NICU Human Milk Dose and Health Care Use after NICU Discharge in Very Low Birth Weight Infants

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Abstract

Objective—To determine the association between human milk (HM) dose and health care utilization at one and two years of life in very low birth weight (birth weight <1500g; VLBW) infants.

Study Design—This study included 345 VLBW infants enrolled in a prospective observational cohort study (2008–2012) who completed a Neonatal High-Risk Follow-up Clinic visit. Subsequent health care utilization included hospitalizations, emergency department visits, pediatric subspecialists and specialized therapies.

Results—Each 10 mL/kg/day increase in HM in the first 14 days of life was associated with 0.26 fewer hospitalizations (p = 0.04) at 1 year and 0.21 fewer pediatric subspecialist types (p = 0.04) and 0.20 fewer specialized therapy types (p = 0.04) at 2 years.

Conclusion—HM dose in early life for VLBW infants was an independent predictor of the number of hospitalizations at 1 year and types of pediatric subspecialists and specialized therapies at 2 years of life.

Introduction

Very low birth weight (birth weight < 1500g; VLBW) infants use more health care services and have higher health care costs after neonatal intensive care unit (NICU) discharge than healthy term infants.(1–6) Health care services that are more frequently used by VLBW infants include hospitalizations, emergency department (ED) visits, pediatric subspecialty medical care, and physical, occupational and speech therapies, all of which increase costs

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for families and society at large.(1–9) Human milk (HM; milk from the infant's mother, excluding donor HM) feedings during critical exposure periods in the NICU hospitalization reduce the risk of neonatal morbidities that increase the risk of chronic medical conditions and neurodevelopmental problems.(10–13)

Previous studies in VLBW and extremely low birth weight (birth weight < 1000g; ELBW) infants have revealed a dose-response relationship between the amount of HM received during the NICU hospitalization and a reduction in rehospitalization and improved neurodevelopmental outcomes in early childhood.(14–18) Additionally, longer durations and exclusivity of HM in term infants are associated with lower incidence of childhood diseases, including acute otitis media,(19) upper and lower respiratory infections,(20) gastrointestinal infections,(20) and acute lymphoblastic leukemia,(21) thereby reducing childhood health care utilization and costs. In contrast, the literature is sparse regarding the association between early HM intake and health care utilization after NICU discharge for VLBW infants.(15,16) To our knowledge no previously published cohort study has examined a spectrum of post-discharge health care utilization through two years of age in relation to the HM dose received during the initial NICU hospitalization. The study objective was to evaluate the relationship between dose of HM received during critical exposure periods in the NICU hospitalization and health care utilization after NICU discharge through two years of life for VLBW infants.

Subjects and Methods

Study Design

The LOVE MOM (**L**ongitudinal **O**utcomes in **V**ery Low Birthweight Infants **E**xposed to **M**others' **O**wn **M**ilk) cohort included 430 VLBW infants admitted to Rush University Medical Center between 2008 and 2012. Detailed inclusion and exclusion criteria and data collection procedures for the study have been previously reported(10) and are briefly summarized here. Infants were enrolled into the study within 24 hours post-birth and received enteral feedings by 14 days of life (DOL). During the study period, all VLBW infants discharged from the NICU were referred to the Neonatal High-Risk Follow-up Clinic for evaluation at 4, 8 and 20 months corrected age (CA). This multidisciplinary clinic monitors and evaluates growth, neurologic and developmental status through the first two years CA. This study was limited to the 345 infants who completed at least one clinic visit for routine care by 20 months CA. NICU follow-up data were obtained retrospectively from the patient record. Informed consent was obtained from a parent or legal guardian for the original prospective LOVE MOM study, and the institutional review board approved both this study and the original cohort study.

HM Dose Data

Nutritional management was per a standard of care protocol in the NICU during the study years. All infants received parenteral nutrition within hours after birth which provided 3 g/kg/d protein and 27 kcal/kg/d on the first day. Parenteral nutrition was continued until enteral nutrition reached 120 ml/kg/d, after which enteral feedings were gradually increased to a total daily fluid volume of 140–150 mL/kg/d. Enteral feedings were initiated with HM

once available or preterm formula if HM was not available after the first few days of life. HM was fortified using powdered HM fortifier when the feeding volume reached 100–140 ml/kg/d. Detailed HM intake data were collected for each enteral feeding during the NICU hospitalization and included the absolute mLs of both HM and formula (no donor HM was used). Daily HM dose was calculated as a weight-adjusted dose (mLs per kilogram body weight per day; mL/kg/d) from the individual feeding data. These daily doses were subsequently used to calculate average daily HM dose (HM-DD) and HM as a percentage of enteral feedings received during the specific exposure periods of 1–14 DOL, 1–28 DOL and for the entire NICU hospitalization.(22)

Health Care Utilization Data

As part of standard care in the Neonatal High-Risk Follow-up Clinic, health care utilization data were acquired from the caregiver at each visit. For the first visit after NICU discharge, the caregiver was asked about health care utilization since NICU discharge, and at subsequent visits, the caregiver was asked about utilization in the interval since the last clinic visit. The number of hospitalizations and ED visits and the types of pediatric subspecialists (pulmonology, surgery, ophthalmology, gastroenterology, nephrology, cardiology, and other) and specialized therapies (physical, speech, developmental, occupational, and nutritional therapy) were collected. The number of hospitalizations, ED visits, types of pediatric subspecialists, and types of specialized therapies at 4 and 8 months CA were summed to calculate health care utilization through 1 year, and the number of visits or provider types at 4, 8 and 20 months CA were summed to calculate health care utilization through 2 years. The health care utilization outcomes were coded as both categorical and continuous variables, depending on the analysis.

