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ARTICLE

Persistent Beneficial Effects of Breast Milk Ingested in the Neonatal Intensive Care Unit on Outcomes of Extremely Low Birth Weight Infants at 30 Months of Age

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ABSTRACT

BACKGROUND. We previously reported beneficial effects of breast milk ingestion by infants with extremely low birth weight in the NICU on developmental outcomes at 18 months' corrected age. The objective of this study was to determine whether these effects of breast milk in infants with extremely low birth weight persisted at 30 months' corrected age.

METHODS. Nutrition data, including enteral and parenteral feeds, were prospectively collected, and 30 months' corrected age follow-up assessments were completed on 773 infants with extremely low birth weight who participated in the National Institute of Child Health and Human Development Neonatal Research Network Glutamine Trial. A total of 593 ingested some breast milk during the neonatal hospitalization, and 180 ingested none. Neonatal feeding characteristics and morbidities and 30-month interim history, neurodevelopmental outcomes, and growth parameters were analyzed. Children were divided into quintiles of breast milk volume to evaluate the effects of volume of human milk ingested during the NICU hospitalization.

RESULTS. At 30 months, increased ingestion of breast milk was associated with higher Bayley Mental Developmental Index scores, higher Bayley behavior score percentiles for emotional regulation, and fewer rehospitalizations between discharge and 30 months. There were no differences in growth parameters or cerebral palsy. For every 10 mL/kg per day increase in breast milk, the Mental Developmental Index increased by 0.59 points, the Psychomotor Developmental Index by 0.56 points, and the total behavior percentile score by 0.99 points, and the risk of rehospitalization between discharge and 30 months decreased by 5%.

CONCLUSIONS. Beneficial effects of ingestion of breast milk in the NICU persist at 30 months' corrected age in this vulnerable extremely low birth weight population. Continued efforts must be made to offer breast milk to all extremely low birth weight infants both in the NICU and after discharge.

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

Abbreviations
ELBW—extremely low birth weight
BM—breast milk
CA—corrected age
BSID-II—Bayley Scales of Infant Development II
MDI—Mental Developmental Index
PDI—Psychomotor Developmental Index

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INFANTS WITH EXTREMELY low birth weight (ELBW) are at increased risk of neurodevelopmental disability and rehospitalization after discharge from the NICU.[1] In the past this vulnerable population of high-risk neonates in the NICU has had limited exposure to breast milk (BM). However, in 1997 and 2005, the American Academy of Pediatrics[2,3] published position statements recommending BM for premature and other high-risk infants by breastfeeding and/or using the mother's own expressed milk. Our previous investigation clearly demonstrated beneficial effects of BM consumed in the NICU by infants with ELBW on development, behavior, and rehospitalization rates at 18 months' corrected age (CA).[4]

The purpose of this study was to identify whether beneficial effects of BM ingestion in the NICU in our cohort of infants with ELBW would continue to be associated with more optimal developmental and behavior test scores and decreased rehospitalization rates at 30 months' CA. It was hypothesized that infants with ELBW who received BM in the NICU would have higher Bayley[5] mental, motor, and behavior scores at 30 months' CA, fewer rehospitalizations between hospital discharge and 30 months' CA, and similar growth rates when compared with infants who receive no BM at 30 months' CA.

METHODS

The study subjects were derived from the original cohort of 1433 infants enrolled at 12 sites of the National Institute of Child Health and Human Development Neonatal Research Network, prospectively enrolled in the Glutamine Trial[6] between October 14, 1999, and June 25, 2001. Three centers that participated in the 18-month assessment were unable to participate in the 30-month assessment. (n = 279). A total of 195 infants expired before discharge from the NICU, and an additional 20 infants expired before 30 months, resulting in 939 eligible children. The final study sample consisted of 773 (82.3%) of 939 infants with ELBW who were participants in 12 of the 15 sites and on whom 30-month follow-up data were collected. A comparison of the infants seen at both 18 and 30 months with those infants seen only at 18 months indicated that the mothers of infants not seen at 30 months were more likely to have a household income last year of less than $20 000 (44% vs 55%; $P < .038$) compared with mothers of infants seen. There were no differences in maternal age, marital status, education, ethnicity, and parity. Infants who were not seen compared with those seen had a higher gestational age (26.7 ± 2.2 vs 26.1 ± 1.9 weeks; $P < .0027$) less late-onset sepsis (31% vs 40%; $P < .02$), decreased length of stay (92.3 ± 40 vs 99.8 ± 44 days), and less ingested BM (2.6 ± 3.7 vs 3.6 ± 4.3 mL/kg per day; $P < .002$, respectively).

