Breastfeeding and motor development in term and preterm infants in a longitudinal US cohort

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ABSTRACT

Background: The relation between breastfeeding and early motor development is difficult to characterize because of the problems in existing studies such as incomplete control for confounding, retrospective assessment of infant feeding, and even the assessment of some motor skills too early.

Objective: We sought to estimate associations between infant feeding and time to achieve major motor milestones in a US cohort.

Design: The Upstate New York Infant Development Screening Program (Upstate KIDS Study) enrolled mothers who delivered live births in New York (2008–2010). Mothers of 4270 infants (boys: 51.7%) reported infant motor development at 4, 8, 12, 18, and 24 mo postpartum; information on infant feeding was reported at 4 mo. Accelerated failure time models were used to compare times to standing or walking across feeding categories while adjusting for parental characteristics, daycare, region, and infant plurality, sex, rapid weight gain, and baseline neurodevelopmental test results. Main models were stratified by preterm birth status.

Results: The prevalence of exclusive breastfeeding in preterm infants was lower than in term infants at 4 mo postpartum (8% compared with 19%). After adjustment for confounders, term infants who were fed solids in addition to breast milk at 4 mo postpartum achieved both standing [acceleration factor (AF): 0.93; 95% CI: 0.87, 0.99] and walking (AF: 0.93; 95% CI: 0.88, 0.98) 7% faster than did infants who were exclusively breastfed, but these findings did not remain statistically significant after correction for multiple testing. We did not identify feeding-associated differences in motor milestone achievement in preterm infants.

Conclusion: Our results suggest that differences in feeding likely do not translate into large changes in motor development. The Upstate KIDS Study was registered at clinicaltrials.gov as NCT03106493. *Am J Clin Nutr* 2017;106:1456–62.

Keywords: breastfeeding, infant nutritional physiological phenomena, longitudinal studies, motor skills, infant formula, premature birth

INTRODUCTION

Breastfeeding is beneficial to infant health for numerous reasons. Breast milk provides nutrition and energy and contains hormones, growth factors, antibodies, and long-chain fatty acids that aid in growth and development (1). Some studies have shown that breastfeeding is associated with aspects of neurodevelopment such as improved cognition (2) although a recent analysis in the Generation R cohort suggested that differences in child intelligence quotients are minimal after controlling for confounding (3). The relation between infant feeding and motor development is also of interest because early motor development may be associated with language development and cognitive ability (4, 5). The evidence linking breastfeeding with early motor development has been mixed, with some studies showing improved motor development in breastfed infants and toddlers (6–8) but other studies showing no associations or, specifically, no improvement in gross motor development (9–11). The relation between breastfeeding and the attainment of motor skills is difficult to characterize because of problems that are common in studies, such as incomplete control for confounding, retrospective exposure assessment, varying assessment of motor skills across studies, and even the assessment of some motor skills too early (10).

Note that previous studies on breastfeeding and motor development have often excluded preterm infants. However, these infants are of particular interest because the second half of pregnancy is a crucial time for brain development, and both gyral formation and myelination begin during this period (12). Preterm infants may miss in utero influences on brain development in late pregnancy, and this may, in turn, influence cognitive and motor development. Relative to term children, preterm children tend to be at risk of motor and cognitive impairments (13). Furthermore, evidence has suggested that preterm breast milk, which often requires fortification, is compositionally different from term milk (14).

With the use of data from a contemporary, prospective cohort, we examined the relation between infant feeding and the age of

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achieving motor milestones longitudinally over the first 2 y of life in both term and preterm infants.

METHODS

Study population

The Upstate New York Infant Development Screening Program (Upstate KIDS Study) is a prospective population-based birth cohort that was designed to study infertility treatment and child development (15). The cohort included live births that occurred between July 2008 and May 2010 and was oversampled for births that were conceived with infertility treatment from New York State (with the exclusion of New York City); recruitment began in September 2008. Women who had singleton live births after conceiving with fertility treatment were invited to enroll in the study, and a random sample of births that were conceived without fertility treatment (1:3 ratio) was frequency matched on the prenatal care region. Mothers of twin live births were invited to enroll regardless of the mode of conception. Study data were compiled from vital records, hospital-discharge data, and maternal self-reports (multiple questionnaires were completed every 4–6 mo postpartum and continued until 36 mo postpartum). The Upstate KIDS Study was registered at clinicaltrials.gov as NCT03106493.

