# Breast Milk Feeding, Brain Development, and Neurocognitive Outcomes: A 7-Year Longitudinal Study in Infants Born at Less Than 30 Weeks' Gestation

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**Objectives** To determine the associations of breast milk intake after birth with neurological outcomes at term equivalent and 7 years of age in very preterm infants

**Study design** We studied 180 infants born at <30 weeks' gestation or <1250 grams birth weight enrolled in the Victorian Infant Brain Studies cohort from 2001-2003. We calculated the number of days on which infants received >50% of enteral intake as breast milk from 0-28 days of life. Outcomes included brain volumes measured by magnetic resonance imaging at term equivalent and 7 years of age, and cognitive (IQ, reading, mathematics, attention, working memory, language, visual perception) and motor testing at 7 years of age. We adjusted for age, sex, social risk, and neonatal illness in linear regression.

**Results** A greater number of days on which infants received >50% breast milk was associated with greater deep nuclear gray matter volume at term equivalent age (0.15 cc/d; 95% CI, 0.05-0.25); and with better performance at age 7 years of age on IQ (0.5 points/d; 95% CI, 0.2-0.8), mathematics (0.5; 95% CI, 0.1-0.9), working memory (0.5; 95% CI, 0.1-0.9), and motor function (0.1; 95% CI, 0.0-0.2) tests. No differences in regional brain volumes at 7 years of age in relation to breast milk intake were observed.

**Conclusion** Predominant breast milk feeding in the first 28 days of life was associated with a greater deep nuclear gray matter volume at term equivalent age and better IQ, academic achievement, working memory, and motor function at 7 years of age in very preterm infants. *(J Pediatr 2016;■■:■■-■■).*

In healthy, full-term populations, breastfeeding seems to be beneficial to neurodevelopment.[1-3] One proposed mechanism linking breastfeeding with brain development is the effect of specific nutrients in breast milk that are either absent from or present in lower amounts in infant formula.[4] Another potential mechanism is through greater sensitivity to the infant shown by mothers who provide breast milk,[5] because maternal sensitivity is associated with better neurodevelopment.[6] Connections between breastfeeding and infant development may also be explained in part by shared social determinants such as maternal education and family income, and maternal IQ.[7]

The effects of breast milk and breastfeeding on neurodevelopment may be quite different in very preterm infants than in those born at full term. Nutritionally, breast milk is considered the optimal food for full term infants, but preterm infants require fortification to match third trimester nutrient accretion rates.[8] Even with fortification, weight gain of breast milk-fed infants lags behind that of infants fed preterm formula,[9,10] suggesting possible undernutrition. In hospitalized very preterm infants, feedings are typically given via tube rather than directly at the breast, thereby uncoupling the ingestion of breast milk from the maternal interactions that occur during the act of breastfeeding. However, the time invested in expressing and delivering breast milk may reflect different levels of attachment or sensitivity. Given these differences between preterm and term infants, focused research is needed to evaluate the potential benefits of breast milk intake on the neurodevelopment of very preterm infants.

Direct imaging of the brain may shed light on mechanisms linking breast milk, brain growth, and neurodevelopment. In full-term infants, magnetic resonance imaging (MRI) of the brain demonstrated greater white matter development from 10 months to 4 years of age[11] and at 8 years of age[12]; and greater cortical thickness in adolescence[13] in relation to early breastfeeding exposure. In preterm infants,

MRI Magnetic resonance imaging

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one small study[14] (n = 50) found positive correlations of breast milk intake with total brain volume at 15 years of age. Another study[15] of preterm infants reported that greater breast milk intake was associated with improved corpus callosum maturation at term equivalent age (40 weeks postmenstrual age), but infants were not followed beyond neonatal discharge. Additional research is needed to determine the extent to which breast milk intake during the neonatal period affects the preterm infant brain and whether effects persist beyond the newborn period.

Our aims in this study were to examine associations of breast milk intake during the neonatal hospitalization with brain MRI characteristics at term equivalent and 7 years of age and neurodevelopmental outcomes at 2 and 7 years of age.

## Methods

We studied participants in the Victorian Infant Brain Studies longitudinal cohort. Two hundred twenty-four infants born at <30 weeks' gestation or <1250 grams birth weight were enrolled before term equivalent age at the Royal Women's Hospital in Melbourne, Australia between July 2001 and December 2003. Exclusion criteria included congenital anomalies likely to affect brain development or function. Parents provided informed consent for their children to participate.

The Royal Women's Hospital and Royal Children's Hospital institutional review boards approved the study. For this analysis, we excluded 44 participants owing to missing breast milk data. The remaining 180 participants had available data for ≥1 outcome (n = 160 with term equivalent brain MRI; n = 173 with 2-year Bayley testing; n = 108 with 7-year brain MRI; and n = 161 with 7-year neurocognitive testing) and were included in the present analysis.

### Breast Milk Intake

Study staff abstracted the daily volume of breast milk and formula intake for the first 28 days of life from the medical record. We focused on breast milk intake in the first 28 days with the goal of minimizing attrition owing to early transfer or discharge that could bias results. In a subset of 20 randomly selected participants, we abstracted data on breast milk intake (mL/kg/d) through day 40, and found a strong correlation with intake from birth to 28 days (Pearson $r = 0.95$). Breast milk was fortified according to unit-based practice. Preterm formula was used when a mother's own breast milk was unavailable or in short supply; donor breast milk was not used.

