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ARTICLE

Beneficial Effects of Breast Milk in the Neonatal Intensive Care Unit on the Developmental Outcome of Extremely Low Birth Weight Infants at 18 Months of Age

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ABSTRACT

OBJECTIVE. Beneficial effects of breast milk on cognitive skills and behavior ratings have been demonstrated previously in term and very low birth weight infants. Extremely low birth weight infants are known to be at increased risk for developmental and behavior morbidities. The benefits of breast milk that is ingested in the NICU by extremely low birth weight infants on development and behavior have not been evaluated previously.

METHODS. Nutrition data including enteral and parenteral feeds were collected prospectively, and follow-up assessments of 1035 extremely low birth weight infants at 18 months' corrected age were completed at 15 sites that were participants in the National Institute of Child Health and Human Development Neonatal Research Network Glutamine Trial between October 14, 1999, and June 25, 2001. Total volume of breast milk feeds (mL/kg per day) during hospitalization was calculated. Neonatal characteristics and morbidities, interim history, and neurodevelopmental and growth outcomes at 18 to 22 months' corrected age were assessed.

RESULTS. There were 775 (74.9%) infants in the breast milk and 260 (25.1%) infants in the no breast milk group. Infants in the breast milk group were similar to those in the no breast milk group in every neonatal characteristic and morbidity, including number of days of hospitalization. Mean age of first day of breast milk for the breast milk infants was 9.3 ± 9 days. Infants in the breast milk group began to ingest non–breast milk formula later (22.8 vs 7.3 days) compared with the non–breast milk group. Age at achieving full enteral feeds was similar between the breast milk and non–breast milk groups (29.0 ± 18 vs 27.4 ± 15). Energy intakes of 107.5 kg/day and 105.9 kg/day during the hospitalization did not differ between the breast milk and non–breast milk groups, respectively. At discharge, 30.6% of

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Key Words
human milk, extremely low birth weight, Bayley, outcomes

Abbreviations
LC-PUFA—long-chain polyunsaturated fatty acids
ELBW—extremely low birth weight
AAP—American Academy of Pediatrics
CA—corrected age
NICHD—National Institute of Child Health and Human Development
BSID II—Bayley Scales of Infant Development II
BRS—Behavior Rating Scale
MDI—Mental Development Index
PSI—Psychomotor Development Index
VLBW—very low birth weight

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infants in the breast milk group still were receiving breast milk. Mothers in the breast milk group were significantly more likely to be white (42% vs 27%), be married (50% vs 30%), have a college degree (22% vs 6%), and have private health insurance (34% vs 18%) compared with the no breast milk group. Mothers who were black, had a low household income (≤$20 000), or had higher parity were less likely to provide breast milk feeds. The analysis of outcomes between the any human milk and no human milk groups were adjusted for maternal age, maternal education, marital status, race/ethnicity, and the other standard covariates. Children in the breast milk group were more likely to have a Bayley Mental Development Index ≥85, higher mean Bayley Psychomotor Development Index, and higher Bayley Behavior Rating Scale percentile scores for orientation/engagement, motor regulation, and total score. There were no differences in the rates of moderate to severe cerebral palsy or blindness or hearing impairment between the 2 study groups. There were no differences in the mean weight (10.4 kg vs 10.4 kg), length (80.5 cm vs 80.5 cm), or head circumference (46.8 cm vs 46.6 cm) for the breast milk and no breast milk groups, respectively, at 18 months. Multivariate analyses, adjusting for confounders, confirmed a significant independent association of breast milk on all 4 primary outcomes: the mean Bayley (Mental Development Index, Psychomotor Development Index, Behavior Rating Scale, and incidence of rehospitalization). For every 10-mL/kg per day increase in breast milk ingestion, the Mental Development Index increased by 0.53 points, the Psychomotor Development Index increased by 0.63 points, the Behavior Rating Scale percentile score increased by 0.82 points, and the likelihood of rehospitalization decreased by 6%. In an effort to identify a threshold effect of breast milk on Bayley Mental Development Index and Psychomotor Development Index scores and Behavior Rating Scale percentile scores, the mean volume of breast milk per kilogram per day during the hospitalization was calculated, and infants in the breast milk group were divided into quintiles of breast milk ingestion adjusted for confounders. Overall, the differences across the feeding quintiles of Mental Development Index and Psychomotor Development Index were significant. There was a 14.0% difference in Behavior Rating Scale scores between the lowest and highest quintiles. For the outcomes (Mental Development Index, Psychomotor Development Index, Behavior Rating Scale, and Rehospitalization <1 year), only the values for the >80th percentile quintile of breast milk feeding were significantly different from the no breast milk values. In our adjusted regression analyses, every 10 mL/kg per day breast milk contributed 0.53 points to the Bayley Mental Development Index; therefore, the impact of breast milk ingestion during the hospitalization for infants in the highest quintile (110 mL/kg per day) on the Bayley Mental Development Index would be 10 × 0.53, or 5.3 points.