These analyses included data from all singletons and one random twin from twin sets; these infants were born to unique mothers (i.e., no sibling enrollments). We excluded mothers who did not complete the baseline questionnaire (4 mo postpartum) on which infant feeding practices were queried (n = 380). We also excluded infants with conditions that could be associated with both feeding and motor-development difficulties (e.g., Down syndrome and metabolic disorders; n = 52). Finally, infants who were missing all outcome data (i.e., age of standing or walking; n = 2) or feeding information (n = 267) were excluded (**Supplemental Figure 1**). Our final analytic sample contained data from 4270 infant-mother dyads. All participants provided informed consent, and study procedures were approved by the New York State Department of Health and University of Albany institutional review boards (07–097 and 08–179, respectively).

Infant feeding

Our primary exposure of interest was infant feeding at 4 mo postpartum. We initially categorized feeding as exclusive breastfeeding, mixed feeding (breastfeeding and formula feeding), and exclusive formula feeding, and these feeding groups were dichotomized according to whether solid foods were also being provided. Exclusive breastfeeding was our reference group. There were no infants who were fed only solid foods at 4 mo postpartum.

Motor-development outcomes

Mothers reported the dates of their children's achievements of motor milestones on questionnaires sent ∼4, 8, 12, 18, and 24 mo postpartum. In these analyses, milestones of interest were standing and walking without assistance. These reported dates were used to calculate the age at which a milestone was achieved. When exact dates of achievement were unavailable, the observations were censored to retain all possible information rather than being removed. Observations were interval censored if the achievement of a milestone was indicated without a date; the age of the infant when the questionnaire reporting the achievement was received was used as an upper bound for the interval, and the age corresponding to the receipt date of the previously returned questionnaire was used as the lower bound. If the questionnaire indicating the achievement was not preceded by an earlier questionnaire indicating the milestone had not yet been achieved, the observation was left censored. For mothers who did not indicate a milestone achievement by the last received questionnaire, the observation was right censored. The number of observations that were classified as noncensored, interval censored, right censored, or left censored are provided in the footnotes of our tables. All participants turned in the 4-mo questionnaire in these analyses; missingness in the analytic population was 26%, 34%, 45%, and 51% on the subsequent questionnaires, respectively.

WHO guidelines for windows of motor milestone achievement were used to determine cutoffs for outlier ages at which milestones were achieved (the first percentile, specifically) (16). Infants whose mothers provided dates for a milestone achievement at $<$7 mo of age for standing or at $<$8 mo of age for walking were classified as missing these outcomes (n = 62 and n = 40, respectively). These cutoffs also helped to minimize recall bias such that all exposure (feeding) information was obtained before the reporting of motor development. Infants who were reported to have achieved these milestones at $>$27 mo of age were classified as outliers and missing an outcome (n = 1 and n = 4 for standing and walking, respectively). In addition, in infants who achieved milestones, but an exact age was not indicated, upper bounds were censored for 17 infants for standing and for 19 infants for walking because they occurred at $>$27 mo of age. Therefore, the total follow-up time for a milestone achievement was $\leq$27 mo of age.

Covariates

We obtained information on covariates from maternal reports or vital records. Potential confounders were selected via knowledge of the literature and directed acyclic graphs (i.e., causal diagrams). These covariates included maternal factors including age (vital records), race (self-report or vital records if missing), BMI (in kg/m^2; maternal report), education (maternal report or vital records if missing), marital status (maternal report), private insurance status (vital records), parity (vital records), and postpartum depression (maternal report); paternal factors including age (vital records) and education (maternal report); and infant characteristics such as plurality and sex (both from vital records), rapid weight gain in the first 4 mo postpartum (derived from maternal report) (17), Ages and Stages Questionnaire pass or fail status at 4 mo postpartum (maternal report), daycare initiation by 8 mo postpartum (maternal report), and conception via fertility treatment (maternal report or birth certificates if missing).

Statistical analyses

To examine and compare the ages at which motor milestones were achieved across infant feeding groups, we used accelerated failure time models. These parametric survival models minimized missing outcome data because they allowed for uncensored, interval-censored, right-censored, or left-censored data. Otherwise, these were complete-case analyses. We chose a log-logistic distribution for all models after comparing Akaike's information criterion across adjusted models with other distributions. Estimated effects from the accelerated failure time models are reported as acceleration factors (AFs) with corresponding 95% CIs. An AF provided the estimate of the effect of feeding on the survival time; an AF=1 indicated no difference in survival time or time to achieve a milestone. An AF >1 indicated that the time to achieve a milestone was stretched out or longer in infants in a feeding group (e.g., exclusively formula fed) than in infants who were exclusively breastfed at 4 mo postpartum. An AF <1 indicated a shorter time to achieve a milestone.