### Brain MRI at Term Equivalent and 7 Years of Age

At term equivalent age (range, 3-42 weeks postmenstrual age), participants underwent brain MRI in a 1.5-T General Electric scanner (Signa Echospeed System; Milwaukee, Wisconsin). Infants were fed, swaddled, and placed in a supportive beanbag. No analgesia or sedation was given. $T_1$ and $T_2$/proton density-weighted images were acquired.[16] Structural images were semi-automatically segmented into white matter (unmyelinated, myelinated), cortical gray matter, deep nuclear gray matter (including basal ganglia and thalamus), and cerebrospinal fluid.[17,18] Hippocampi and cerebella were traced manually.[19,20]

At 7 years of age (range, 6.6-8.1), participants again underwent brain MRI. Children were scanned on a 3-esla Siemens Magnetom Trio scanner, with $T_1$-weighted images acquired (0.85 mm sagittal slices, flip angle = 9°, repetition time = 1900 ms, echo time = 2.27 ms, field of view = 210 × 210 mm, matrix = 256 × 256). Brain volumes were obtained using FreeSurfer, an automated imaging processing package (stable release version 4.4.0, http://surfer.nmr.mgh.harvard.edu), with manual editing as required. Cortical and cerebellar gray and white matter, and deep nuclear gray matter (thalamus, nucleus accumbens, caudate, putamen, pallidum) were estimated and volumes combined from both hemispheres. Cerebellar volume was calculated as the total cerebellar white plus gray matter. Total brain volume was the combined volumes of all brain structures. Hippocampi were traced manually.[21]

### Neurodevelopmental Assessments at 2 and 7 Years of Age

Trained examiners administered the Bayley Scales of Infant Development, 2nd edition (Bayley-2) when children were 2 years of corrected age. The Bayley-2 comprises the Mental Development Index, which measures cognition, and the Psychomotor Development Index, which measures motor skills. Domains tested at 7 years of age included general intelligence (Wechsler Abbreviated Scale of Intelligence),[22] academic achievement (Word Reading and Math Computation subtests of the Wide Range Achievement Test),[23] attention (score subtest of the Test of Every Day Attention for Children),[24] working memory (Backward Digit Recall subtests of the Working Memory Test Battery for Children),[25] language (Core Language Index from the Clinical Evaluation of Language Fundamentals),[26] visual perception (Visual Closure subtest of the Test of Visual Perceptual Skills),[27] and motor function (Movement Assessment Battery for Children).[28] Higher scores on all of these measures indicate better performance. Scores from the Bayley-2, Wechsler Abbreviated Scale of Intelligence, Wide Range Achievement Test, Working Memory Test Battery for Children, and Clinical Evaluation of Language Fundamentals were age-standardized to a mean of 100 and SD of 15; the remaining tests were standardized to a mean of 10 (SD 3). We used corrected age for all scores. On the Bayley-2, children who fell below the basal threshold for testing were assigned a score of 45; children too impaired for testing were assigned a score of 40.

Covariates included infant sex, gestational age, exposure to antenatal or postnatal corticosteroids, supplemental oxygen requirement at 36 weeks, and diagnosis of sepsis or necrotizing enterocolitis were abstracted from the medical record. The Clinical Risk Index for Babies score is an illness severity indicator.[29] We calculated a social risk score comprising maternal age, parent marital status, education level of baby's primary caregiver, employment status and income of primary income earner, and language spoken at home.[30] Participants were categorized as being of lower (score, 0 or 1) or higher (score, ≥2) social risk. Using infant weight obtained with a digital scale at birth and



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at the time of the term equivalent MRI, we calculated the weight *z*-score change from birth to term equivalent age.[31]

### Statistical Analyses

We calculated 2 measures of breast milk intake: number of days on which the infant received >50% of enteral intake as breast milk and mean daily breast milk intake (mL/kg/d). Main outcomes were regional brain volumes (term equivalent and 7 years of age) and neurodevelopmental test scores (2 and 7 years of age). We estimated associations between exposures and outcomes in linear regression, fitted using generalized estimating equations with an exchangeable correlation structure to account for clustering owing to multiple births. In model 0, we adjusted for the child's sex, exact age at scan or assessment, and gestational age at birth. In model 1, we additionally adjusted for social risk score (higher vs lower), and in model 2 we additionally included variables that reflect neonatal illness severity. In model 3 we included neonatal weight gain (a proxy for nutritional adequacy) to explore its mediating effect, hypothesizing that adjusting for weight *z*-score change from birth to term would strengthen associations of breast milk intake with outcomes, given associations of breast milk intake with slower weight gain[9] and slower weight gain with poorer developmental outcomes.[32,33]

## Results

**Table I** shows characteristics of our participants, who had rates of perinatal complications and long-term outcomes typical of their immaturity (mean [SD] gestational age, 27.3 [1.8] weeks) at birth. The mean number of days from day 0-28 on which infants received breast milk as >50% of their feedings was 21 (SD 7). Mean breast milk intake in the first 28 days was 90 mL/kg/d (SD 43). Multiple gestations comprised 45% of the cohort. As compared with singletons, mean breast milk intake for multiples was slightly lower (86 mL/kg/d).

**Table II** shows the linear associations of the estimated brain volumes at term equivalent with the number of days on which breast milk comprised >50% of enteral intake during the first 28 days of life. In a model adjusted only for age, sex, and gestational age at birth (model 0), for each additional day of breast milk >50% of intake, the deep nuclear gray matter volume was 0.11 cc/d greater 95% CI, 0.02-0.20). This association persisted after additional adjustment for social risk score (model 1) and markers of neonatal illness (model 2, 0.15 cc/d; 95% CI, 0.05-0.25). Additionally adjusting for neonatal weight gain (model 3) did not change these estimates. Other brain volumes were not associated substantially with days of breast milk intake of >50% (**Table II**). In **Table III** (available at www.jpeds.com), we show associations of average daily breast milk intake on days 0-28 with brain volumes at term, with evidence for a relationship with hippocampal volume (0.02 cc per 10 mL/kg/d breast milk; 95% CI, 0.01-0.03) that persisted after adjustment for covariates. Associations of average daily breast milk intake with other brain volumes seemed to be minimal (**Table III**).