Neonatal and Sociodemographic Risk Factors

Infant and maternal characteristics were collected from the prospective LOVE MOM cohort study database of the initial NICU hospitalization. Neonatal risk factors included gestational age, small for gestational age status at birth,(23) mode of delivery (vaginal or cesarean), multiple or singleton birth, antenatal steroid administration, presence of morbidities and feeding characteristics. Patent ductus arteriosus (PDA) treatment (medical and/or surgical) served as a proxy for infants who were unable to undergo standard enteral feed advancement and were at higher risk for poor health outcomes, thus controlling for acuity during the early post-birth time frame.(24) During the study years of 2008–2012 when subjects were hospitalized in the NICU, feedings were withheld during PDA treatment and then resumed at the previous feeding volume once therapy was completed. Feeding characteristics included DOL at feeding initiation and DOL at full enteral feedings. Infant sociodemographic characteristics included gender and primary insurance. Maternal sociodemographic characteristics included maternal race/ethnicity and education. Additionally, we included completion of the 4-month and 8-month follow-up visits as binary variables to account for possible differential recall in the number of visits and types of providers based on whether both the 4 and 8-month visits were completed, or only one of the visits was completed.

Presence of morbidities during the NICU hospitalization included necrotizing enterocolitis (NEC; stage 2 or 3, according to Bell),(25) culture-proven late onset sepsis (sepsis), bronchopulmonary dysplasia (BPD; receipt of oxygen or positive pressure ventilation at 36 weeks) and severe brain injury (grades 3–4 intraventricular hemorrhage, periventricular leukomalacia or hydrocephalus). While we initially included severe retinopathy of prematurity (stage 3 or greater), only 2 infants had the morbidity.

Statistical Analysis

One-way analysis of variance (ANOVA) was used to test the association between health care utilization and DD-HM through DOL14, DOL28 and NICU discharge, and Levene's test for equality of variance was used to test for homogeneity of variance. In cases of unequal variance, Welch's ANOVA was used. Generalized linear regression models with a negative binomial distribution and log link function were fit to test the association between DD-HM and each of the health care utilization outcomes (number of hospitalizations, number of ED visits, number of types of pediatric subspecialists, number of types of specialized therapies) through 1 and 2 years, respectively. For each health care utilization outcome, a generalized linear regression model was first estimated with only DD-HM. To determine the neonatal and sociodemographic risk factors to be included as covariates, a second model was estimated that included only risk factors. The final model included DD-HM, gestational age, completion of the 4 and 8-month follow-up visits to account for potential recall and selection biases in visit completion, and all other covariates that were significantly associated (p < 0.10) with each health care utilization outcome in the model that included only risk factors. This resulted in one regression model (for each DD-HM: through DOL14, DOL28 and NICU discharge) for each of the 4 health care utilization outcomes for the 2 time periods (1 year and 2 years). Since DD-HM through DOL28 and NICU discharge were not significantly associated with the 4 health care utilization outcomes, only models utilizing DD-HM through DOL14 are reported, resulting in a total of 8 regression models. The marginal effect of DD-HM was computed as $(\exp(\beta) - 1)$ x average DD-HM (in 10 mL/kg/d increments) of 2.996. SAS version 9.2 (Cary, NC) was used for all statistical analyses, and the programming code for the statistical analyses can be obtained from an author (TJJ).

Results

Of the 430 infants in the LOVE MOM cohort, 421 infants survived to 4-month follow-up (98%). Of the 345 (82%) infants completing at least one follow-up visit, 338 (80%) completed a visit at 4 and/or 8-months CA, and 251 (60%) completed a follow-up visit at 20-months CA (Figure). Infants who did not complete any follow-up visit were more likely to have a mother of black/African American race/ethnicity with less than a college degree, were less likely to have BPD, had shorter NICU length of stay and lower HM intake through NICU discharge. There was no difference in HM intake for the first 14 or 28 DOL. Infants who completed at least one follow-up visit at the 1-year follow-up were born to predominantly minority mothers and were low income, with 78% minority and 72% enrolled in Medicaid, and a majority receiving exclusive HM during the first 14 DOL (Table 1), and the 251 infants who completed the two-year follow-up visit were similar to the infants who completed the one-year follow-up visit. At the 1-year follow-up, 31% had one or more

hospitalizations, 41% had one or more ED visits, 47% had seen at least one pediatric subspecialist and 34% had received at least one specialized therapy (Table 2).

Table 3 reports the bivariate association between health care utilization after NICU discharge and DOL14 DD-HM. At the 1-year follow-up, infants with two or more hospitalizations had the lowest DOL14 DD-HM, while infants with no hospitalizations had the highest DOL14 DD-HM. Similar associations between DOL14 DD-HM and the types of pediatric subspecialists and specialized therapies were detected. These associations between DOL14 DD-HM and utilization were similar at the 2-year follow-up.

Associations were also detected between DD-HM over other exposure periods (DOL28 and NICU) and health care utilization after NICU discharge. At both 1 and 2-year follow-up, DD-HM was the lowest for infants who had seen two or more types of pediatric subspecialists for both DOL28 DD-HM and NICU DD-HM (results not shown). Additionally, DOL28 DD-HM was lower for infants with two or more hospitalizations compared with infants who had no hospitalizations at the 1-year follow-up.