Stabilized inverse probability of exposure weights were used to account for potential mediating factors that may also have acted as confounders; all potential confounders as well as prenatal care regions were used for weighting (i.e., weights for the probability of an infant being in a specific feeding group) (18, 19). These variables were used to weight the data rather than being included as covariates in the final models.

Because of the important influence of gestational age at delivery on infant neurodevelopment (13), we made an a priori decision to stratify our results by preterm birth status (gestational age at delivery <37 wk compared with infants who were born ≥37 wk of gestation from vital records). We also performed secondary analyses in preterm infants who were stratified by early preterm birth (<34 wk of gestation) and late preterm birth (≥34 and <37 wk of gestation). We assessed the statistical interaction between preterm birth status and infant feeding for each outcome by examining a likelihood ratio test comparing models with and without interaction terms.

Median ages for motor milestone achievement were calculated for each feeding group in term and preterm infants with the use of unadjusted model variables and the formula that was specific to log-logistic accelerated failure time models described by Kleinbaum and Klein (20). All analyses were performed with SAS 9.4 software (SAS Institute Inc.).

RESULTS

The most common form of infant feeding at 4 mo postpartum was formula and solids (n = 1659; 39%). Mothers in this group were more likely to be <28 y of age than mothers in all other feeding groups (**Table 1**); these mothers were also more likely to have BMI >29.9 and have completed fewer years of education and less likely to have private insurance than were mothers who were exclusively breastfeeding. Mothers who were breastfeeding, providing formula, and providing solids were more likely to be nulliparous. Postpartum depression was more prevalent in mothers who were not breastfeeding (22.9% in women who exclusively provided formula and 25.1% in those who provided formula and solids). The prevalence of preterm birth was lowest in women who were not providing formula (8.4% in those who were exclusively breastfeeding and 9.1% in those who were providing breastfeeding and solids). Similarly, the prevalence of twins and rapid infant weight gain in the first 4 mo postpartum were lowest in these feeding groups.

The prevalence of preterm birth in our analytic population was 17% (n = 737 of 4270); 28% of preterm infants were early preterm (<34 wk; n = 209). Preterm delivery was associated with maternal age >33 y, having private insurance, and being parous (not tabled). The prevalence of twins was highest in preterm infants as were rapid weight gain in the first 4 mo postpartum, conception with fertility treatment, and formula use with the addition of solid foods.

We identified a statistical interaction between preterm birth and infant feeding for the time to walking (P = 0.081) but not for the time to standing (P = 0.828). The median age to achieve standing without assistance was ∼12 mo in term infants, whereas the median age in preterm infants was slightly older by 1–2 mo (**Table 2**). After adjustment for confounders, infants who were fed solids in addition to breast milk achieved standing 7% faster than did infants who were exclusively breastfed at 4 mo postpartum (AF: 0.93; 95% CI: 0.87, 0.99). We did not identify other statistically significant differences in the time to standing by feeding group in term or preterm infants. Although estimates were imprecise, the AF magnitudes suggested null or minimal differences in times to achieve standing across all feeding groups relative to exclusive breastfeeding regardless of preterm status (Table 2).

Similar observations were made with regard to walking without assistance (**Table 3**). The median age to achieve walking was 13–14 mo in term infants and 15–16 mo in preterm infants. After adjustment, a faster achievement of walking was identified in term infants who were breastfed and given solids (AF: 0.93; 95% CI: 0.88, 0.98). Again, our results suggest that differences in the achievement of walking that were due to feeding were minimal in both term and preterm infants.

In secondary analyses, we stratified the preterm birth group into early preterm and late preterm (**Supplemental Table 1**). After adjustment, we observed that breastfeeding with formula use or with solids was associated with a faster time to standing in late-term infants than in infants who were exclusively breastfed. Faster times to walking were suggested but were imprecise in late-term infants. Several feeding practices were associated with slower times to standing and walking in early term infants. However, our reference group was small because only 7 exclusively breastfed, early term infants remained in our models after adjustment.