CONCLUSIONS. An increase of 5 points potentially would optimize outcomes and decrease costs by decreasing the number of very low birth weight children who require special education services. The societal implications of a 5-point potential difference (one third of an SD) in IQ are substantial. The potential long-term benefit of receiving breast milk in the NICU for extremely low birth weight infants may be to optimize cognitive potential and reduce the need for early intervention and special education services.

NUMEROUS BENEFICIAL EFFECTS of breast milk have been demonstrated for term and near-term infants, including improved cognitive skills,[1–10] improved behavior ratings,[11–13] and decreased rates of infection.[14–19] Improved neurodevelopment has been related to the presence of long-chain polyunsaturated fatty acids (LC-PUFA; arachidonic and docosahexaenoic), which are found in human milk but not bovine milk.[20–29] Premature infants are immunologically immature at birth and may have deficiencies of LC-PUFA because accretion occurs in the third trimester. Decreased rates of infection have been associated with the enhanced immunologic properties of breast milk, including lactoferrin, lysozyme, and secretory IgA.[30,31] Extremely low birth weight (ELBW) infants are at increased risk for neurodevelopmental disability and for rehospitalization after discharge from the NICU.[32] In the past, this vulnerable population of high-risk neonates has had limited exposure to breast milk in the NICU. However, in 1997 and 2005, the American Academy of Pediatrics (AAP)[33,34] published position statements recommending breast milk for premature and other high-risk infants by breastfeeding and/or using the mother's own expressed milk.

The purpose of this study was to identify the rate of breast milk ingestion in the NICU in a cohort of ELBW infants who were born after the publication of the 1997 AAP statement and to assess the relationship of breast milk ingestion with developmental and behavior test scores and rehospitalization after discharge from the NICU. It was hypothesized that ELBW infants who received breast milk in the NICU would have (1) higher Bayley[35] mental, psychomotor, and behavior scores at 18 to 22 months' corrected age (CA) and (2) fewer rehospitalizations between hospital discharge and 18 to 22 months' CA.

METHODS

The study cohort was derived from the 1433 infants who were enrolled prospectively in the Glutamine Trial[36] at 15 sites of the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network between October 1999 and June 2001. A total of 251 infants died before discharge, and 23 infants died before the 18-month visit. A total of 124 infants were lost to follow-up. The final sample consisted of 1035 (89.4%) of 1159 ELBW infant survivors on whom follow-up data were available. Mothers of infants who were seen in follow-up were more likely to have received prenatal care than mothers of infants who were not seen (93% vs 86%; $P < .01$, respectively). There were no differences in infant characteristics or morbidities between those who were and were not seen in follow-up.

The Glutamine Trial encouraged early parenteral nutrition but did not prescribe an enteral feeding protocol. Nutrition data were collected daily until the infants were on full enteral feeds (≥462 kJ/kg per day). Thereafter, data were collected on Monday, Wednesday, and Friday of each week until discharge or 120 days; values were interpolated for days of the week on which the data were not collected: Tuesday data were the weighted average of Monday and Wednesday data. The total volume of breast milk feeds per kilogram per day for the duration of hospitalization was calculated. A total of 775 (74.9%) of the infants received some breast milk during their NICU hospitalization. None of the centers used banked breast milk during the trial. The proportion of infants who received breast milk feeds at centers ranged from a low of 39.1% to a high of 97.3%. Information was not collected on breast milk ingestion after discharge. Neonatal characteristics and morbidities were collected, including gestational age by best obstetric estimate, birth weight, and neonatal course. Institutional Review Board approval and informed consent were obtained as previously described.[36]

Infants were evaluated at 18 to 22 months' CA. The assessment included standardized interim medical history, a developmental evaluation, neurologic assessment, and physical examination that included growth parameters.[32] A neurologic examination that was based on the Amiel-Tison[37] assessment was performed by certified examiners. The neurologic assessment included an evaluation of tone, strength, reflexes, angles, and posture. Infants were scored as normal when no abnormalities were observed in the neurologic examination. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture.