In **Table IV**, we show associations of breast milk intake with estimated brain volumes at 7 years of age. With adjustment for age, sex, and gestational age, the intracranial volume was larger (2.67 cc/d that breast milk >50% of intake; 95% CI, 0.37-4.97). With adjustment for social risk and neonatal illness, the estimate remained similar (2.42 cc/d), but the 95% CI

**Table I. Patient characteristics (n = 180)**

| | Mean (SD) |
|---|---|
| Gestational age at birth, weeks | 27.3 (1.8) |
| Birth weight, g | 947 (210) |
| Weight *z*-score change, birth to term | –1 (1.5) |
| | **Median (IQR)** |
| Clinical Risk Index for Babies[28] score | 3 (1, 6) |
| | **Number (%)** |
| Sex | |
| Male | 88 (49) |
| Female | 92 (51) |
| Multiple gestation | 81 (45) |
| Antenatal corticosteroids | 162 (91) |
| Neonatal illness | |
| Supplemental oxygen dependency at 36 weeks* | 61 (34) |
| Postnatal corticosteroids | 17 (9) |
| Sepsis (proven or suspected) | 66 (37) |
| Necrotizing enterocolitis | 20 (11) |
| Social risk score[29] | |
| Low | 63 (40) |
| High | 94 (60) |
| | **Mean (SD)** |
| Number of days breast milk >50%, 0-28 d | 21 (7) |
| Mean breast milk intake, 0-28 d | 90 (43) |
| Brain volumes at term equivalent, cc | |
| Intracranial volume | 441 (67) |
| Total brain volume | 394 (58) |
| Total gray matter | 157 (39) |
| Total white matter | 223 (31) |
| Myelinated white matter | 9.8 (4.6) |
| Unmyelinated white matter | 213 (31) |
| Deep nuclear gray matter | 13.4 (3.8) |
| Cerebellum | 21.2 (3.8) |
| Hippocampus | 2.2 (0.3) |
| Bayley-2 scores at 2 years corrected age | |
| Mental Development Index | 84 (20) |
| Psychomotor Development Index | 88 (17) |
| Brain volumes at 7 years, cc | |
| Intracranial volume | 1326 (118) |
| Total brain volume | 1258 (112) |
| Total gray matter | 783 (68) |
| Total white matter | 400 (45) |
| Deep nuclear gray matter | 36.3 (3.2) |
| Cerebellum | 147 (14) |
| Hippocampus | 6.5 (0.7) |
| Neurodevelopment at 7 years | |
| General intelligence (WASI) | |
| Full scale IQ | 97 (14) |
| Performance IQ | 97 (14) |
| Verbal IQ | 96 (14) |
| Word Reading (WRAT4) | 99 (19) |
| Math Computations (WRAT4) | 89 (17) |
| Attention (TEA-Ch) | 7.6 (3.6) |
| Working memory (WMTBC) | 87 (16) |
| Language (CELF-IV) | 92 (17) |
| Visual perception (TVPS-3) | 8.3 (3.6) |
| Motor function (MABC2) | 8.6 (3.5) |

*CELF-IV*, Clinical Evaluation of Language Fundamentals[25]; *MABC2*, Movement Assessment Battery for Children[27]; *TEA-Ch*, Test of Every Day Attention for Children[23]; *TVPS-3*, Test of Visual Perceptual Skills[26]; *WASI*, Weschler Abbreviated Scale of Intelligence[21]; *WMTBC*, Working Memory Test Battery for Children[24]; *WRAT4*, Wide Range Achievement Test.[22] Higher scores on all of these measures indicate better performance. *Did not receive postnatal corticosteroids.



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**Table II. Number of days on which enteral intake was >50% breast milk and estimated brain volumes at term equivalent age**

| | Model 0 (n = 147) | | Model 1 (n = 133) | | Model 2 (n = 132) | | Model 3 (n = 131) | |
|---|---|---|---|---|---|---|---|---|
| | β indicates cc increment in estimated brain volume per 1 additional day on which breast milk was >50% of enteral intake during the first 28 days of life | | | | | | | |
| | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| Intracranial volume | −0.05 | −2.05, 1.05 | −0.22 | −1.93, 1.50 | −0.42 | −1.84, 0.99 | −0.30 | −1.57, 0.97 |
| Total brain size | −0.07 | −1.36, 1.22 | 0.18 | −1.25, 1.61 | 0.00 | −1.21, 1.21 | 0.06 | −1.06, 1.17 |
| Total gray matter | −0.29 | −1.12, 0.55 | −0.20 | −1.12, 0.73 | −0.32 | −1.17, 0.53 | −0.29 | −1.11, 0.52 |
| Total white matter | 0.10 | −0.58, 0.77 | 0.20 | −0.54, 0.94 | 0.17 | −0.48, 0.82 | 0.19 | −0.42, 0.81 |
| Myelinated white matter | −0.01 | −0.10, 0.09 | −0.03 | −0.12, 0.07 | −0.03 | −0.12, 0.07 | −0.02 | −0.12, 0.07 |
| Unmyelinated white matter | 0.10 | −0.56, 0.76 | 0.21 | −0.52, 0.94 | 0.17 | −0.46, 0.81 | 0.19 | −0.41, 0.79 |
| Deep nuclear gray matter | **0.11** | **0.02, 0.20** | **0.14** | **0.05, 0.23** | **0.15** | **0.05, 0.25** | **0.15** | **0.05, 0.25** |
| Cerebellum | 0.03 | −0.07, 0.12 | 0.04 | −0.06, 0.15 | 0.03 | −0.07, 0.12 | 0.03 | −0.06, 0.11 |
| Hippocampus | 0.003 | −0.004, 0.01 | 0.003 | −0.01, 0.01 | 0.001 | −0.01, 0.01 | 0.002 | −0.01, 0.01 |

Model 0 is adjusted for exact age at assessment, sex, gestational age at birth.
Model 1 = Model 0 + social risk score.
Model 2 = Model 1 + multiple gestation, Clinical Risk Index for Babies score, antenatal or postnatal corticosteroids, neonatal illness (supplemental oxygen dependency at 36 weeks, sepsis, or necrotizing enterocolitis).
Model 3 = Model 2 + birth-to-term weight z-score change.
Results presented in bold are statistically significant ($P < .05$).

included 0 (−0.19-5.04). We also observed a small association with hippocampal volume that was attenuated with covariate adjustment (Table IV). There was little evidence of associations between average daily breast milk intake and other regional brain volumes at 7 years of age (Table III).