DISCUSSION

Overall, results from our cohort suggest that feeding differences at 4 mo postpartum likely do not greatly affect the timing of gross motor milestone achievement. In general, we observed no differences in ages of gross motor milestone achievement across infant feeding patterns although the feeding of solid foods in addition to breastfeeding was associated with slightly faster times to standing and walking in term infants. A direct comparison of the present study with previous reports should be made cautiously because of differences in study designs and adjustments. Several studies have reported no association between feeding and motor development (9–11), whereas other studies have shown that breastfeeding improves motor development (6–8). A retrospective exposure assessment and assessment of motor skills out of appropriate age ranges (e.g., querying breastfeeding and motor achievement at 9–12 mo postpartum), incomplete control for confounding (e.g., by paternal factors or postpartum depression), and not fully exploring the role of complementary feeding have been limitations in most of these studies. We were able to build on previous studies by controlling for sociodemographic factors of both parents, including information on multiple feeding

TABLE 1
Comparisons of study-population characteristics by feeding at 4 mo postpartum in the Upstate KIDS Study (2008–2010)[1]

	Exclusive breastfeeding (*n* = 715)	Breastfeeding and formula feeding (*n* = 360)	Breastfeeding and solids (*n* = 419)	Breastfeeding, formula feeding, and solids (*n* = 486)	Exclusive formula feeding (*n* = 631)	Formula feeding and solids (*n* = 1659)
Maternal characteristic, *n* (%)						
Age, y						
≤28	197 (27.6)	89 (24.7)	136 (32.5)	133 (27.4)	224 (35.5)	735 (44.3)
>28 and ≤33	271 (37.9)	125 (34.7)	161 (38.4)	175 (36.0)	203 (32.2)	484 (29.2)
>33	247 (34.6)	146 (40.6)	122 (29.1)	178 (36.6)	204 (32.3)	440 (26.5)
Race						
Non-Hispanic white	603 (84.3)	286 (79.4)	362 (86.4)	382 (78.6)	500 (79.2)	1334 (80.4)
Other	112 (15.7)	74 (20.6)	57 (13.6)	104 (21.4)	131 (20.8)	325 (19.6)
BMI post pregnancy, kg/m^2						
≤24.9	363 (52.8)	160 (48.2)	195 (49.1)	179 (39.4)	213 (35.6)	567 (35.9)
>24.9 and ≤29.9	201 (29.3)	106 (31.9)	124 (31.2)	153 (33.7)	173 (28.9)	414 (26.2)
>29.9	123 (17.9)	66 (19.9)	78 (19.7)	122 (26.9)	213 (35.6)	599 (37.9)
Missing	28	28	22	32	32	79
Education completed						
High school or less	65 (9.1)	41 (11.4)	36 (8.6)	54 (11.1)	140 (22.2)	409 (24.7)
More than high school and college or less	357 (49.9)	179 (49.7)	231 (55.1)	271 (55.8)	294 (46.6)	922 (55.6)
More than college	293 (41.0)	140 (38.9)	152 (36.3)	161 (33.1)	197 (31.2)	328 (19.8)
Marital status						
Married	677 (97.0)	321 (93.3)	381 (93.4)	436 (92.8)	529 (86.4)	1338 (83.3)
Not married	21 (3.0)	23 (6.7)	27 (6.6)	34 (7.2)	83 (13.6)	268 (16.7)
Missing	17	16	11	16	19	53
Private insurance status						
Has	598 (83.6)	291 (80.8)	349 (83.3)	408 (84.0)	459 (72.7)	1136 (68.5)
Does not have	117 (16.4)	69 (19.2)	70 (16.7)	78 (16.1)	172 (27.3)	522 (31.5)
Missing	0	0	0	0	0	1
Parity						
Nulliparous	417 (59.4)	198 (55.5)	218 (52.4)	230 (47.7)	350 (55.8)	892 (54.0)
Parous	285 (40.6)	159 (44.5)	198 (47.6)	252 (52.3)	277 (44.2)	760 (46.0)
Missing	13	3	3	4	4	7
Self-reported postpartum depression						
Yes	98 (14.0)	52 (15.0)	64 (15.8)	86 (18.0)	141 (22.9)	407 (25.1)
Missing	14	12	14	9	14	40
Paternal characteristic, *n* (%)						
Age, y						
≤30	203 (29.4)	91 (26.3)	138 (34.2)	129 (27.7)	208 (35.6)	624 (41.2)
>30 and ≤35	285 (41.3)	128 (37.0)	156 (38.7)	177 (38.1)	196 (33.6)	505 (33.4)
>35	202 (29.3)	127 (36.7)	109 (27.1)	159 (34.2)	180 (30.8)	384 (25.4)
Missing	25	14	16	21	47	146
Education completed						
High school or less	110 (15.5)	61 (17.0)	87 (21.0)	96 (19.9)	205 (32.9)	601 (36.7)
More than high school and college or less	378 (53.2)	204 (56.8)	230 (55.4)	274 (56.7)	321 (51.4)	862 (52.6)
More than college	222 (31.3)	94 (26.2)	98 (23.6)	113 (23.4)	98 (15.7)	177 (10.8)
Missing	5	1	4	3	7	19
Infant characteristic, *n* (%)						
Preterm birth, yes	60 (8.4)	52 (14.4)	38 (9.1)	86 (17.7)	137 (21.7)	364 (21.9)
Plurality						
Singleton	646 (90.4)	262 (72.8)	393 (93.8)	378 (77.8)	440 (69.7)	1235 (74.4)
Twin	69 (9.7)	98 (27.2)	26 (6.2)	108 (22.2)	191 (30.3)	424 (25.6)
Sex						
M	365 (51.1)	177 (49.2)	223 (53.2)	252 (51.9)	311 (49.3)	879 (53.0)
F	350 (49.0)	183 (50.8)	196 (46.8)	234 (48.2)	320 (50.7)	780 (47.0)
Rapid infant weight gain during first 4 mo postpartum						
Yes	98 (14.6)	79 (23.4)	56 (14.4)	110 (24.4)	178 (32.1)	500 (34.3)
Missing	42	22	29	36	77	199