Before adjusting for neonatal and sociodemographic risk factors, DOL14 DD-HM was associated with reductions in each of the health care utilization outcomes at 1-year follow-up (Table 4). After adjusting for neonatal and sociodemographic risk factors, DOL14 DD-HM remained significantly associated with a reduction in the number of hospitalizations, with a marginal effect of 0.26 fewer hospitalizations per 10 mL/kg/d increase in DOL14 DD-HM (p = 0.04) at 1 year (full model results are presented in Supplemental Table 1). DOL14 DD-HM was significantly associated with the number of types of pediatric subspecialists at 2 years, with 0.21 fewer subspecialist types per 10 mL/kg/d increase in DOL14 DD-HM (p = 0.04) and the number of specialized therapy types, with 0.20 fewer types of specialized therapies per 10 mL/kg/d increase in DOL14 DD-HM (p = 0.04) (full model results are presented in Supplemental Table 2). DOL28 DD-HM and NICU DD-HM were not significantly associated with the health care utilization outcomes after controlling for risk factors (results not shown).

Discussion

To our knowledge, this is the first cohort study to examine the relationship between dose of HM (defined as milk from the infant's mother, excluding donor HM, throughout the Discussion) received during the initial NICU hospitalization and subsequent health care utilization through 2 years of life in VLBW infants. We found that every 10 mL/kg/d increase in HM intake in the first 14 DOL was associated with a significant reduction in hospitalizations over the first 1 year of life and with a significant reduction in the types of pediatric subspecialists and specialized therapies over the first 2 years of life. In contrast to findings by Vohr et al in ELBW infants,(15) we did not find an association between HM dose received during the entire NICU stay and subsequent hospitalization. We speculate that this may have been due to differences in our cohort which was a larger, healthier group of VLBW infants who reached full enteral feedings at a mean of 22.1 days and, therefore, were receiving a significant volume of HM at DOL14 compared to ELBW infants in the Vohr et al study who reached full enteral feedings at a mean of 27.4–29 DOL.

An obvious question is whether this dose-dependent relationship is a function of the biological impact of HM in this early post-birth critical window or represents healthier infants receiving higher volumes of HM. To account for infants who were sicker or not receiving feedings in the first 14 DOL, we controlled for infant maturity, feeding characteristics and other factors that could impact early feedings and potentially the outcomes of interest, and found that DOL14 HM-DD remained significantly associated with the number of hospitalizations through the first year. While we could not identify specific clinical reasons for variation in feeding initiation, we attempted to adjust for covariates that may be associated with variation in enteral feedings and/or HM feedings. Ehrenkranz et al reported in ELBW infants that early nutrition acts as a mediator of the relationship between critical illness in the first weeks of life and later outcomes, including neurodevelopment in the second year of life.(26) They also demonstrated an independent effect of early nutrition on post-discharge outcomes even after controlling for infant acuity. While Ehrenkranz et al utilized total energy from parenteral and enteral sources as a measure of early nutrition, our study focused on enteral nutrition only, and specifically HM. Although our analysis did not include parenteral nutrition, all infants were managed on the same parenteral nutrition protocol.

Several recent publications link high-dose HM feedings in the first 10 to 28 DOL to improved health outcomes in premature infants that manifest well past this early window and through to seven years of age.(12,27,28) In a secondary analysis of data from the NICHD-funded Glutamine Trial that enrolled 1433 ELBW infants from 15 centers,(29) Meinzen-Derr et al reported a dose-response relationship between HM intake in the first 14 DOL and a reduction in the risk of NEC or death later in the NICU hospitalization.(28) Similarly, Sisk et al found that VLBW infants who received 50% of enteral feedings as HM during the first 14 DOL were six times less likely to develop NEC later in the NICU hospitalization,(30) and Corpeleijn et al found that VLBW infants receiving any HM feedings during the first 5 DOL and at least 50% of intake as HM during DOL 6–10 had a reduction in NEC, sepsis and mortality to 60 DOL.(12) Additionally, in a matched case control study of infants with and without late onset sepsis, Trend et al found that the daily and cumulative amount of HM consumed by infants prior to developing sepsis was significantly lower than consumption by infants who did not develop sepsis.(31) Most recently, receipt of predominantly HM feedings during the first 28 DOL was associated with greater deep nuclear grey matter, IQ, academic achievement, working memory and motor function at 7 years in infants born <30 weeks of gestation.(27) Our study cohort differs significantly from subjects in these studies in that 96% of infants in our cohort received some HM during the first 14 DOL, with 66% receiving exclusive HM and a mean HM dose of 84% ± 31%. In contrast, Meinzen-Derr et al reported 73% of infants received some HM in the first 14 DOL with 32% receiving exclusive HM and a mean HM dose of 53% ± 46%. (28) Corpeleijn et al reported 88% of infants received some HM in the first 10 DOL with 2% receiving exclusive HM.(12) Thus, our high rate of exclusive HM intake may have limited our ability to detect an effect using HM percent as the method to quantify HM dose in the first 14 DOL.