There was also little evidence of associations between breast milk intake and Bayley scores at 2 years of age (Table V). Regarding 7-year outcomes, in model 0, the full-scale IQ was 0.5 points (95% CI 0.3-0.8) higher for each additional day of breast milk intake >50%; estimates were similar with additional adjustment for covariates (models 1-3). A similar pattern was observed for verbal and performance IQ, math computation, and working memory. Motor functioning was also higher with increasing days of breast milk >50% in covariate-adjusted models (Table IV); for example, 0.1 points per day (95% CI, 0.03-0.2) after adjustment for social risk and neonatal illness factors (model 2). In Table VI (available at www.jpeds.com), we show similar associations of full-scale IQ with average daily breast milk intake (0.7 points per 10 mL/kg/d; 95% CI, 0.1-1.3) that attenuated slightly with covariate adjustment. Positive associations of average daily breast milk intake with working memory were also noted, whereas greater breast milk intake was associated with lower visual perception scores (−0.2 points per 10 mL/kg/d; 95% CI, −0.3, −0.03 in Model 2; Table VI).

## Discussion

In a contemporary cohort of 180 very preterm infants, we found favorable associations of maternal breast milk intake in the first 28 days of life with neurodevelopmental outcomes at 7 years of age. For example, IQ was 0.5 points higher per additional day that breast milk intake was >50% of total enteral intake, and 0.7 points higher per additional 10 mL/kg/d breast milk ingested. Even if residual confounding explains some of this effect, our results nonetheless suggest a substantial impact of breast milk intake in the first month of life on very preterm infant neurodevelopment assessed at school age. We also saw associations of breast milk intake with size of the deep nuclear

**Table IV. Number of days on which enteral intake was >50% breast milk and estimated brain volumes at 7 years of age**

| | Model 0 (n = 108) | | Model 1 (n = 104) | | Model 2 (n = 103) | | Model 3 (n = 102) | |
|---|---|---|---|---|---|---|---|---|
| | β indicates cc increment in estimated brain volume per 1 additional day on which breast milk was >50% of enteral intake during the first 28 days of life | | | | | | | |
| | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| Intracranial volume | **2.67** | **0.37, 4.97** | **2.67** | **0.23, 5.10** | 2.42 | −0.19, 5.04 | 2.43 | −0.18, 5.04 |
| Total brain size | 2.04 | −0.06, 4.15 | 1.94 | −0.32, 4.20 | 1.77 | −0.86, 4.39 | 1.78 | −0.86, 4.41 |
| Total gray matter | 1.44 | −0.20, 3.07 | 1.39 | −0.32, 3.10 | 0.94 | −1.13, 3.01 | 0.94 | −1.15, 3.03 |
| Total white matter | 0.52 | −0.20, 1.23 | 0.49 | −0.25, 1.23 | 0.52 | −0.38, 1.42 | 0.53 | −0.38, 1.44 |
| Deep nuclear gray matter | 0.04 | −0.03, 0.11 | 0.03 | −0.04, 0.10 | −0.01 | −0.10, 0.07 | −0.01 | −0.10, 0.07 |
| Cerebellum | 0.09 | −0.23, 0.40 | 0.08 | −0.26, 0.41 | −0.13 | −0.48, 0.23 | −0.13 | −0.49, 0.23 |
| Hippocampus | **0.01** | **0.002, 0.03** | 0.01 | −0.002, 0.03 | 0.01 | −0.01, 0.03 | 0.01 | −0.01, 0.03 |

Model 0 is adjusted for exact age at assessment, sex, gestational age at birth.
Model 1 = Model 0 + social risk score.
Model 2 = Model 1 + multiple gestation, Clinical Risk Index for Babies score, antenatal or postnatal corticosteroids, neonatal illness (supplemental oxygen dependency at 36 weeks, sepsis, or necrotizing enterocolitis).
Model 3 = Model 2 + birth-to-term weight z-score change.
Results presented in bold are statistically significant ($P < .05$).



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**Table V. Number of days on which enteral intake was >50% breast milk and neurodevelopmental outcomes at 2 and 7 years of age**

| | | Model 0 (n = 150) | | Model 1 (n = 140) | | Model 2 (n = 136) | | Model 3 (n = 136) | |
|---|---|---|---|---|---|---|---|---|---|
| | | β indicates increment in test points per 1 additional day on which breast milk was >50% of enteral intake during the first 28 days of life | | | | | | | |
| | N | β | 95% CI | β | 95% CI | β | 95% CI | β | 95% CI |
| 2 Years | | | | | | | | | |
| Bayley MDI | 173 | 0.3 | –0.2, 0.8 | 0.4 | –0.1, 0.9 | 0.4 | –0.1, 1.0 | 0.4 | –0.1, 1.0 |
| Bayley PDI | 173 | 0.1 | –0.3, 0.6 | 0.1 | –0.3, 0.6 | 0.1 | –0.4, 0.6 | 0.1 | –0.4, 0.6 |
| 7 Years | | | | | | | | | |
| General intelligence (WASI) | | | | | | | | | |
| Full scale IQ | 154 | **0.5** | **0.3, 0.8** | **0.5** | **0.2, 0.8** | **0.5** | **0.2, 0.8** | **0.5** | **0.2, 0.8** |
| Verbal IQ | 156 | **0.4** | **0.1, 0.7** | **0.4** | **0.1, 0.7** | **0.4** | **0.1, 0.7** | **0.4** | **0.1, 0.8** |
| Performance IQ | 155 | **0.5** | **0.2, 0.8** | **0.5** | **0.2, 0.8** | **0.5** | **0.2, 0.8** | **0.5** | **0.2, 0.7** |
| Word Reading (WRAT4) | 153 | 0.5 | –0.03, 0.9 | 0.4 | –0.1, 0.9 | 0.5 | –0.03, 1.0 | 0.5 | –0.03, 1.0 |
| Math Computations (WRAT4) | 152 | **0.6** | **0.2, 0.9** | **0.5** | **0.1, 0.9** | **0.5** | **0.1, 0.9** | **0.5** | **0.1, 1.0** |
| Attention (TEA-Ch) | 148 | 0.1 | –0.04, 0.2 | 0.1 | –0.1, 0.2 | 0.02 | –0.1, 0.1 | 0.02 | –0.1, 0.1 |
| Working memory (WMTBC) | 144 | **0.5** | **0.1, 0.8** | **0.4** | **0.1, 0.8** | **0.5** | **0.1, 0.9** | **0.5** | **0.1, 0.9** |
| Language (CELF-IV) | 149 | 0.5 | –0.03, 1.0 | 0.4 | –0.1, 1.0 | 0.4 | –0.1, 1.0 | 0.5 | –0.1, 1.0 |
| Visual perception (TVPS-3) | 142 | 0.03 | –0.1, 0.1 | 0.01 | –0.1, 0.1 | –0.03 | –0.1, 0.09 | –0.01 | –0.1, 0.1 |
| Motor function (MABC2) | 136 | **0.1** | **–0.001, 0.2** | 0.1 | –0.01, 0.2 | **0.1** | **0.02, 0.2** | **0.1** | **0.03, 0.2** |