(Continued)

TABLE 1 (*Continued*)

	Exclusive breastfeeding (n = 715)	Breastfeeding and formula feeding (n = 360)	Breastfeeding and solids (n = 419)	Breastfeeding, formula feeding, and solids (n = 486)	Exclusive formula feeding (n = 631)	Formula feeding and solids (n = 1659)
Ages and stages questionnaire status at 4 mo postpartum						
Pass	630 (96.8)	295 (93.4)	343 (98.6)	386 (96.0)	547 (92.7)	1379 (95.2)
Missing	64	44	71	84	41	210
Daycare initiation at 8 mo postpartum						
Not started	333 (57.6)	131 (44.9)	181 (52.5)	164 (44.6)	223 (51.3)	538 (49.2)
Started at ≤4 mo of age	157 (27.2)	117 (40.1)	116 (33.6)	154 (41.9)	158 (36.3)	391 (35.7)
Started at >4 mo of age	88 (15.2)	44 (15.1)	48 (13.9)	50 (13.6)	54 (12.4)	165 (15.1)
Missing	137	68	74	118	196	565
Conceived with fertility treatment, yes	210 (29.4)	125 (34.7)	138 (32.9)	178 (36.6)	195 (30.9)	432 (26.0)

[1] The following covariates did not have missing values: maternal age, race, and education, and preterm birth status, plurality, sex, and conceived with fertility treatment. Upstate KIDS Study, Upstate New York Infant Development Screening Program.

practices, and examining preterm and term infants from the same base population.

Our finding regarding breastfeeding in conjunction with solid foods may be interpreted as gross motor milestone achievement being ∼7% faster in these infants than in exclusively breastfed infants at any given age within our 27-mo follow-up. This result is comparable with observations from the Davis Area Research on Lactation, Infant Nutrition and Growth study because Heinig et al. (21) similarly reported an earlier milestone achievement in breastfed infants who were given solids between 4 and 6 mo postpartum. However, note that our finding would not remain statistically significant after correction for multiple testing ($P > 0.01$, correcting for 5 tests). We also observed that other forms of feeding, such as formula use, were not detrimental to motor development relative to exclusive breastfeeding although we did not formally test for the equivalence of effects. This finding was not surprising because formula content has evolved along with our understanding of breast-milk composition, nutrition, and biotechnology (22). Compared with breast milk, formula is low in cholesterol and lacks the unique combinations of hormones, antibodies, and growth factors (22). Therefore, manufacturers have focused on the development of formulas that replicate the growth and developmental outcomes of breastfed infants rather than on matching breastmilk composition, and many modern formulas are enriched for fatty acids (22).

Because of the exclusion of preterm infants from many studies, our findings in these infants are of particular interest. Motor development is one of the first developmental domains that may deviate from the normal trajectory in young children, and motor development may predict later cognitive function (5). There are limited data as to what constitutes normal motor development in preterm infants especially in relation to infant feeding. These infants are at risk of developmental delay (13), and some research has suggested that fatty acid concentrations (e.g., DHA) in the cerebrum increase with gestational age, thereby putting these infants at risk of fatty acid imbalances because the infants would compensate for this deficiency at birth solely through feeding (23). A Cochrane review identified only 9 trials on feeding and development in preterm infants; no differences in psychomotor development at 18 mo of age were associated with the use of formula compared with donor breast milk, but only 2 studies reported on this outcome (24). Human milk (either breastfeeding or donor milk) is recommended for preterm infants, but fortification is generally needed for low-birth-weight infants (25). Although preterm infant formulas are enriched for fats that are digestible to the preterm infant, breast-milk fat is more easily absorbed than fats in cow milk and vegetable oils, which are used in many formulas (26). Despite the importance of fatty acids, such as DHA, in the central nervous system and great research interest in their relation with cognition (27), further study on the benefits to preterm infants is needed before supplementation is recommended (26). We showed no differences in motor milestone achievement that were associated with feeding in preterm infants, but our findings by early preterm status and late preterm status need replication in larger cohorts.