Nutrition data were collected daily during the hospitalization until the infants were on full enteral feeds (≥462 kJ [110 kcal]/kg per day) for 72 hours. Data were then collected on Monday, Wednesday, and Friday of each week. The total volume of BM feeds (milliliters per kilogram per day) for the duration of hospitalization was calculated. Data were interpolated for days on which the data were not collected. A total of 593 (77%) of the infants received some BM during their NICU hospitalization, and 180 (23%) received none. Feeding characteristics of the cohort were reported previously.[7]

Neonatal characteristics and morbidities were collected as reported previously.[7] The 30-month assessment reported in this study included interim medical history, a developmental evaluation, neurologic assessment, and physical examination including growth parameters.[1,7] A neurologic examination based on the Amiel Tison[8] assessment was performed by certified examiners who had been trained to reliability in an examination procedure in a 2-day workshop on the neurologic assessment. The neurologic assessment included an evaluation of tone, strength, reflexes, angles, and posture. Infants were scored as normal if 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 ≥1 extremity and abnormal control of movement and posture. Moderate-to-severe cerebral palsy was defined as infants who were unable to sit independently or walk independently.

The Bayley Scales of Infant Development II (BSID-II),[5] including the mental scale, motor scale, and behavior rating scale, were administered by testers trained to reliability by 1 of 4 study "gold standard" examiners. Gold standard examiners were experienced clinicians specifically trained in BSID-II test procedures. Examiner certification at sites was obtained by the successful completion of 2 videotaped demonstrations of accurate performance and scoring of the Bayley on 30-month-old children. The gold-standard examiners reviewed the tapes for accuracy and reliability, granted certification when indicated, and served as a training resource. Bayley scores of 100 ± 15 represent the mean ± SD.

The primary caretaker who brought the child for the visit stayed with the child during the Bayley examination, which was administered early in the clinic visit before the medical assessment and interviews. Examiners were not able to successfully administer parts or all of the Bayley to 69 children seen. The following reasons were given: acute illness (n = 3), language barrier (n = 1), behavior problem (n = 21), sensory impaired but otherwise normal (n = 1), reason unknown (n = 15), and other (n = 28). Although every effort was made to test children within the window of 29.5 to 34.5 months' CA, 59 infants were evaluated beyond the window because of illness or tracking issues. These data were included because the BSID-II is age adjusted. Neurodevelopmental impairment was defined as the presence of any of the following: Bayley Mental Developmental Index (MDI) < 70, Bayley Psychomotor Developmental Index (PDI) < 70, blind in both eyes, hearing impairment requiring amplification in both ears, and moderate-to-severe cerebral palsy.

Social and economic status information, including maternal, paternal, and caretaker education and occupation; marital status; insurance status; 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 for both ears. 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 of <20 to 200.

Statistical analyses were completed by the Research Triangle Institute (Research Triangle Park, NC). The analyses were conducted by using SAS (SAS Institute, Inc, Cary NC). Bivariate analyses for group differences consisted of *t* tests, χ^2, Kruskal-Wallis, or Fisher's exact tests. Infants were divided into quintiles of BM ingestion (milliliters per kilogram per day during the hospitalization), adjusted for confounders, to identify threshold effects of BM on neonatal and 30-month outcomes. Multivariable analyses to evaluate the effects of BM on outcomes consisted of multiple linear regression (SAS Proc GLM) and logistic regression (SAS Proc Logistic) analyses. Adjustments were made for the following confounders: maternal age, education, marital status and race, and infant gestation, gender, sepsis, intraventricular hemorrhage 3 to 4, periventricular leukomalacia, O_2 at 36 weeks, necrotizing enterocolitis, and weight <10th percentile at 18 months. Adjusted *P* values are either based on an F statistic for GLM or χ^2 for logistic regression. Quintile cutoffs of BM feeding during the hospitalization (≤120 days, for days when BM was given) have been defined for the whole cohort as follows: <20th pact, ≤23.12 mL/kg per day; 20th to 40th, ≤53.01 mL/kg per day; 40th to 60th, ≤83.20 mL/kg per day; 60th to 80th, ≤112.45 mL/kg per day; and >80th, >112.45 mL/kg per day. With the no-human-milk feeding group included, these categories provide a framework for examining a threshold for the effect of human milk feeding. Volume of human milk as milliliters per kilogram per day was entered as a continuous variable in multiple regression models estimating overall effect size. A repeated-measures multiple regression model (SAS Proc Mixed) allowed us to use the maximum data available to assess the degree of consistency in the relationship between MDI/PDI and any BM feeding at the earlier 18- and 30-month follow-up visits among the sites participating in the 30-month follow-up. This model was run with a BM feeding-time interaction term, which enabled testing of differences over time within a BM feeding group. Also, the model was specified with a random intercept, with subjects nested within a given center, which allowed us to account for within-subject variance. Study participation was approved by each site's institutional review board, and informed consent was obtained.