*MDI*, Mental Development Index.
Numbers in multivariable models are slightly lower owing to missing covariate data. Exact numbers are available upon request.
Model 0 is adjusted for exact age at assessment, sex, gestational age at birth.
Model 1 = Model 0 + social risk score.
Model 2 = Model 1 + multiple gestation, Clinical Risk Index for Babies score, antenatal corticosteroids, neonatal illness (chronic lung disease, sepsis, necrotizing enterocolitis).
Model 3 = Model 2 + birth-to-term weight *z*-score change.
Results presented in bold are statistically significant ($P < .05$).

gray matter and hippocampus at term equivalent age, although this effect was not present on brain volumes assessed at 7 years of age. Previous studies supporting the beneficial effects of breast milk intake on neurodevelopment in very preterm infants have examined infant or toddler outcomes,[10,34,35] which have limitations in the prediction of later cognitive abilities.[36,37] Assessment at school age as in the current study also allows for more detailed measurement of cognitive functioning, including memory, attention, and school achievement. These domains are particularly important to assess in very preterm infants, who are prone to difficulties in these areas.[38-41]

We identified only 2 studies[42,43] of very preterm or very low birth weight (<1500 g) infants born in 1990 or beyond that examined breast milk intake or breastfeeding in relation to school age neurodevelopmental measures, as we did in this study. An analysis[42] of data from the EPIPAGE cohort of French infants <33 weeks' gestation found that the risk of nonoptimal neurodevelopment at age 5 years was substantially lower (OR, 0.7; 95% CI, 0.5-0.9) for infants who were breastfeeding at the time of neonatal discharge versus not. A notable limitation of the EPIPAGE study was the method of categorizing infants based on any versus no breast milk at the time of discharge. That method could have led to an underestimation of the effect size if many of the infants who received breast milk early in the hospitalization were no longer receiving it at discharge. In contrast, we had detailed data about the amount of breast milk ingested during the first 28 days of life. Additionally, EPIPAGE[42] used as their outcome measure the Kaufman Assessment Battery for Children Mental Processing Composite, which reflects general intelligence. In addition to measures of IQ, our study found evidence of associations between breast milk intake and measures of word reading and mathematics, working memory, and motor function. Overall, it seems that greater exposure to breast milk is associated not only with higher general intelligence, but also with better academic achievement, memory, and motor function in children who were born very preterm.

In contrast with our results, a US study[43] of very low birth weight infants showed no advantages of feeding expressed breast milk or directly breast feeding through 6 months of age on a battery of tests at 6-8 years of age, including general intelligence, verbal ability, fine motor skills, and visual-spatial skills, and a small advantage on visual motor skill tests. A major difference from our study was their reliance on parental report of breastfeeding type and duration (<1 weeks, 1-4 weeks, 4-6 months, and ≥6 months), whereas we used the medical record to quantify the volume of breast milk ingested in the first 28 days of the neonatal hospitalization. It is possible that the preterm brain is more sensitive to the beneficial effects of breast milk earlier in development, specifically before term when developmental processes such as dendritic and axonal growth and synaptogenesis are ongoing and distinct from the processes that predominate after term, such as pruning and myelination.

In our study, there was little statistical evidence for associations between breast milk intake and Bayley scores at 2 years of age. However, the effect estimate for the Mental Development Index (0.4 points per day receiving >50% breast milk) was similar in magnitude to our estimate for IQ at 7 years (0.5 points per day), with more variability in estimates at 2 than at 7 years. In a larger (~1000 participants) US cohort[44] of extremely low birth weight (<1000 g) infants, for every 10 mL/kg average daily breast milk intake, the Mental Development

Index at 18 months was 0.5 points higher; our results were similar in magnitude (0.4 points higher). Some[10] but not all[34,45] previous studies have found similar results with outcomes measured in infancy through preschool age. Our study is unique in that we assessed the same children both at 2 and 7 years of age. In a previous analysis[2] of full-term children who underwent cognitive assessment at 3 and 7 years, we found beneficial effects of greater duration and exclusivity of breastfeeding on cognition at 7 but not 3 years of age. It is possible that assessment early in childhood is too soon to detect subtle effects of breast milk that are more evident at school age. It is also possible that the influence of the shared determinants of breastfeeding and neurodevelopment, such as environmental, social, and economic factors, increases over time.

Another feature of our study was the analysis of regional brain volumes in relation to early breast milk intake in very preterm infants. In particular, we found that a greater dose of breast milk (more days on which breast milk comprised >50% of intake) was associated with g deep nuclear gray matter. The thalamus and basal ganglia are the major relay stations in the brain[46] and are central to cortical connectivity and effective neural functioning. Reductions in thalamic and basal ganglia volumes have previously been associated with more impairments in functioning in preterm populations.[47-49] We also noted that greater average daily breast milk intake was associated with larger hippocampus volume at term equivalent. The hippocampus is important for memory and learning[50] and we have shown previously in this cohort that larger hippocampal volume is associated with better working memory,[51] with similar findings in another study of preterm adolescents.[52] Possibly related to our current finding of larger hippocampal volume associated with breast milk, we also noted better working memory in association with greater breast milk intake. Overall, these findings regarding volume of the deep nuclear gray matter and hippocampus may offer clues regarding mechanisms by which breast milk feeding influences later neurodevelopmental outcomes.