The Bayley Scales of Infant Development II (BSID II),[35] including the Mental Scale, Motor Scale, and the Behavior Rating Scale (BRS), were administered by testers who were trained to reliability by 1 of 4 study Gold Standard examiners. Examiner certification at sites was obtained by the successful completion of 2 videotaped demonstrations of accurate performance and scoring of the BSID II on preterm children at 18 to 22 months' CA.[32] BSID II scores of 100 ± 15 represent the mean ± 1 SD. An abnormal score (<70) is >2 SD below the mean. BRS percentile scores range from 1 to 99; scores of 11 to 25 are considered questionable, and scores of 1 to 10 are nonoptimal.

The primary caregiver or adult who brought the child for the visit stayed with the child during the BSID II examination, which was administered early in the clinic visit before the medical assessment and interviews. Examiners were not able to administer parts or all of the BSID II successfully to 95 children who were seen. The following reasons were given: acute illness ($n = 10$), language barrier ($n = 2$), behavior problem ($n = 24$), developmental delay ($n = 18$), and other ($n = 41$). The other category included children who had sensory loss (blindness or deafness) and could not be administered the BSID II items. These data therefore were not included in the analysis. Although every effort was made to test children within the window of 18 to 22 months' CA, 22 infants were evaluated outside the window because of illness or tracking issues. These data were included because the BSID II is age adjusted.

Social and economic status information, including maternal and paternal education and occupation, marital status, insurance status, and income level, and a detailed interim medical history, including data on hearing and vision status, were obtained. Hearing status information was obtained from the parent and follow-up audiologic test results when available. Hearing impairment was defined as use of hearing aids. A history of postdischarge eye examinations and procedures was obtained from the parent. In addition, a standard eye examination was completed to evaluate tracking, esotropia, nystagmus, or roving eye movements. Blind was defined as functional corrected vision <20/200.

Statistical analyses were completed by RTI International. Bivariate analyses for group differences (any breast milk versus no breast milk) consisted of t tests, χ^2, or Fisher's exact tests. We evaluated the relationship between breast milk feeding and developmental outcomes in 3 ways: (1) whether any breast milk feeding was beneficial (breast milk yes versus breast milk no), (2) whether the amount of breast milk feeding was associated with better developmental outcomes (breast milk as a continuous variable), and (3) whether there was a threshold beyond which breast milk feeding provided benefits. Infants who received breast milk were divided into quintiles of mean intake of breast milk per kilogram per day during the entire hospitalization, including 0 for days with no intake, for analysis. Mean volume of human milk (mL/kg per day) for the entire hospitalization was entered as a continuous variable. Multivariate analyses to evaluate the effects of breast milk on outcomes consisted of multiple linear-regression and logistic-regression analyses. Adjustments were made for the following confounders: mother's age, education, marital status, and race/ethnicity and infant's gestational age, gender, culture-positive sepsis, intraventricular hemorrhage 3 to 4,[38] periventricular leukomalacia, oxygen at 36 weeks' CA, necrotizing enterocolitis, and weight <10th percentile at 18 months.

RESULTS

There were 775 (74.9%) infants in the breast milk group and 260 (25.1%) infants in the no breast milk group. Table 1 shows the infant characteristics and morbidities of the breast milk and no breast milk groups. Infants in the breast milk group were similar to those in the no breast milk group in every neonatal characteristic and morbidity, including number of days of hospitalization.

Mean age of first day of breast milk for the breast milk infants was 9.3 ± 9 days. Infants in the breast milk group began to ingest non–breast milk formula later (22.8 vs 7.3 days) compared with the non–breast milk group. Age at achieving full enteral feeds was similar between the breast milk and non–breast milk groups (29.0 ± 18 vs 27.4 ± 15). Energy intakes of 107.5 kg/day and 105.9 kg/day during hospitalization did not differ between the breast milk and non–breast milk group, respectively. There were center differences in the rate of use of human milk fortifiers; however, 74.7% of the breast milk feeds without parenteral nutrition were fortified (61.7% with breast milk fortifiers; 13% with other nutritional additives). At discharge, 30.6% of infants in the breast milk group still were receiving breast milk.