RESULTS

Maternal characteristics of the cohort evaluated at 30 months are shown in Table 1. Mothers in the BM group had higher socioeconomic status and were more likely to be married (49% vs 31%; $P < .0001$), college educated (24% vs 7%; $P < .0001$), have private insurance (35% vs 18%; $P < .0001$), be of white ethnicity (44% vs 31%; $P = .0001$), be of Hispanic ethnicity (14% vs 6%; $P = .0020$), and have annual income more than $20 000 (59% vs 43%; $P = .0006$).

Infant birth weight and gestational age were similar among the BM quintile groups and no-BM group as shown in Table 2. Number of days of hospitalization differed significantly across quintiles, with earlier feeding and shorter stays of >80th percentile.

Table 3 shows the study outcomes by quintile of BM ingestion and the no-BM group at 30 months of age. Across quintiles of BM feeding, a general pattern emerges of better outcomes associated with increased BM feeding. Overall, the neurodevelopmental differences across quintiles were significant for Bayley MDI and Bayley emotional regulation (model-adjusted $P < .0326$ and $P < .0271$, respectively). Posthoc adjusted analyses indicated that both Bayley MDI and PDI in the

TABLE 1 **Maternal Characteristics According to BM Feeding**

Data	BM Feeding		*P*
	Yes	No	
No. (%) of subjects	593 (76.6)	180 (23.3)	NA
Maternal age, y	NA	NA	.0969
<20	83 (14)	31 (17)	NA
20–29	257 (43)	84 (47)	NA
≥30	253 (43)	65 (36)	NA
Married, *n* (%)	293 (49)	56 (31)	<.0001
Education, *n* (%)	NA	NA	<.0001
Less than high school diploma	147 (26)	57 (36)	NA
High school diploma	154 (28)	68 (43)	NA
Partial college	122 (22)	21 (13)	NA
College degree or above	135 (24)	11 (7)	NA
Private insurance or health maintenance organization, *n* (%)	198 (35)	31 (18)	<.0001
Race/ethnicity, *n* (%)	NA	NA	<.0001
Black	235 (40)	111 (62)	NA
White	262 (44)	56 (31)	NA
Hispanic	84 (14)	10 (6)	NA
Other	12 (2)	3 (2)	NA
Income last year less than $20 000, *n* (%)	207 (41)	82 (57)	.0006
Parity, mean ± SD	2.2 ± 1.4	2.8 ± 1.8	<.0001

NA indicates not applicable.

TABLE 2 Neonatal Characteristics by BM Quintiles

Data	No BM	≤20th	20th–40th	40th–60th	60th–80th	>80th	*P*
No. of subjects	180	94	110	120	135	134	—
BM quintile cutoffs, mL/kg per d	0.0	≤23.1	23.1–53.0	53.0–83.2	83.2–112.5	>112.5	—
BM mL/kg per d for days BM ingested in hospital, mean	0.0	13.4	41.0	68.2	97.6	125.3	—
Birth weight, mean, g	795	768	784	774	791	811	.1351
Gestation, mean, completed wk	26.2	25.8	26.2	25.8	26.0	26.7	.0039
First enteral feed, mean, d	7.2	6.3	6.1	6.6	5.6	6.1	.3232
Full feeds, mean, d	28.4	40.2	32.1	29.0	25.6	21.2	<.0001
Length of stay, mean, d	97.6	115.5	104.7	109.3	94.4	85.0	<.0001

— indicates no data.