Major strengths of this study are our prospective collection of breastfeeding information and our longitudinal assessment of motor skills over appropriate age ranges that allowed for the use of survival modeling. Note that our median ages to achieve standing and walking alone were slightly older than those reported in the international WHO Multicentre Growth Reference Study (in which the median ages were ∼11 and 12 mo for standing and walking, respectively) (16). These differences are likely explained by our inclusion of twin births, our use of maternal report compared with trained field workers, and cultural differences that are unique to our US-based population although the aforementioned WHO study also used failure time models. Similar to many studies, we are unable to completely rule out differences in maternal reporting or monitoring of their infant's motor skills as contributing to our findings. As such, associations between feeding and motor development may be due to biologic mechanisms (such as nutritional differences in fatty acids or energy intake) or psychological and emotional differences between parents who chose one feeding method over another. It is possible that mothers perceived their infants to be healthier and active if they were consuming more than breastmilk, or perhaps mothers of infants who were more active in early infancy may have initiated solids earlier to provide energy.

TABLE 2
Feeding status at 4 mo postpartum in term and preterm infants and relative time to standing in the Upstate KIDS Study (2008–2010)[1]

	Term births			Preterm births		
		AF (95% CI)			AF (95% CI)	
	Median time to standing, mo	Unadjusted	Adjusted[2]	Median time to standing, mo	Unadjusted	Adjusted[2]
Exclusive breastfeeding (reference)	12	—	—	14	—	—
Breastfeeding and formula feeding	13	1.06 (0.99, 1.13)	1.02 (0.95, 1.10)	15	1.10 (0.90, 1.35)	0.91 (0.74, 1.11)
Breastfeeding and solids	11	0.94 (0.89, 1.00)[3]	0.93 (0.87, 0.99)[3]	13	0.99 (0.80, 1.22)	0.93 (0.78, 1.12)
Breastfeeding, formula feeding, and solids	12	0.97 (0.91, 1.03)	0.98 (0.91, 1.04)	14	1.02 (0.86, 1.20)	0.96 (0.81, 1.14)
Exclusive formula feeding	12	1.01 (0.96, 1.07)	1.00 (0.94, 1.06)	14	1.02 (0.87, 1.19)	0.96 (0.81, 1.13)
Formula feeding and solids	12	1.00 (0.96, 1.05)	0.98 (0.94, 1.03)	14	1.04 (0.91, 1.20)	1.01 (0.88, 1.16)

[1] Information for term births in the unadjusted model was as follows—observations used: n = 3533; noncensored values: n = 1823; right-censored values: n = 1255; left-censored values: n = 120; and interval-censored values: n = 335. Information for term births in the adjusted model was as follows—observations used: n = 2011; noncensored values: n = 1315; right-censored values: n = 454; left-censored values: n = 49; and interval-censored values: n = 193. Information for preterm births in the unadjusted model was as follows—observations used: n = 737: noncensored values: n = 299; right-censored values: n = 320; left-censored values: n = 36; and interval-censored values: n = 82. Information for preterm births in the adjusted model was as follows—observations used: n = 396; noncensored values: n = 218; right-censored values: n = 114; left-censored values: n = 13; and interval-censored values: n = 51. Preterm was defined as birth at <37 wk of gestational age. AF, acceleration factor; Upstate KIDS Study, Upstate New York Infant Development Screening Program.

[2] Accelerated failure time models were adjusted for maternal age, race, BMI, education, marital status, private insurance status, parity, and postpartum depression; paternal age and education; infant plurality, sex, rapid weight gain in the first 4 mo postpartum, Ages and Stages Questionnaire pass or fail status at 4 mo, daycare initiation, and conception via fertility treatment; and region via inverse probability weighting. P-interaction between preterm birth status and infant feeding for time to standing was 0.828.

[3] Significant at α = 0.05.