The strengths of our study include the high follow-up rate to 7 years, detailed measures of neurodevelopment, and brain MRIs performed at 2 time points. This study focused on regional volumetric outcome measures from structural MRI. Future analysis of data from our cohort in relation to breast milk intake could include diffusion measures that reflect white matter microstructural organization.[16] We could not assess brain growth during the neonatal hospitalization (eg, change in size from birth to term), which would be of interest given concerns that even fortified breast milk may not provide adequate nutrition for very preterm infants.[9,10,42] We focused on breast milk intake in the first 28 days of life, with the advantage that there was very little attrition owing to early transfer or discharge that could bias results. In a subset of our participants, intake during the first 28 days was highly correlated with intake later in the hospitalization; it is likely that continued breast milk intake beyond 28 days contributed to outcomes. A limitation is that we did not collect information about breast milk intake or breastfeeding after neonatal discharge. Additionally, like any observational study, ours is subject to residual confounding. It is notable that many of our estimates were unaffected by adjustment for social and other risks; however, we lacked data on maternal IQ or parenting style and therefore could not adjust for these potential confounders.

We found that greater breast milk feeding in the first 28 days of life was associated with greater deep nuclear gray matter and hippocampal volume at term equivalent age, and with higher IQ, academic achievement, working memory, and motor scores at 7 years of age in very preterm infants. These results provide support for national[53] and international[54] recommendations to provide breast milk as the primary diet for preterm infants. ■

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## References

1. Kramer MS, Aboud F, Mironova E, Vanilovich I, Platt RW, Matush L, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry 2008;65:578-84.
2. Belfort MB, Rifas-Shiman SL, Kleinman KP, Guthrie LB, Bellinger DC, Taveras EM, et al. Infant feeding and childhood cognition at ages 3 and 7 years: effects of breastfeeding duration and exclusivity. JAMA Pediatr 2013;167:836-44.
3. Smithers LG, Kramer MS, Lynch JW. Effects of breastfeeding on obesity and intelligence: causal insights from different study designs. JAMA Pediatr 2015;169:707-8.
4. Demmelmair H, Koletzko B. Importance of fatty acids in the perinatal period. World Rev Nutr Diet 2015;112:31-47.
5. Britton JR, Britton HL, Gronwaldt V. Breastfeeding, sensitivity, and attachment. Pediatrics 2006;118:e1436-43.
6. Rahkonen P, Heinonen K, Pesonen AK, Lano A, Autti T, Puosi R, et al. Mother-child interaction is associated with neurocognitive outcome in extremely low gestational age children. Scand J Psychol 2014;55:311-8.
7. Der G, Batty GD, Deary IJ. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis. BMJ 2006;333:945.
8. Kleinman RE. Pediatric nutrition handbook. 6th ed. Elk Grove Village, (IL): American Academy of Pediatrics; 2009.
9. Colaizy TT, Carlson S, Saftlas AF, Morriss FH Jr. Growth in VLBW infants fed predominantly fortified maternal and donor human milk diets: a retrospective cohort study. BMC Pediatr 2012;12:124.
10. O'Connor DL, Jacobs J, Hall R, Adamkin D, Auestad N, Castillo M, et al. Growth and development of premature infants fed predominantly human milk, predominantly premature infant formula, or a combination of human milk and premature formula. J Pediatr Gastroenterol Nutr 2003;37:437-46.
11. Deoni SC, Dean DC 3rd, Piryatinsky I, O'Muircheartaigh J, Waskiewicz N, Lehman K, et al. Breastfeeding and early white matter development: a cross-sectional study. Neuroimage 2013;82:77-86.
12. Ou X, Andres A, Cleves MA, Pivik RT, Snow JH, Ding Z, et al. Sex-specific association between infant diet and white matter integrity in 8-y-old children. Pediatr Res 2014;76:535-43.