TABLE 3 Outcomes at 30 Months' CA Within BM Feeding (ml/kg per Day) Quintiles

Variable	No BM	≤20th	20th–40th	40th–60th	60th–80th	>80th	Adjusted *P*
No. of MDI subjects	163	81	98	110	126	126	—
Bayley MDI, mean	76.5	78.8	76.5	82.7	86.4	89.7	.0326
Bayley PDI, mean	78.4	83.2	79.9	85.2	87.3	90.2	.0639
Bayley behavior score %							
Orientation/engagement	54.7	57.4	56.4	61.6	62.8	62.5	.8383
Emotional regulation	50.8	57.6	54.2	63.5	61.8	66.1	.0271
Motor quality	49.3	52.9	55.4	56.0	59.9	64.0	.1392
Total	52.6	54.3	54.7	61.2	61.0	66.1	.2129
No. of PDI subjects	180	94	110	120	135	134	—
Rehospitalization, any, birth to 30 mo, %	60.0	68.1	60.0	53.3	53.3	53.3	.0238
Rehospitalization, respiratory, %	31.7	37.2	35.8	35.0	26.7	16.4	.0417
PDI, %	36.7	31.9	38.2	30.8	25.9	22.4	.7289
Blind in both eyes, %	0.0	1.1	0.0	0.0	1.5	0.0	.1362[a]
Hearing aids needed, %	1.7	1.1	0.9	0.0	0.7	3.0	.4613[a]
Cerebral palsy, moderate to severe, %	7.3	6.5	5.5	4.2	6.0	3.7	.7890[b]
No. of subjects, weight	177	93	110	119	135	132	—
Weight, mean, kg	12.6	12.8	12.3	12.6	12.6	12.3	.6103
Length, mean, cm	90.3	88.7	95.9	90.1	90.0	89.9	.4278
Head circumference, mean, cm	48.1	47.8	47.8	48.1	48.5	48.3	.2083

[a] Full model would not converge; unadjusted *P* values are presented (Fisher's exact).
[b] Full model would not converge, only gestational age and gender were used as covariates.

3 highest quintiles (40th–60th, 60th–80th, and >80th) were significantly higher ($P < .05$) than the no-BM group. Bayley emotional regulation score was significantly higher ($P < .05$) in 2 of those 3 highest quintiles. Motor quality was significantly higher ($P < .05$) in the 2 highest quintiles, and the Bayley total behavior score was significantly higher or trended higher than the no-BM group in the 3 highest BM intake quintiles. There were no differences in the rates of moderate-to-severe cerebral palsy, blind or hearing-impaired children, neurodevelopmental impairment, or growth parameters between the no-BM and BM groups. Rates for any rehospitalization and rehospitalization for respiratory illness were significantly lower between discharge and 30 months for infants in the highest BM quintile compared with the no-BM group (model-adjusted *P*: any = .0238 and respiratory = .0417). Rates of rehospitalization because of infection, surgery, or growth were not significantly different across the BM feeding quintiles.

Multiple regression analyses using a continuous measure of BM intake (in 10 mL/kg per day units), while adjusting for confounders, was undertaken to get a point estimate of the relationship between a fixed increase in BM feeding (10 mL/kg per day) and outcomes that exhibited a significant association in the quintile analysis. The analysis of BM as a continuous measure confirmed significant independent effects of BM on all 4 of the primary outcomes (MDI, PDI, Bayley behavior score, and rehospitalization) at 30 months, as shown in Table 4. Therefore, for every 10 mL/kg per day increase in BM ingestion, the MDI increased by an estimated 0.59 points, the PDI by 0.56 points, and the Bayley total behavior percentile score by 0.99 points. The odds of any rehospitalization between discharge and 30 months decreased by 5% for every 10 mL/kg per day of BM ingestion during the NICU stay. Additional analyses indicated that the reduction in rehospitalization was accounted for by respiratory illness that occurred in the first 2 years of life. No effects were observed between 2 years and the 30-month visit.