Heinig et al. (21) similarly acknowledged the possibility of reverse causation because "infants showing interest and developmental readiness may have been more likely to receive solids earlier." We attempted to address this issue by adjusting for rapid infant weight gain in all models because the perception of early infant activity and nutritional needs may have influenced both feeding at 4 mo postpartum and the perception of later motor development. We were also not able to examine why mothers did not breastfeed or why formula or solid foods were initiated by 4 mo postpartum. Factors such as inadequate milk intake, maternal workplace accommodations for breast-milk pumping, physician advice, or infant growth needs may influence both feeding and actual or perceived motor development. Breastfeeding also may be contraindicated because

TABLE 3
Feeding status at 4 mo postpartum in term and preterm infants and relative time to walking in the Upstate KIDS Study (2008–2010)[1]

	Term births			Preterm births		
		AF (95% CI)			AF (95% CI)	
	Median time to walking, mo	Unadjusted	Adjusted[2]	Median time to walking, mo	Unadjusted	Adjusted[2]
Exclusive breastfeeding (reference)	14	—	—	15	—	—
Breastfeeding and formula feeding	14	1.03 (0.98, 1.08)	1.03 (0.98, 1.09)	16	1.11 (0.96, 1.27)	0.95 (0.82, 1.11)
Breastfeeding and solids	13	0.94 (0.90, 0.99)[3]	0.93 (0.88, 0.98)[3]	16	1.06 (0.91, 1.23)	1.07 (0.92, 1.24)
Breastfeeding, formula feeding, and solids	13	0.95 (0.91, 0.99)[3]	0.97 (0.92, 1.02)	15	1.03 (0.91, 1.16)	0.99 (0.86, 1.13)
Exclusive formula feeding	14	1.03 (0.98, 1.07)	1.03 (0.99, 1.08)	15	1.04 (0.93, 1.16)	0.98 (0.86, 1.11)
Formula feeding and solids	13	0.99 (0.96, 1.03)	0.99 (0.95, 1.03)	15	1.04 (0.94, 1.15)	0.96 (0.86, 1.07)

[1] Information for term births in the unadjusted model was as follows—observations used: n = 3533; noncensored values: n = 1950; right-censored values: n = 1309; left-censored values: n = 28; and interval-censored values: n = 246. Information for term births in the adjusted model was as follows—observations used: n = 2011: noncensored values: n = 1417; right-censored values: n = 457; left-censored values: n = 9; and interval-censored values: n = 128. Information for preterm births in the unadjusted model was as follows—observations used: n = 737; noncensored values: n = 344; right-censored values: n = 327; left-censored values: n = 9; and interval-censored values: n = 57. Information for preterm births in the adjusted model was as follows—observations used: n = 396; noncensored values: n = 256; right-censored values: n = 109; left-censored values: n = 5; and interval-censored values: n = 26. Preterm was defined as birth at <37 wk of gestational age. AF, acceleration factor; Upstate KIDS Study, Upstate New York Infant Development Screening Program.

[2] Accelerated failure time models were adjusted for maternal age, race, BMI, education, marital status, private insurance status, parity, and postpartum depression; paternal age and education; infant plurality, sex, rapid weight gain in the first 4 mo, Ages and Stages Questionnaire pass/fail status at 4 mo, daycare initiation, and conception via fertility treatment; and region via inverse probability weighting. The P-interaction between preterm birth status and infant feeding for time to walking was 0.081.

[3] Significant at α = 0.05.

of infant metabolic disorders and certain maternal infections (25). However, we excluded infants with conditions that might have affected both feeding and neurodevelopment, and we stratified by preterm birth status to account for increased risk of gastrointestinal problems in these infants (26).

In conclusion, our results suggest that differences in infant feeding at 4 mo postpartum likely have minimal impact on the ages at which motor milestones are achieved. Our findings regarding solid foods should be interpreted cautiously until they are replicated in future studies. Ultimately, breastfeeding provides many benefits for infants beyond motor development and is still recommended by organizations such as the American Academy of Pediatrics (25).