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13. Kafouri S, Kramer M, Leonard G, Perron M, Pike B, Richer L, et al. Breastfeeding and brain structure in adolescence. Int J Epidemiol 2013;42:150-9.
14. Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of breast milk on intelligence quotient, brain size, and white matter development. Pediatr Res 2010;67:357-62.
15. Pogribna U, Yu X, Burson K, Zhou Y, Lasky RE, Narayana PA, et al. Perinatal clinical antecedents of white matter microstructural abnormalities on diffusion tensor imaging in extremely preterm infants. PLoS ONE 2013;8:e72974.
16. Thompson DK, Lee KJ, Egan GF, Warfield SK, Doyle LW, Anderson PJ, et al. Regional white matter microstructure in very preterm infants: predictors and 7 year outcomes. Cortex 2014;52:60-74.
17. Warfield S. Fast k-NN classification for multichannel image data. Pattern Recognit Lett 1996;17:713-21.
18. Warfield SK, Kaus M, Jolesz FA Kilinis R. Adaptive, template moderated, spatially varying statistical classification. Med Image Anal 2000;4:43-55.
19. Shah DK, Anderson PJ, Carlin JB, Pavlovic M, Howard K, Thompson DK, et al. Reduction in cerebellar volumes in preterm infants: relationship to white matter injury and neurodevelopment at two years of age. Pediatr Res 2006;60:97-102.
20. Thompson DK, Ahmadzai ZM, Wood SJ, Inder TE, Warfield SK, Doyle LW, et al. Optimizing hippocampal segmentation in infants utilizing MRI post-acquisition processing. Neuroinformatics 2012;10:173-80.
21. Omizzolo C, Thompson DK, Scratch SE, Stargatt R, Lee KJ, Cheong J, et al. Hippocampal volume and memory and learning outcomes at 7 years in children born very preterm. J Int Neuropsychol Soc 2013;19:1065-75.
22. Weschler D. Weschler Abbreviated Scale of Intelligence (WASI). The Psychological Corporation; 1999.
23. Wilkinson G, Robertson G. Wide range achievement test. 4th ed. Lutz, (FL): Psychological Assessment Resources; 2006.
24. Manly T, Anderson V, Nimmo-Smith I, Turner A, Watson P, Robertson IH. The differential assessment of children's attention: the Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. J Child Psychol Psychiatry 2001;42:1065-81.
25. Pickering SJ, Gathercole SE. Working memory test battery for children. London, UK: The Psychological Corporation; 2001.
26. Semel E, Wiig EH, Secord W. Clinical evaluation of language fundamentals. 4th ed. Marrackville, Australia: Harcourt Assessment; 2006 Australian standardized.
27. Martin N. Test of visual perceptual skills. 3rd ed. Novato, (CA): Academic Therapy Publications; 2006.
28. Henderson SE, Sugden DA, Barnett AL. Movement assessment battery for children. 2nd ed. London, UK: The Psychological Corporation; 2007.
29. The CRIB (Clinical Risk Index for Babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. Lancet 1993;342:193-8.
30. Roberts G, Howard K, Spittle AJ, Brown NC, Anderson PJ, Doyle LW. Rates of early intervention services in very preterm children with developmental disabilities at age 2 years. J Paediatr Child Health 2008;44:276-80.
31. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr 2013;13:59.
32. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253-61.
33. Belfort MB, Rifas-Shiman SL, Sullivan T, Collins CT, McPhee AJ, Ryan P, et al. Infant growth before and after term: effects on neurodevelopment in preterm infants. Pediatrics 2011;128:e899-906.
34. Pinelli J, Saigal S, Atkinson SA. Effect of breastmilk consumption on neurodevelopmental outcomes at 6 and 12 months of age in VLBW infants. Adv Neonatal Care 2003;3:76-87.
35. 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.
36. Luttikhuizen dos Santos ES, de Kieviet JF, Konigs M, van Elburg RM, Oosterlaan J. Predictive value of the Bayley scales of infant development on development of very preterm/very low birth weight children: a meta-analysis. Early Hum Dev 2013;89:487-96.
37. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. Pediatrics 2005;116:333-41.
38. Anderson PJ, Doyle LW. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. Pediatrics 2004;114:50-7.
39. Litt JS, Gerry Taylor H, Margevicius S, Schluchter M, Andreias L, Hack M. Academic achievement of adolescents born with extremely low birth weight. Acta Paediatr 2012;101:1240-5.
40. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta- analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics 2009;124:717-28.
41. Anderson PJ. Neuropsychological outcomes of children born very preterm. Semin Fetal Neonatal Med 2014;19:90-6.
42. Roze JC, Darmaun D, Boquien CY, Flamant C, Picaud JC, Savagner C, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. BMJ Open 2012;2:e000834.
43. Smith MM, Durkin M, Hinton VJ, Bellinger D, Kuhn L. Influence of breastfeeding on cognitive outcomes at age 6-8 years: follow-up of very low birth weight infants. Am J Epidemiol 2003;158:1075-82.
44. 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.
45. Furman L, Taylor G, Minich N, Hack M. The effect of maternal milk on neonatal morbidity of very low-birth-weight infants. Arch Pediatr Adolesc Med 2003;157:66-71.
46. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357-81.
47. Inder TE, Warfield SK, Wang H, Hüppi PS, Volpe JJ. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005;115:286-94.
48. Lind A, Parkkola R, Lehtonen L, Munck P, Maunu J, Lapinleimu H, et al. Associations between regional brain volumes at term-equivalent age and development at 2 years of age in preterm children. Pediatr Radiol 2011;41:953-61.
49. Zubiaurre-Elorza L, Soria-Pastor S, Junqué C, Fernandez-Espejo D, Segarra D, Bargalló N, et al. Thalamic changes in a preterm sample with periventricular leukomalacia: correlation with white-matter integrity and cognitive outcome at school age. Pediatr Res 2012;71:354-60.
50. Cabeza R, Nyberg L. Neural bases of learning and memory: functional neuroimaging evidence. Curr Opin Neurol 2000;13:415-21.
51. Beauchamp MH, Thompson DK, Howard K, Doyle LW, Egan GF, Inder TE, et al. Preterm infant hippocampal volumes correlate with later working memory deficits. Brain 2008;131:2986-94.
52. Isaacs EB, Lucas A, Chong WK, Wood SJ, Johnson CL, Marshall C, et al. Hippocampal volume and everyday memory in children of very low birth weight. Pediatr Res 2000;47:713-20.
53. American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827-41.
54. World Health Organization. Mother's milk for low-birth-weight infants. http://www.who.int/elena/titles/mothersmilk_infants/en/. Accessed November 16, 2016.

**Table III. Average breast milk intake in the first 28 days of life and brain volumes at term equivalent and 7 years of age**

| | Model 0 (n = 96) | Model 1 (n = 85) | Model 2 (n = 84) | Model 3 (n = 84) |
|---|---|---|---|---|
| | β (95% CI) indicates estimated cc increment in brain volume per additional 10 mL average breast milk intake in the first 28 days of life | | | |
| Term equivalent | | | | |
| Intracranial volume | 0.01 (–2.78, 2.80) | 0.81 (2.24, 3.87) | 0.13 (–2.49, 2.76) | –0.28 (–2.74, 2.18) |
| Total brain size | 0.89 (–1.40, 3.17) | 1.54 (–0.87, 3.95) | 1.33 (–0.76, 3.42) | 1.12 (–0.88, 3.12) |
| Total gray matter | –0.02 (–1.48, 1.44) | 0.06 (–1.48, 1.61) | 0.71 (–0.64, 2.07) | 0.65 (–0.76, 2.06) |
| Total white matter | 0.60 (–0.85, 2.05) | 0.97 (–0.64, 2.57) | 0.77 (–0.64, 2.19) | 0.70 (–0.69, 2.08) |
| Myelinated white matter | –0.07 (–0.25, 0.11) | –0.09 (–0.27, 0.10) | –0.10 (–0.27, 0.07) | –0.11 (–0.28, 0.05) |
| Unmyelinated white matter | 0.67 (–0.78, 2.12) | 1.06 (–0.54, 2.65) | 0.88 (–0.53, 2.29) | 0.82 (–0.57, 2.21) |
| Deep nuclear gray matter | 0.06 (–0.11, 0.23) | 0.12 (–0.05, 0.29) | 0.14 (–0.03, 0.30) | 0.13 (–0.03, 0.29) |
| Cerebellum | 0.08 (–0.05, 0.22) | 0.10 (–0.05, 0.25) | 0.08 (–0.05, 0.21) | 0.06 (–0.05, 0.17) |
| Hippocampus | **0.02 (0.002, 0.03)** | **0.02 (0.01, 0.04)** | **0.02 (0.004, 0.03)** | **0.02 (0.003, 0.03)** |
| 7 years | | | | |
| Intracranial volume | 1.72 (–3.87, 7.32) | 1.96 (–3.74, 7.66) | 1.60 (–4.11, 7.31) | 1.93 (–3.97, 7.82) |
| Total brain size | 0.33 (–5.14, 5.81) | 0.54 (–4.89, 5.96) | 0.12 (–5.70, 5.93) | 0.43 (–5.54, 6.41) |
| Total gray matter | 0.19 (–3.48, 3.86) | 0.42 (–3.10, 3.94) | –2.45 (–7.62, 2.72) | –0.35 (–4.83, 4.12) |
| Total white matter | 0.09 (–2.14, 2.32) | 0.06 (–2.16, 2.28) | 0.16 (–1.99, 2.32) | 0.17 (–2.05, 2.40) |
| Deep nuclear gray matter | –0.01 (–0.15, 0.14) | –0.01 (–0.16, 0.15) | 0.00 (–0.15, 0.15) | –0.01 (–0.17, 0.14) |
| Cerebellum | –0.30 (–0.94, 0.33) | –0.31 (–0.95, 0.33) | –0.25 (–0.84, 0.35) | –0.34 (–0.97, 0.29) |
| Hippocampus | 0.01 (–0.02, 0.04) | 0.00 (–0.03, 0.04) | 0.00 (–0.03, 0.03) | –0.00 (–0.04, 0.03) |