While the cumulative findings from the clinical studies above do not specifically address health care utilization, they suggest a critical window in the very early post-birth period

during which HM may be especially important in selective growth, development and protection of immature organs and pathways. This explanation is supported by several mechanistic studies that posit a role for HM in the programming of the infant gut microbiota via the HM microbiome and HM oligosaccharides as well as roles for HM in gut integrity, immunomodulation, neuroprotection and the downregulation of inflammation and oxidative stress.(32–35) We speculate that the effect of HM-DD on hospitalizations may be mediated by a reduction in the incidence of neonatal morbidities that are commonly associated with re-hospitalizations after NICU discharge.(2,4,10–13)

Our findings have significant societal implications in terms of cost savings because HM acquisition from the mother during the initial NICU hospitalization is low cost relative to its benefits.(35) National data indicate the median cost per rehospitalization in the first year of life was $6000 in 2001 US dollars (approximately $10,440 in 2017 US dollars) for preterm and low birth weight infants.(36,37) Thus, reducing potentially preventable hospitalizations through HM feedings during the early post-birth period could translate into substantial health care savings.

In the unadjusted models, HM-DD was also associated with reductions in early intervention services to prevent and treat developmental disability, such as speech and language, occupational, physical and behavioral therapy.(9) However, we found only an association between HM-DD and specialized therapy utilization after adjustment for risk factors at 2 years. This finding may reflect the fact we categorized infants according to receipt of specialized therapies rather than by whether infants qualified for therapy, although 43% of the infants in our study were automatically eligible for Early Intervention services in Illinois due to birth weights less than 1000g. We have previously shown that up to 28% of ELBW infants seen in NICU follow-up require referral for therapies not being received,(38) and as such, our numbers may underestimate the services these infants should be receiving. Thus, the impact of early HM feedings on the types of specialized therapies used may be underestimated in our data.

Although a strength of our study is the detailed, prospectively collected HM dose and neonatal data, there are several limitations. Health care utilization data were collected retrospectively from clinic medical records based on information reported by the caregivers, and our findings are limited to hospitalizations, ED visits, subspecialists and therapies and do not include hospital admission diagnoses, reason for visit, or information on primary care. Utilization data were obtained by parent report and thus subject to recall bias. While 95% of eligible infants were enrolled in the original prospective study, and 80% completed at least one clinic visit, only 60% completed the 2-year visit. Children who did not complete any follow-up visit were less likely to have BPD and more likely to be born to Black/African American mothers with less than a college degree. Inclusion of this group may have altered our results; however, there were no significant differences between the groups with respect to DOL14 DD-HM, birth weight, gestational age, and insurance coverage which may be associated with high health care use.(39–42) Additionally, poverty has been shown to be associated with greater health care utilization(40,42) and lower rates of HM provision.(43) However, in our minority and low-income cohort, the majority of infants received 100% HM during the first 14 DOL. Additionally, we adjusted for sociodemographic factors in our

analyses by including insurance status and maternal education. Another limitation is the potential that our findings reflect that DOL14 DD-HM may serve as a surrogate for infant acuity, with healthier infants receiving higher DD-HM, rather than an independent relationship between DD-HM and health care utilization. Through our inclusion of multiple covariates that could impact DD-HM as well as later health care utilization, we attempted to account for this limitation. While common neonatal morbidities have been associated with later health care utilization,(2,4) these were not included in the regression models. This exclusion was based on the fact that these morbidities might serve as mediators of the effect of DD-HM on later outcomes, since HM has been demonstrated in numerous studies to provide risk-reduction for these morbidities.(10–13)

We have demonstrated in this diverse, urban cohort of VLBW infants that there is a dose-dependent relationship between increasing HM intake during the first 14 DOL and a reduction in hospitalizations after NICU discharge. The impact of HM on hospitalizations was seen even after controlling for neonatal and social risk. Conversely, increasing HM intake over the first 28 days or the entire NICU hospitalization was not associated with a reduction in health care utilization, thus suggesting there may be a critical window during which time HM dose may have the greatest benefit. Thus high-dose HM intake should be prioritized early in the NICU stay to help alleviate the risks and costs of health problems in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations:

VLBW	very low birth weight
NICU	neonatal intensive care unit
ED	emergency department
HM	human milk
LOVEMOM	**L**ongitudinal **O**utcomes in **V**ery Low Birthweight Infants **E**xposed to **M**others' **O**wn **M**ilk
DOL	days of life
CA	corrected age
HM-DD	human milk daily dose
NEC	necrotizing enterocolitis

| **BPD** | bronchopulmonary dysplasia |
| **PDA** | patent ductus arteriosus |

References

(1). Underwood MA, Danielsen B, Gilbert WM. Cost, causes and rates of rehospitalization of preterm infants. J Perinatol 2007; 27: 614–619. [PubMed: 17717521]

(2). Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD, National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. Community supports after surviving extremely low-birth-weight, extremely preterm birth: special outpatient services in early childhood. Arch Pediatr Adolesc Med 2008; 162: 748–55. [PubMed: 18678807]

(3). Korvenranta E, Lehtonen L, Peltola M, Hakkinen U, Andersson S, Gissler M, et al. Morbidities and hospital resource use during the first 3 years of life among very preterm infants. Pediatrics 2009; 124: 128–34. [PubMed: 19564292]

(4). Luu TM, Lefebvre F, Riley P, Infante-Rivard C. Continuing utilisation of specialised health services in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed 2010; 95: F320–5. [PubMed: 20688861]

(5). Petrou S Economic consequences of preterm birth and low birthweight. BJOG 2003; 110 Suppl 20: 17–23. [PubMed: 12763106]

(6). Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC Pediatr 2014; 14: 93–2431-14–93.