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REFERENCES

1. American Academy of Pediatrics Committee on Nutrition. Development of gastrointestinal function. In: Kleinman R, Greer FR, editors. Pediatric nutrition. 7th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2014. p. 15–40.
2. Julvez J, Guxens M, Carsin AE, Forns J, Mendez M, Turner MC, Sunyer J. A cohort study on full breastfeeding and child neuropsychological development: the role of maternal social, psychological, and nutritional factors. Dev Med Child Neurol 2014;56:148–56.
3. Sajjad A, Tharner A, Kiefte-de Jong JC, Jaddoe VV, Hofman A, Verhulst FC, Franco OH, Tiemeier H, Roza SJ. Breastfeeding duration and non-verbal IQ in children. J Epidemiol Community Health 2015; 69:775–81.
4. van Batenburg-Eddes T, Henrichs J, Schenk JJ, Sincer I, de Groot L, Hofman A, Jaddoe VW, Verhulst FC, Tiemeier H. Early infant neuromotor assessment is associated with language and nonverbal cognitive function in toddlers: the Generation R Study. J Dev Behav Pediatr 2013;34:326–34.
5. Ghassabian A, Sundaram R, Bell E, Bello SC, Kus C, Yeung E. Gross motor milestones and subsequent development. Pediatrics 2016;138:1–8.
6. McCrory C, Murray A. The effect of breastfeeding on neurodevelopment in infancy. Matern Child Health J 2013;17:1680–8.
7. Dewey KG, Cohen RJ, Brown KH, Rivera LL. Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: results of two randomized trials in Honduras. J Nutr 2001;131:262–7.
8. Sacker A, Quigley MA, Kelly YJ. Breastfeeding and developmental delay: findings from the millennium cohort study. Pediatrics 2006;118:e682–9.
9. Leventakou V, Roumeliotaki T, Koutra K, Vassilaki M, Mantzouranis E, Bitsios P, Kogevinas M, Chatzi L. Breastfeeding duration and cognitive, language and motor development at 18 months of age: Rhea mother-child cohort in Crete, Greece. J Epidemiol Community Health 2015;69:232–9.
10. Eickmann SH, de Lira PI, Lima Mde C, Coutinho SB, Teixeira Mde L, Ashworth A. Breast feeding and mental and motor development at 12 months in a low-income population in northeast Brazil. Paediatr Perinat Epidemiol 2007;21:129–37.
11. Oddy WH, Robinson M, Kendall GE, Li J, Zubrick SR, Stanley FJ. Breastfeeding and early child development: a prospective cohort study. Acta Paediatr 2011;100:992–9.
12. Cunningham F, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. Embryogenesis and fetal morphological development. In: Cunningham F, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS, editors. Williams obstetrics. 24th ed. New York: McGraw-Hill; 2013.
13. Moreira RS, Magalhaes LC, Alves CR. Effect of preterm birth on motor development, behavior, and school performance of school-age children: a systematic review. J Pediatr (Rio J) 2014;90:119–34.
14. Gidrewicz DA, Fenton TR. A systematic review and meta-analysis of the nutrient content of preterm and term breast milk. BMC Pediatr 2014;14:216.
15. Buck Louis GM, Hediger ML, Bell EM, Kus CA, Sundaram R, McLain AC, Yeung E, Hills EA, Thoma ME, Druschel CM. Methodology for establishing a population-based birth cohort focusing on couple fertility and children's development, the Upstate KIDS Study. Paediatr Perinat Epidemiol 2014;28:191–202.
16. WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: windows of achievement for the gross motor developmental milestones. Acta Paediatr Suppl 2006;450:86–95.
17. Yeung EH, Sundaram R, Bell EM, Druschel C, Kus C, Xie Y, Buck Louis GM. Infertility treatment and children's longitudinal growth between birth and 3 years of age. Hum Reprod 2016;31:1621–8.
18. Greenland S. Introduction to regression modeling. In: Rothman KJ, Greenland S, Lash TL, editors. Modern epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 444–51.
19. Austin PC. The performance of different propensity score methods for estimating marginal hazard ratios. Stat Med 2013;32:2837–49.
20. Kleinbaum DG, Klein M. Parametric survival models. In: Survival analysis: a self-learning text. 3rd ed. New York: Springer; 2012. p. 312.
21. Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. Intake and growth of breast-fed and formula-fed infants in relation to the timing of introduction of complementary foods: the DARLING study. Davis Area Research on Lactation, Infant Nutrition and Growth. Acta Paediatr 1993;82:999–1006.
22. American Academy of Pediatrics Committee on Nutrition. Formula feeding of term infants. In: Kleinman R, Greer FR, editors. Pediatric nutrition. 7th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2014. p. 61–82.
23. Martinez M. Tissue levels of polyunsaturated fatty acids during early human development. J Pediatr 1992;120:S129–38.
24. Quigley M, McGuire W. Formula versus donor breast milk for feeding preterm or low birth weight infants. Cochrane Database Syst Rev 2014; 4:CD002971.
25. American Academy of Pediatrics Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics 2012;129:e827–41.
26. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman R, Greer FR, editors. Pediatric nutrition. 7th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2014. p. 83–121.
27. Lauritzen L, Brambilla P, Mazzocchi A, Harsløf LB, Ciappolino V, Agostoni C. DHA effects in brain development and function. Nutrients 2016;8;pii: E6.