The Bayley MDI and PDI scores on the children were evaluated at both 18 and 30 months to assess the effect of any BM feeding in the NICU with increasing age. Significant differences were identified at 30 months for

TABLE 4 **Summary of the Overall Effect of BM on Outcome With Consumption Measured in Continuous 10-mL/kg per Day Units**

Outcomes	Parameter Estimate	SE	Adjusted *P*
Bayley MDI, patients per 10 mL	0.59	0.17	.0005
Bayley PDI, patients per 10 mL	0.56	0.21	.0092
Total behavior score, % per 10 mL	0.99	0.33	.0028
Rehospitalization for respiratory or infection, odds ratio (95% confidence interval)			
Any (birth to 30-mo visit)	0.95 (0.91–0.99)	NA	.0115
<1 y	0.93 (0.88–0.98)	NA	.0038
1–2 y	0.93 (0.88–0.98)	NA	.0107
>2 y (to 30-mo visit)	1.01 (0.93–1.09)	NA	.8756

NA indicates not applicable.

Bayley MDI and PDI between the BM and no-BM groups; these data are presented in Fig 1. The model-adjusted *P* values in Fig 1 were obtained from separate models for each time period for MDI and PDI. Repeated-measures analyses adjusted for covariates were performed on the 18- and 30-month Bayley MDI and PDI scores to assess effects of BM with increasing age. In this analysis, both MDI and PDI scores for subjects with BM feeding were significantly higher than scores of the no-BM group at 30 months. The MDI and PDI scores at 18 months trended higher for the BM-feed group, although not significantly. Estimated MDI scores of children in the BM group increased significantly between 18 and 30 months by 2.7 points ($P < .0001$), whereas estimated PDI scores remained statistically unchanged. MDI scores of the non-BM group remained essentially unchanged between 18 and 30 months, and PDI scores trended lower at 30 months by an estimated 2.3 points.

DISCUSSION

Our previous evaluation on this cohort of infants identified beneficial effects of BM at 18 months' CA. Infants who received BM had significantly higher Bayley MDI scores, PDI scores, and behavior rating scores and fewer rehospitalizations in the first year of life compared with the no-BM group. In fact, there was a dose relationship, and increasing quintiles of BM ingestion were associated with incrementally higher 18-month CA Bayley scores.

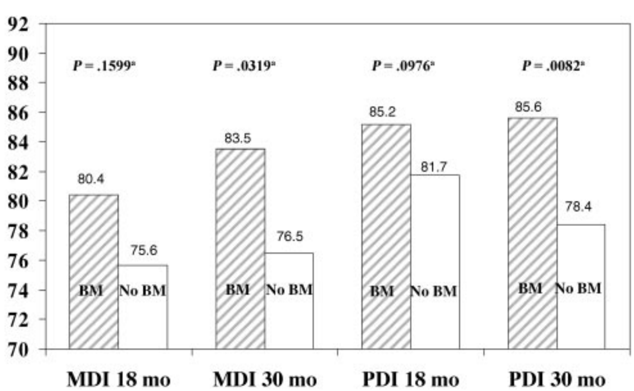

FIGURE 1
Mean MDI and PDI scores at 18 and 30 months according to any BM feeding. [a] Adjusted *P* values.

In our previous report of 18-month outcomes of this cohort, we identified no differences in neonatal morbidities, days to first enteral feed, or days of hospitalization when comparing the BM to the no-BM group. Because we had identified BM threshold effects for 18-month neurodevelopmental outcomes, we analyzed the 30-month child outcome data by quintiles to assess threshold effects. After adjusting for confounders, we identified that ingestion of BM (>80th percentile) was associated with significantly lower numbers of days to achieve full enteral feeds and length of stay compared with the no-BM group. Beneficial effects of BM were the significantly earlier attainment of full enteral feeds by 1 week and earlier discharge by 2 weeks after adjusting for confounders. These findings may be associated with improved digestion and absorption of nutrients, enhanced host defense mechanisms, and lower illness severity during the NICU stay.