(7). Petrou S, Johnson S, Wolke D, Marlow N. The association between neurodevelopmental disability and economic outcomes during mid-childhood. Child Care Health Dev 2013; 39: 345–57. [PubMed: 22372844]

(8). Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and Neonatal Morbidity Among Infants 501 to 1500 Grams From 2000 to 2009. Pediatrics 2012; 129: 1019–1026. [PubMed: 22614775]

(9). Clements KM, Barfield WD, Ayadi MF, Wilber N. Preterm birth-associated cost of early intervention services: an analysis by gestational age. Pediatrics 2007; 119: e866–74. [PubMed: 17339387]

(10). Patel AL, Johnson TJ, Engstrom JL, Fogg LF, Jegier BJ, Bigger HRM,PP Impact of early human milk on sepsis and health care costs in very low birthweight infants. J Perinatol 2013;33(7):514–9. [PubMed: 23370606]

(11). Patel AL, Johnson TJ, Robin B, Bigger HR, Buchanan A, Christian E, et al. Influence of own mother's milk on bronchopulmonary dysplasia and costs. Arch Dis Child Fetal Neonatal Ed 2017; 102: F256–61. [PubMed: 27806990]

(12). Corpeleijn WE, Kouwenhoven SM, Pappa MC, van Vilet I, Scheerder I, Mulzer Y, et al. Intake of own mother's milk during the first days of life is associated with decreased morbidity and mortality in very low birth weight infants during the first 60 days of life. Neonatology 2012; 102: 276–81. [PubMed: 22922675]

(13). Johnson TJ, Patel AL, Bigger HR, Engstrom JL, Meier PP. Cost savings of human milk as a strategy to reduce the incidence of necrotizing enterocolitis in very low birth weight infants. Neonatology 2015; 107: 271–6. [PubMed: 25765818]

(14). Patra K, Hamilton M, Johnson TJ, Greene M, Dabrowski E, Meier PP, et al. NICU human milk dose and 20-month neurodevelopmental outcome in very low birth weight infants. Neonatology 2017; 112: 330–6. [PubMed: 28768286]

(15). Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Wright LL, Langer JC, et al. 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. Pediatrics 2006; 118: e115–23. [PubMed: 16818526]

(16). Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, et al. 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. Pediatrics 2007; 120: e953–9. [PubMed: 17908750]

(17). Gibertoni D, Corvaglia L, Vandini S, Rucci P, Savini S, Alessandroni R, et al. Positive effect of human milk feeding during NICU hospitalization on 24 month neurodevelopment of very low birth weight infants: An Italian cohort study. PLoS One 2015; 10: e0116552. [PubMed: 25590630]

(18). Vohr B, McGowan E, McKinley L, Tucker R, Keszler L, Alksninis B. Differential effects of the single-family room neonatal intensive care unit on 18- to 24-month Bayley scores of preterm infants. J Pediatr 2017; 185: 42–48.e1. [PubMed: 28238479]

(19). Bowatte G, Tham R, Allen KJ, Tan DJ, Lau M, Dai X, et al. Breastfeeding and childhood acute otitis media: A systematic review and meta-analysis. Acta Paediatr 2015; 104(467): 85–95. [PubMed: 26265016]

(20). Duijts L, Jaddoe VW, Hofman A, Moll HA. Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. Pediatrics 2010; 126: e18–25. [PubMed: 20566605]

(21). Amitay EL, Keinan-Boker L. Breastfeeding and childhood leukemia incidence: A meta-analysis and systematic review. JAMA Pediatr 2015; 169: e151025. [PubMed: 26030516]

(22). Bigger HR, Fogg LJ, Patel A, Johnson T, Engstrom JL, Meier PP. Quality indicators for human milk use in very low-birthweight infants: Are we measuring what we should be measuring? J Perinatol 2014; 34: 287–91. [PubMed: 24526005]

(23). Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010; 125: e214–24. [PubMed: 20100760]

(24). Madan JC, Kendrick D, Hagadorn JI, Frantz ID, 3rd, National Institute of Child Health and Human Development Neonatal Research Network. Patent ductus arteriosus therapy: Impact on neonatal and 18-month outcome. Pediatrics 2009; 123: 674–681. [PubMed: 19171637]

(25). Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978; 187: 1–7. [PubMed: 413500]

(26). Ehrenkranz RA, Das A, Wrage LA, Poindexter BB, Higgins RD, Stoll BJ, et al. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res 2011; 69: 522–9. [PubMed: 21378596]

(27). Belfort MB, Anderson PJ, Nowak VA, Lee KJ, Molesworth C, Thompson DK, et al. Breast milk feeding, brain development, and neurocognitive outcomes: A 7-year longitudinal study in infants born at less than 30 weeks' gestation. J Pediatr 2016; 177: 133–9.e1. [PubMed: 27480198]

(28). Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. J Perinatol 2009; 29: 57–62. [PubMed: 18716628]

(29). Poindexter BB, Ehrenkranz RA, Stoll BJ, Wright LL, Poole WK, Oh W, et al. Parenteral glutamine supplementation does not reduce the risk of mortality or late-onset sepsis in extremely low birth weight infants. Pediatrics 2004; 113: 1209–1215. [PubMed: 15121931]

