HC with several measures of neurodevelopment at 5.4 years may support the hypothesis that there is a sensitive period during late pregnancy and early neonatal life during which malnutrition may result in impaired long-term neurodevelopment.[42] A randomized, controlled trial powered to evaluate long-term neurodevelopment will be necessary to test this hypothesis.

According to our linear regression models, roughly 3% of the variability of the mental processing composite score was explained by growth. Although small, the contribution of growth to the mental processing composite score was exceeded only by the contribution of severe IVH/PVH and the duration of mechanical ventilation. Furthermore, the contribution of measures of growth to the predictive value of the model may have been underestimated by deliberately entering the measures of growth after selection of perinatal and socioeconomic risk factors. In addition, the contribution of growth to long-term neurodevelopment may be more important in settings of less intensive nutritional support. More than half of the variability of the mental processing composite was not explained by these models' taking into account major perinatal risk factors, socioeconomic factors, and growth, suggesting that additional factors contribute to long-term cognitive outcome.

The strengths of our study are the relative long-term follow-up, the high follow-up rate, the standardized assessment, and the uniform nutritional policy followed throughout the study period. The weaknesses of the study are the lack of data on actual nutritional intakes both in hospital and after discharge, the noninterventional and single-center design, and the relatively small number of children.

CONCLUSIONS

Poor intrauterine growth and poor early neonatal in-hospital growth were common in our extremely preterm infants and were associated with impaired long-term development. Supporting growth in the NICU may result in improved neurodevelopment, although the effect may be small. After discharge, extremely preterm infants showed catch-up growth of weight but not of HC. Whereas poor postdischarge HC growth was weakly associated with lower mental processing composite scores, postdischarge weight gain did not seem to have an additional impact on neurodevelopment in this group of infants.

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