Table 2 shows the maternal characteristics of the 2 study groups. Mothers in the breast milk group were significantly more likely to be white (42% vs 27%), be married (50% vs 30%), have a college degree (22% vs 6%), and have private health insurance (34% vs 18%) compared with the no breast milk group. Mothers who were black, had a low household income (≤$20 000), or had higher parity were less likely to provide breast milk feeds.

Table 3 shows the results of the analyses of the outcomes between the any breast milk and no breast milk groups adjusted for maternal age, maternal education, marital status, race/ethnicity, and the other standard covariates. Children in the breast milk group were more likely to have a Bayley Mental Development Index (MDI) ≥85, higher mean Bayley Psychomotor Development Index (PDI), and higher Bayley BRS percentile scores for orientation/engagement, motor regulation, and total score. There were no differences in the rates of moderate to severe cerebral palsy or blindness or hearing impairment between the 2 study groups

There were no differences in the mean weight (10.4 kg vs 10.4 kg), length (80.5 cm vs 80.5 cm), or head circumference (46.8 cm vs 46.6 cm) for the breast milk and no breast milk groups at 18 months' CA. Rehospitalization between birth and the first birthday was lower in the breast milk group (23.3% vs 30.1%; $P < .028$) compared with the no breast milk group. There were no differences in rehospitalization rates between the first birthday and the visit at 18 to 22 months' CA (data not shown).

Multiple-regression analyses, adjusting for confounders, confirmed a significant independent association of breast milk on all 4 primary outcomes: the mean Bayley (MDI, PDI, BRS, and incidence of rehospitalization) as shown in Table 4. For every 10-mL/kg per day increase in breast milk ingestion, the MDI increased by 0.53 points, the PDI increase by 0.63 points, the BRS percentile score increased by 0.82 points, and the likelihood of rehospitalization decreased by 6%. We repeated the multivariate analysis excluding the 237 (30.6%) children who were discharged on breast milk to determine whether breast milk effects remained for infants who received breast milk only in the NICU. Effects of breast

TABLE 1 **Infant Characteristics and Morbidities**

	Breast Milk	No Breast Milk	P
N (%)	775 (74.9)	260 (25.1%)	—
Female gender	425 (55)	140 (54)	.781
Birth weight, g	785 ± 129	794 ± 133	.363
Gestational age, wk	26.5 ± 2	26.7 ± 2	.331
IVH grade 3–4	84 (11)	25 (10)	.586
PVL	29 (4)	10 (4)	.931
Proven necrotizing enterocolitis	54 (7)	26 (10)	.113
Early-onset sepsis ≤72 h	6 (1)	3 (1)	.568
Late-onset sepsis >72 h	311 (40)	91 (35)	.142
Bronchopulmonary dysplasia[a]	349 (46)	120 (47)	.714
Days in hospital	99 ± 42	96 ± 41	.301

Data are mean ± SD or *n* (%). IVH indicates, intraventricular hemorrhage; PVL, periventricular leukomalacia.

[a] Bronchopulmonary dysplasia was defined as oxygen administration at 36 weeks' postmenstrual age.

TABLE 2 **Maternal Characteristics by Breast Milk Feeding**

	Breast Milk	No Breast Milk	P
N (%)	775 (74.9)	260 (25.1)	—
Maternal age, y			
<20	113 (15)	45 (17)	
20–29	363 (47)	128 (49)	.2793
≥30	299 (39)	87 (33)	
Married	387 (50)	78 (30)	.001
Education			
Less than high school graduate	206 (28)	83 (35)	
High school graduate	197 (27)	94 (40)	.0001
Some college	162 (22)	35 (15)	
College degree or above	163 (22)	15 (6)	
Private insurance or HMO	253 (34)	43 (18)	.001
Race/ethnicity			
Black	303 (39)	167 (64)	
White	325 (42)	71 (27)	.0001
Hispanic	133 (17)	18 (7)	
Other	14 (2)	4 (2)	
Income last year <$20 000	280 (42)	127 (59)	.001
Parity, mean ± SD	2.1 ± 1.3	2.7 ± 1.8	.001

Data are *n* (%) except where indicated. HMO indicates health maintenance organization.