(30). Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Maternal and infant characteristics associated with human milk feeding in very low birth weight infants. J Hum Lact 2009; 25: 412–9. [PubMed: 19602575]

(31). Trend S, Strunk T, Hibbert J, Kok CH, Zhang G, Doherty DA, et al. Antimicrobial protein and Peptide concentrations and activity in human breast milk consumed by preterm infants at risk of late-onset neonatal sepsis. PLoS One 2015; 10: e0117038. [PubMed: 25643281]

(32). Pannaraj PS, Li F, Cerini C, Bender JM, Yang S, Rollie A, et al. Association between breast milk bacterial communities and establishment and development of the infant gut microbiome. JAMA Pediatr 2017; 171: 647–54. [PubMed: 28492938]

(33). Lemay DG, Pollard KS, Martin WF, Freeman Zadrowski C, Hernandez J, Korf I, et al. From genes to milk: genomic organization and epigenetic regulation of the mammary transcriptome. PLoS One 2013; 8: e75030. [PubMed: 24086428]

(34). Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am 2013; 60: 49–74. [PubMed: 23178060]

(35). Meier PP, Johnson TJ, Patel AL, Rossman B. Evidence-based methods that promote human milk feeding of preterm infants: An expert review. Clin Perinatol 2017; 44: 1–22. [PubMed: 28159199]

(36). Russell R, Green NS, Steiner CA, Meikle S, Howes JL, Poschman K, et al. Cost of hospitalization for preterm and low birth weight infants in the United States. Pediatrics 2007; 120: e1-e1–e9. [PubMed: 17606536]

(37). Bureau of Labor Statistics. Consumer Price Index - All Urban Consumers, Medical Care, Series ID Series ID CUSR0000SAM. 2017; Available at: http://data.bls.gov/cgi-bin/dsrv. Accessed Dec, 2017.

(38). Greene M, Patra K. Part C early intervention utilization in preterm infants: Opportunity for referral from a NICU follow-up clinic. Res Dev Disabil 2016; 53-54: 287–95. [PubMed: 26955914]

(39). Rodriguez-Martinez CE, Acuna-Cordero R, Sossa-Briceno MP. Predictors of prolonged length of hospital stay or readmissions for acute viral lower respiratory tract infections among infants with a history of bronchopulmonary dysplasia. J Med Virol 2018; 90: 405–11. [PubMed: 28975628]

(40). Laugier O, Garcia P, Boucekine M, Daguzan A, Tardieu S, Sambuc R, et al. Influence of socioeconomic context on the rehospitalization rates of infants born preterm. J Pediatr 2017; 190: 174–9.e1. [PubMed: 28893384]

(41). Kuint J, Lerner-Geva L, Chodick G, Boyko V, Shalev V, Reichman B, et al. Rehospitalization through childhood and adolescence: Association with neonatal morbidities in infants of very low birth weight. J Pediatr 2017; 188: 135–141.e2. [PubMed: 28662947]

(42). Klitkou ST, Iversen T, Stensvold HJ, Ronnestad A. Use of hospital-based health care services among children aged 1 through 9 years who were born very preterm - a population-based study. BMC Health Serv Res 2017; 17: 571–017-2498–3.

(43). Anstey EH, Chen J, Elam-Evans LD, Perrine CG. Racial and geographic differences in breastfeeding - United States, 2011–2015. MMWR Morb Mortal Wkly Rep 2017; 66: 723–7. [PubMed: 28704352]
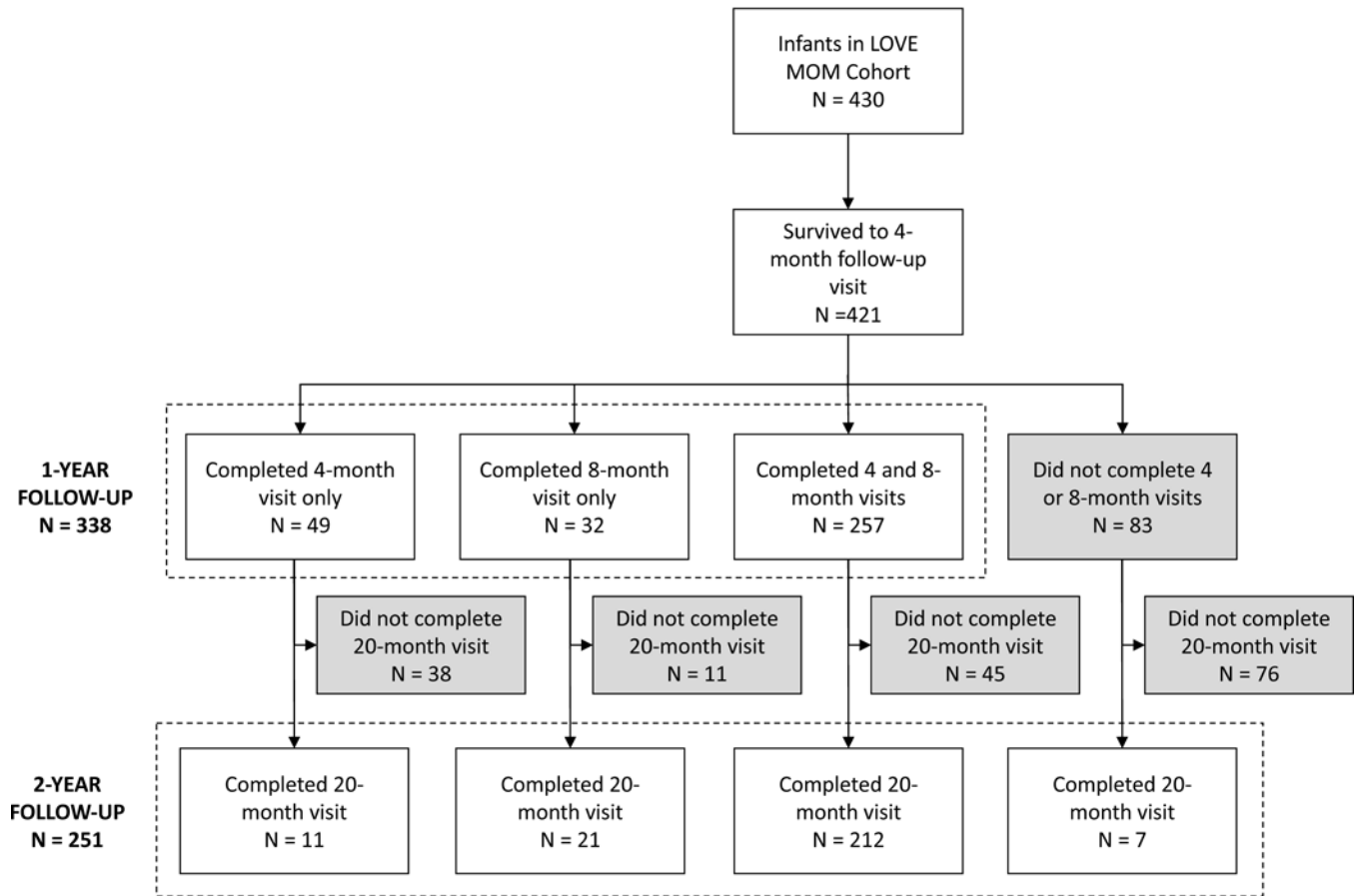
Figure:

Table 1.

Infant Characteristics

	Through 1 Year Follow-up N = 338	Through 2 Year Follow-up N = 251
Male gender, n (%)	179 (53)	135 (55)
Insurance, n (%)		
Private insurance	95 (28)	65 (26)
Medicaid	243 (72)	186 (74)
Maternal race/ethnicity, n (%) [i]		
White	68 (20)	53 (21)
Black/African American	163 (49)	111 (44)
Hispanic/Latino	98 (29)	80 (32)
Other	8 (2)	6 (2)
Maternal education, n (%) [ii]		
Less than high school degree	53 (16)	46 (18)
High school degree	99 (30)	67 (27)
Some college	112 (33)	83 (33)
College degree or above	72 (21)	54 (22)
Birth weight, mean (s.d.)	1039 (259)	1025 (255)
Birth weight < 1000g (automatic eligibility for Early Intervention Program services), n (%)	144 (43)	113 (45)
Gestational age, mean (s.d.)	27.9 (2.5)	27.9 (2.5)
Small for gestational age, n (%)	68 (20)	56 (22)
Delivery – cesarean, n (%)	221 (65)	167 (67)
Multiple, n (%)	51 (15)	38 (15)
Antenatal steroids, n (%)	305 (90)	224 (89)
Necrotizing enterocolitis, n (%)	28 (8)	23 (9)
Late onset sepsis (confirmed), n (%)	37 (11)	35 (14)
Severe retinopathy of prematurity, n (%)	2 (0.6)	1 (0.4)
Bronchopulmonary dysplasia, n (%)	112 (33)	92 (37)
Severe brain injury (IVH 3–4 or PVL), n (%)	18 (5)	12 (5)
Patent ductus arteriosus treatment, n (%)	134 (40)	106 (42)
First feeding, DOL, mean (s.d.)	4.6 (2.7)	4.8 (2.9)
First full feeding, DOL, mean (s.d.)	22.1 (14.2)	23.2 (15.4)
HM intake		
DOL 1–14, average mL/kg/day, mean (s.d.)	30.0 (27.8)	28.9 (27.1)
DOL 1–28, average mL/kg/day, mean (s.d.) (n = 315)	52.4 (38.2)	52.0 (37.5)
NICU stay, average mL/kg/day, mean (s.d.)	63.5 (49.6)	64.6 (49.1)
DOL 1–14, cumulative percent HM, median (25th – 75th percentiles)	100 (89 – 100)	100 (93 – 100)

	Through 1 Year Follow-up N = 338	Through 2 Year Follow-up N = 251
DOL 1–14, exclusive (100%) HM, n (%)	223 (66)	172 (68.5)
NICU length of stay, mean (s.d.)	75.0 (35.7)	77.7 (36.1)

Abbreviations: s.d., standard deviation; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; DOL, day of life; HM, human milk; NICU, neonatal intensive care unit.

[i] unknown for 1 infant;

[ii] unknown for 2 infants.

Table 2.