Model 0 is adjusted for exact age at assessment, sex, gestational age at birth.
Model 1 = Model 0 + social risk score.
Model 2 = Model 1 + multiple gestation, Clinical Risk Index for Babies score, antenatal or postnatal corticosteroids, neonatal illness (supplemental oxygen dependency at 36 weeks, sepsis, or necrotizing enterocolitis).
Model 3 = Model 2 + birth-to-term weight *z*-score change.
Results presented in bold are statistically significant ($P < .05$).

**Table VI. Average breast milk intake in the first 28 days of life and neurodevelopmental outcomes at 2 and 7 years of age**

| | | Model 0 | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|---|
| | n | β (95% CI) indicates estimated increment in test points per additional 10 mL average breast milk intake in the first 28 days of life | | | |
| 2 Years | | | | | |
| Bayley MDI | 116 | 0.4 (–0.5, 1.3) | 0.5 (–0.3, 1.2) | 0.4 (–0.3, 1.2) | 0.5 (–0.3, 1.2) |
| Bayley PDI | 116 | –0.02 (–0.7, 0.7) | 0.2 (–0.5, 0.8) | –0.01 (–0.6, 0.6) | –0.1 (–0.6, 0.5) |
| 7 Years | | | | | |
| General intelligence (WASI) | | | | | |
| Full scale IQ | 105 | **0.7 (0.1, 1.3)** | **0.7 (0.1, 1.3)** | **0.7 (0.1, 1.3)** | **0.7 (0.1, 1.2)** |
| Verbal IQ | 105 | 0.5 (–0.1, 1.1) | 0.6 (–0.02, 1.2) | 0.5 (–0.03, 1.1) | **0.6 (0.02, 1.2)** |
| Performance IQ | 106 | 0.6 (–0.002, 1.2) | 0.5 (–0.1, 1.2) | 0.6 (–0.1, 1.1) | 0.5 (–0.1, 1.0) |
| Word Reading (WRAT4) | 103 | 0.2 (–0.5, 0.9) | 0.2 (–0.6, 1.0) | 0.2 (–0.6, 0.9) | 0.3 (–0.5, 1.0) |
| Math Computations (WRAT4) | 103 | **0.7 (0.002, 1.4)** | 0.6 (–0.1, 1.4) | 0.6 (–0.2, 1.3) | 0.5 (–0.2, 1.3) |
| Attention (TEA-Ch) | 99 | 0.1 (–0.1, 0.3) | 0.08 (–0.1, 0.3) | 0.1 (–0.2, 0.3) | 0.04 (–0.2, 0.2) |
| Working memory (WMTBC) | 97 | **0.9 (0.1, 1.7)** | **0.8 (0.1, 1.5)** | **0.8 (0.1, 1.5)** | **0.8 (0.1, 1.6)** |
| Language (CELF-IV) | 100 | 0.1 (–0.7, 0.8) | 0.1 (–0.7, 0.8) | 0.1 (–0.7, 0.8) | 0.1 (–0.6, 0.8) |
| Visual perception (TVPS-3) | 100 | –0.1 (–0.3, 0.01) | –0.1 (–0.3, 0.01) | **–0.2 (–0.3, –0.03)** | **–0.2 (–0.3, –0.04)** |
| Motor ability (MABC2) | 93 | 0.1 (–0.02, 0.3) | 0.1 (–0.03, 0.3) | 0.1 (–0.0, 0.3) | 0.1 (–0.01, 0.3) |

*CELF-IV*, Clinical Evaluation of Language Fundamentals[25]; *CI*, confidence interval; *MABC2*, Movement Assessment Battery for Children[27]; *MDI*, Mental Development Index; *TEA-Ch*, Test of Every Day Attention for Children[23]; *TVPS-3*, Test of Visual Perceptual Skills[26]; *WASI*, Weschler Abbreviated Scale of Intelligence[21]; *WMTBC*, Working Memory Test Battery for Children[24]; *WRAT4*, Wide Range Achievement Test.[22] Higher scores indicate better performance.
Numbers in multivariable models are slightly lower owing to missing covariate data. Exact numbers are available upon request.
Model 0 is adjusted for exact age at assessment, sex, gestational age at birth.
Model 1 = Model 0 + social risk score.
Model 2 = Model 1 + multiple gestation, Clinical Risk Index for Babies score, antenatal or postnatal corticosteroids, neonatal illness (supplemental oxygen dependency at 36 weeks, sepsis, or necrotizing enterocolitis).
Model 3 = Model 2 + birth-to-term weight *z*-score change.
Results presented in bold are statistically significant ($P < .05$).



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