TABLE 3 **Outcomes by Breast Milk Feeding**

Outcomes	Breast Milk, *n* (%) or Mean ± SD	No Breast Milk, *n* (%) or Mean ± SD	Adjusted *P*
MDI	79.9 ± 18	75.8 ± 16	.0709
MDI <85	421 (58.1)	168 (70.9)	.0355
PDI	84.6 ± 19	81.3 ± 17	.0227
PDI <85	307 (42.9)	116 (49.2)	.0939
BRS			
Orientation/engagement	53.8 ± 30	48.5 ± 29	.0351
Emotional regulation	53.0 ± 29	47.1 ± 29	.0825
Motor quality	50.1 ± 35	44.1 ± 33	.0296
Total	52.0 ± 31	45.6 ± 30	.0280
Blind in both eyes	4 (0.5)	0 (0.0)	.5773[a]
Hearing aids	9 (1.2)	4 (1.6)	.7472[a]
Cerebral palsy (moderate/severe)	43 (5.6)	16 (6.2)	.7327[a]
Rehospitalizations before first birthday	180 (23.3)	78 (30.1)	.028

Adjustments were made for the following confounders: mother's age, education, marital status, and race and infant's gestation, gender, sepsis, IVH 3 to 4, PVL, O_2 at 36 weeks, necrotizing enterocolitis, weight <10th percentile at 18 months, and volume of breast milk (mL/kg per day) for every day of hospitalization (a continuous variable).

[a] Unadjusted *P*.

TABLE 4 **Effect of Breast Milk Feeding (mL/kg per day) on Developmental Outcomes and Rehospitalization: Multiple Regression Results**

Outcomes	Parameter Estimate	*P*
MDI	0.53	.0002
PDI	0.63	<.0001
BRS	0.82	.0025
Logistic regression	OR	95% CI
Rehospitalization for infection or respiratory morbidity	0.94	0.90–0.98

Estimates are adjusted for standard covariates listed previously. OR indicates odds ratio; CI, confidence interval.

milk on all of our study outcomes remained significant. (data not shown).

In an effort to identify a threshold effect of breast milk on Bayley MDI and PDI scores and BRS percentile scores, we calculated the mean volume of breast milk per kilogram per day during the hospitalization, and infants in the breast milk group were divided into quintiles of breast milk ingestion adjusted for confounders as shown in Table 5. Quintiles were analyzed relative to the no breast milk group. Breast milk intake by quintile ranged from 1.0 mL/kg per day to 110.6 mL/kg per day. In addition, total breast milk on days when only breast milk was ingested was calculated and ranged from 22.1 mL/kg per day to 124.0 mL/kg per d. The proportion of infants who were discharged on breast milk ranged from ~0.7% for the lowest quintile to 85.1% for the highest quintile. Mean Bayley MDI, PDI, and BRS were calculated for the quintiles, and the relationship between BSID II scores and quintiles of breast milk are shown. For MDI, there was a 13.1-point difference between ≤20th quintile and >80th quintile, and for PDI, there was an 8.8-point difference between ≤20th quintile and >80th quintile. Overall, the differences across the feeding quintiles of MDI and PDI were significant (model-adjusted $P < .0044$ and $P < .0027$, respectively). There was a 14.0% difference in BRS scores between the lowest and highest quintiles ($P < .028$). For the outcomes presented in Table 4 (MDI, PDI, BRS, and Rehospitalization <1 year), only the values for the >80th percentile of breast milk feeding are significantly different from the no breast milk values at $P < .01$ within the multiple-regression analyses. The values for MDI, PDI,

TABLE 5 **Breast Milk Feeding Measures, Developmental Outcomes, and Rehospitalization by Quintiles of Breast Milk Intake During Hospitalization**

	No Breast Milk	Percentile					Adjusted *P*
		≤20th	20th–40th	40th–60th	60th–80th	>80th	
Total breast milk (mL/kg per day) for every day of hospitalization	0.0	1.0	7.3	24.0	63.8	110.6	—
Total breast milk (mL/kg per day) on days breast milk received	0.0	22.1	45.0	66.8	95.3	124.0	—
% Discharged on breast milk	0.0	0.7	2.1	8.6	40.2	85.1	—
Mean MDI score	75.8	74.2	76.9	78.3	80.4	87.3[a]	<.0044
Mean PDI score	81.3	80.6	82.7	84.2	84.4	89.4[a]	.0027
Mean total BRS percentile score	45.6	44.8	52.1	50.1	51.8	58.8[a]	.0281
Rehospitalized <1 y	30.2	25.2	32.2	26.0	23.2	12.7[a]	.0460

[a] Value significantly different from no breast milk value at $P < .01$.