Repeated-measures analysis, however, adjusted for study covariates, revealed that the Bayley MDI and PDI scores were significantly higher for the BM group compared with the no-BM group only at 30 months and that MDI scores increased significantly between 18 and 30 months of age only for infants in the BM group, increasing from 80.4 to 83.5 points. Bayley PDI scores, however, did not increase significantly between 18 and 30 months. Multiple regression analyses controlling for morbidities and factors known to impact on Bayley scores supported the independent effects of BM on 30-month Bayley mental and motor scores. Beneficial effects of BM on cognitive skills are consistent with previous reports in term and larger preterm infants.[9–18] This is the first outcome report of infants with ELBW who received BM in the NICU and were followed to 30 months to assess the effects of BM. The fact that 77% of the 30-month BM group had stopped receiving BM at discharge suggests that important effects of BM in this extremely preterm population occurred in the NICU. There is increasing evidence that nutrition plays a major role in development and may well be based in the beneficial effects of components of BM, including arachidonic acid and docohexanoic acid.[19–27]

Two indicators that have been shown to be associated with better developmental, cognitive, and behavioral outcomes, which were not collected in our study, are maternal IQ and quality of the home environment. There are a limited number of studies that have included these variables in their study design and adjusted for the effects relative to the effects of BM on child outcomes.[28–30] In the recent analysis of data from the US National Longitudinal Survey of Youth, which includes maternal and child interviews and assessments, the investigators reported that, after adjusting for maternal IQ and home stimulation, breastfeeding no longer significantly predicted child IQ in term infants at 10 years of age.[28] However, when the investigators divided the children into quartiles of duration of BM ingested and completed supplemental data analysis, they did identify significant effects of BM in the highest quartile of duration of ingestion on the Peabody Individual Achievement test, mathematics scores, and comprehension scores. Our data on premature infants also are highly suggestive of a threshold effect of BM. Limitations to the Der et al[28] study, however, include short duration of breastfeeding (median: 3 months), exclusion of preterm infants, and lack of data on quantity of BM ingested. The effects of quantity and duration of BM on the outcomes of infants with ELBW adjusted for maternal IQ and home environment, as well as for standard confounders, need to be evaluated.

Children in our BM group at 30 months' CA also continued to have more optimal Bayley behavior scores for emotional regulation, motor quality, and total behavior scores. This BM advantage for 30-month behavior scores is consistent with our previous finding at 18 months. Multiple regression analysis again confirmed an independent association between BM and total behavior scores after adjusting for known confounders. The behavior advantage is consistent with a previous finding in neonates receiving BM.[31,32]

We previously reported a decreased rehospitalization rate for the BM infant group in the first year of life. Our analyses at 30 months was more revealing, because we evaluated the specific reason for hospital admission and determined that the primary effects of BM were in preventing admission for respiratory illness and that there were specific age effects. Benefits were observed between discharge and 1 year and between 1 year and 2 years and not after 2 years. This suggests that the immune advantage derived from BM ingestion during neonatal hospitalization is most effective during the first 2 years after discharge from the NICU.

Growth parameters for weight, height, and head circumference were almost identical for our 2 study groups at 30 months' CA similar to our findings at 18 months. In addition, the BM and the no-BM groups had very similar neurologic and neurosensory findings. These were similar to our findings at 18 months' CA, suggesting that the principal effects of BM in children at 30 months CA are on cognition and behavior.

A limitation of this report was that 3 centers that participated in the study at 18 months' CA did not evaluate children at 30 months. To address this difference we analyzed for differences between those mothers and children seen at 18 months' CA and those seen at both visits. Differences were minor. Mothers of children seen at 30 months had similar age, marital status, education, ethnicity, and parity compared with mothers of children not evaluated at 30 months. The only difference identified was a higher rate of income more than $20 000 for mothers of infants seen (66% vs 44%, respectively). Children seen and not seen had similar rates of intraventricular hemorrhage 3 to 4, periventricular leukomalacia, chronic lung disease, necrotizing enterocolitis, and day of first enteral feed. Children not seen had 0.6-week higher gestational age, 9% less late-onset sepsis, and an 8.5-day shorter hospital stay. A second limitation was that, although we collected data on maternal demographics and education, we did not evaluate maternal IQ. Although the mothers who provided BM had higher education and income levels than the no-BM group, beneficial effects of BM were observed after controlling for the level of education in the multiple regression analyses.

CONCLUSIONS

On the basis of findings of persistent effects of BM on cognition at 30 months' CA, we reiterate our recommendation that efforts must be made to introduce all of the mothers to the benefits of BM. Efforts should be initiated not only by the obstetrician, neonatologist, lactation consultant, and primary care provider but should begin before pregnancy with supports after discharge from the birthing hospital. To optimize efforts, the introduction of the concept of breastfeeding can be considered in elementary school as part of healthy-living education.

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