Follow-up Health Care Utilization

	Through 1 Year Follow-up N = 338	Through 2 Years Follow-up N = 251
Hospitalizations, n (%)		
0	232 (69)	154 (61)
1	81 (24)	59 (24)
2 or more	25 (7)	38 (15)
Emergency department visits, n (%)		
0	198 (59)	93 (37)
1	96 (28)	75 (30)
2 or more	44 (13)	83 (33)
Pediatric subspecialists		
Type, n (%)		
Pulmonology	45 (13)	47 (19)
Surgery	40 (12)	35 (14)
Ophthalmology	38 (11)	39 (16)
Gastroenterology	35 (10)	30 (12)
Nephrology	25 (7)	25 (10)
Cardiology	25 (7)	24 (10)
Number of types, n (%)		
0	179 (53)	113 (45)
1	84 (25)	65 (26)
2 or more	75 (22)	73 (29)
Specialized therapies		
Type, n (%)		
Physical therapy	99 (29)	107 (43)
Occupational therapy	34 (10)	54 (22)
Developmental therapy	26 (8)	49 (20)
Speech therapy	25 (7)	68 (27)
Nutritional therapy	2 (0.6)	2 (0.8)
Number of types, n (%)		
0	223 (66)	123 (49)
1	67 (20)	43 (17)
2 or more	48 (14)	85 (34)

Table 3.

Relationship between Human Milk Dose (mL/kg/day) at 14 Days of Life and Follow-up Health Care Utilization (Number of Visits and Number of Provider Types)

	Through 1 Year Follow-up (N = 338) HM dose, mL/kg/day, Mean (s.d.)				Through 2 Years Follow-up (N = 251) HM dose, mL/kg/day, Mean (s.d.)			
	0 Visits	1 Visit	2+ Visits	p-value	0 Visits	1 Visit	2+ Visits	p-value
Hospitalizations[i]	33.3 (28.0)	24.5 (27.7)	16.3 (17.8)	0.002	30.6 (26.2)	33.0 (32.1)	15.5 (16.4)	0.003
ED visits[i]	32.7 (28.5)	27.1 (26.7)	23.8 (25.5)	0.08	32.2 (27.7)	26.3 (27.0)	27.5 (26.4)	0.31
	0 Types	1 Type	2+ Types	p-value	0 Types	1 Type	2+ Types	p-value
Pediatric subspecialists[ii,iii]	37.0 (29.1)	22.3 (24.4)	21.8 (23.4)	<0.001	38.2 (30.4)	24.5 (22.2)	18.4 (20.1)	<0.001
Specialized therapies[ii, iv]	33.7 (28.6)	23.9 (25.9)	21.1 (22.5)	0.002	36.3 (29.5)	24.3 (25.7)	20.5 (20.5)	<0.001

Abbreviations: HM, human milk; s.d., standard deviation; ED, emergency department.

[i]Classified by number of visits;

[ii]classified by number of provider types;

[iii]pediatric subspecialist types include cardiology, gastroenterology, nephrology, ophthalmology, pulmonology, surgery and other;

[iv]Specialized therapy types include developmental, nutritional, occupational, physical and speech therapies; obtained using one-way analysis of variance.

Table 4.

Generalized Linear Regression Models Examining the Association of Human Milk Dose at 14 Days of Life (in 10 mL/kg/day increments) and Follow-up Health Care Utilization (Number of Visits and Number of Provider Types)

Health Care Utilization Outcome[ii]	Unadjusted Model[i]			Adjusted Model		
	Marginal Effect for HM[iii]	95% CI	p-value	Marginal Effect for HM[iii]	95% CI	p-value
Through 1 Year Follow-up (n = 334)						
Number of hospitalizations[iv-a]	−0.42	−0.63, −0.20	<0.001	−0.26	−0.49, −0.01	0.04
Number of ED visits[iv-b]	−0.27	−0.45, −0.08	0.006	0.01	−0.21, 0.26	0.92
Types of pediatric subspecialists[iv-c]	−0.40	−0.54, −0.25	<0.001	−0.09	−0.25, 0.09	0.32
Types of specialized therapies[iv-d]	−0.34	−0.52, −0.15	<0.001	−0.15	−0.35, 0.11	0.19
Through 2 Years Follow-up (n = 248)						
Number of hospitalizations[iv-e]	−0.39	−0.61, 0.15	0.002	−0.15	−0.41, 0.13	0.28
Number of ED visits[iv-f]	−0.17	−0.34, 0.00	0.05	0.13	−0.08, 0.35	0.23
Types of pediatric subspecialists[iv-g]	−0.48	−0.64, −0.32	<0.001	−0.21	−0.39, −0.01	0.04
Types of specialized therapies[iv-h]	−0.39	−0.55, −0.21	<0.001	−0.20	−0.38, −0.01	0.04

Abbreviations: HM, human milk; ED, emergency department; DOL, day of life.

[i] Unadjusted models include only HM through DOL14 in 10 mL/kg/day as an independent variable.

[ii] Each row reports the results for a different model.

[iii] Marginal effect for HM computed as $(\exp(\beta) - 1)$ x average dose of HM at DOL14 (in 10 mL/kg/d increments).

[iv] Adjusted models include gestational age, completion of 4 and 8-month follow-up visits and other independent variables significantly associated with the outcome (see Supplemental Tables for full model results), including

[iv-a] gender, maternal education, and maternal race/ethnicity;

[iv-b] gender, maternal education, insurance and patent ductus arteriosis treatment;

[iv-c] DOL of first full feeding;

[iv-d] maternal education and insurance;

[iv-e] gender, maternal education and insurance;

[iv-f] gender, maternal education, maternal race/ethnicity, insurance and DOL of first full feeding;

[iv-g] DOL of first full feeding and birth SGA; and

[iv-h] gender, maternal race/ethnicity and insurance.