BRS, and rehospitalization at the 40th to 60th percentiles and the 60th to 80th percentiles trended toward significant.

DISCUSSION

ELBW infants are known to be at increased risk for developmental delays, neurosensory impairments, poor growth, and rehospitalization after discharge. The primary objective of perinatal and neonatal studies of ELBW infants has been to identify interventions that improve these outcomes. Breast milk has been shown consistently to have beneficial effects for term infants. Studies in premature infants have shown both positive effects[1–6,8–10,39] and no effects[40] on cognitive outcome and positive effects on behavior ratings.[11–13]

Our study to investigate the effects of breast milk on BSID II scores and rehospitalization would be difficult to assess in a breast milk/no breast milk randomized trial because method of feeding is determined by the mother. In addition, the AAP recommends breast milk for premature infants; therefore, there is no true equipoise. In the studies of Lucas et al,[1–6] randomization to study group was made after the mothers made the choice to bottle or breastfeeding. These studies compared breast milk in various combinations to term formula, preterm formula, and banked breast milk. The prospective detailed daily neonatal enteral, including breast milk, and parenteral nutritional intake data that were collected longitudinally as part of the NICHD Network Glutamine Trial[36] on a large population of ELBW infants who were assessed at 18 to 22 months' CA allowed us to examine the relationship between breast milk and outcome. The nutritional intake data revealed that 75% of the infants received some breast milk during their NICU stay and 30.6% of infants were still receiving breast milk at the time of discharge.

Consistent with previous reports,[41,42] mothers who provided breast milk were more likely to be married, be better educated, have private health insurance, have higher income, and have lower parity. Black mothers were less likely to provide breast milk. It is of interest that there were no differences in any of the neonatal characteristics or morbidities compared in bivariate analysis. This is similar to an NICHD Network study[43] that evaluated the relationship between late-onset sepsis and breast milk. The bivariate relationship between any breast milk feeding and sepsis versus no sepsis was not significant. However, on multivariate logistic regression, it was identified that for every 10% increase in breast milk, there was a 5% decrease in the rate of sepsis. Furman et al[44] also reported a dose relationship between increasing breast milk ingestion and decreasing rate of sepsis.

Despite the limited amount of breast milk ingested during the NICU hospitalization, our results support our hypothesis that breast milk ingestion in the NICU by ELBW infants during their NICU stay was associated with higher Bayley MDI and PDI developmental scores, higher BRS scores, and fewer rehospitalizations during the first year. These effects of breast milk on Bayley MDI scores remained significant after adjustment for important environmental confounders, including marital status, education, health insurance, income, race/ethnicity, and parity. Although there was a 6% reduction in rehospitalization, other factors are associated with increased likelihood of rehospitalization, including smoking in the household and child care attendance, which were not available.

There were no differences between the any breast milk and no breast milk study groups in growth parameters at 18 to 22 months' CA, which we attribute to current NICU and postdischarge management of providing enhanced nutritional intake for ELBW infants. Enteral feeds consist of either high-nutrient preterm formulas or breast milk supplemented with breast milk fortifier and preterm formulas.

There also were no differences in neurosensory outcomes, including the number of children with cerebral palsy or blindness or hearing impairment. The differences in rehospitalization in the first year of life seem to be associated with fewer serious infections and respiratory illnesses reported by the parents after discharge and are suggestive of enhanced immune protection. This effect was not observed in the second year of life. Although we do not have postdischarge data on breast milk ingestion, we do know that only 30.6% of mothers were still providing breast milk at discharge. It is well documented that the percentage of mothers of ELBW infants who still provide breast milk at discharge decreases rapidly after discharge.[45–47]

On the Bayley BRS, which is administered by a Bayley examiner who is unaware of the neonatal feeding history, infants who were fed breast milk had significantly higher (more optimal) scores for orientation/engagement, emotional regulation, motor quality, and total behavior scores. Higher ratings for orientation, motor, and state regulation have been reported for breastfed infants using the Brazelton Neonatal Behavior Assessment Scale.[11] Enhanced arousability also has been demonstrated in breastfed infants.[12] Our data suggest that effects of breast milk on the behavior of ELBW infants continue to be observed at 18 to 22 months' CA. We do not, however, have information allowing us to differentiate effects of breastfeeding from breast milk provided by tube or bottle feeding.

There are several mechanisms by which breast milk ingestion by infants might contribute to more optimal cognitive/behavioral outcomes. It has been postulated that the act of feeding at the breast, as well as the interaction between mother and child, account for improved cognitive and behavioral outcome.[48] However, few ELBW infants in the NICU are feeding at the breast, and none are breastfeeding exclusively. Differences in parenting style and maternal intelligence, which were not a part of this study protocol, also have been proposed to be important. These factors are difficult to measure and cannot be ruled out. Our results, however, were adjusted for maternal education. Another factor that was not evaluated is that there is greater bioavailability of protein in breast milk compared with formula. The fourth proposed mechanism is the role of specific components of breast milk, including LC-PUFA (arachidonic acid and docosahexanoic acid), choline, glycoproteins, phospholipids, growth factors, and hormones, on cognitive function.[20,36,49–51] These mechanisms may complement each other.

Our findings suggest that the effects of breast milk on the ELBW population are similar to that previously found in very low birth weight (VLBW) infants.[1–6] The mean gestation of infants in our study was lower at 26.6 weeks. We speculate that the 12 to 14 weeks before term may be an important window of opportunity for this vulnerable population of infants. Active brain development, neurogenesis, migration, and synaptogenesis occur during this time, and brain development may be particularly responsive to "maternal nutrition." Previous studies have shown beneficial effects of arachidonic acid and docosahexanoic acid in breast milk on neurodevelopment.[20–24,26–29] During the study period, preterm formulas with these nutrients were not available. Additional prospective studies need to be initiated to examine the relationships between breast milk ingestion and brain development before term and after discharge.

Strengths of the study include the large study population, the detailed nutritional intake data collected, and the finding of breast milk effects after controlling for known environmental and biological confounders. The 13.1-point difference in Bayley MDI scores (74.2–87.3) between the lowest and highest quintiles adjusted for environmental confounders at 18 months is remarkable and provides a measure of the gap between those with the highest and lowest amount of breast milk feeding. In our regression analyses adjusted for important maternal social/environmental and infant biological confounders, every 10 mL/kg per day of breast milk contributed 0.53 points to the Bayley MDI. Therefore the impact on the Bayley MDI of breast milk for infants who were in the highest quintile and ingested 110 mL/kg per day would be 10×0.53, or 5.3 points. The societal implications of a 5-point potential difference (one third of an SD) in IQ are substantial.[52] Annually, ~56 000 (1.4%) of infants in the United States are born VLBW.[53] Reports[54–57] indicate that 50% of VLBW infants (~28 000 children) require remedial or special education services at school age. Hack[56] reported a history of lower academic achievement in adult VLBW survivors for whom the IQ was 5 points lower than that in term control subjects (87 vs 92, respectively). An increase of 5 points potentially would optimize outcomes and decrease costs by decreasing the number of VLBW children who required special education services. Lucas et al[5] reported that increased volume of breast milk was significantly associated with higher test scores in VLBW infants and that effects remained significant at 7.5 to 8 years of age. Although critics of breast milk studies have suggested that higher family socioeconomic status is the major contributor to higher developmental scores, both in our own cohort and in that of Lucas et al,[5] breast milk effects remained significant after adjustment of measures of socioeconomic status confounders. A limitation of our study is that we did not assess maternal IQ. The potential long-term benefit of receiving breast milk in the NICU for the ELBW infant and family may be to optimize cognitive potential and to reduce the needs for early intervention and special education services. Long-term follow-up of ELBW infants is needed to determine whether these effects persist at school age. A weakness of this study is that we do not have data on use of breast milk after discharge, and we do not have specific information on the home environment.

CONCLUSION

The provision of breast milk to ELBW infants during the neonatal period is an easy-to-implement, cost-effective intervention with a potential payoff that includes better developmental outcomes, more optimal behavior, and fewer rehospitalizations.

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Beneficial Effects of Breast Milk in the Neonatal Intensive Care Unit on the Developmental Outcome of Extremely Low Birth Weight Infants at 18 Months of Age

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