Developmental Status of 1-Year-Old Infants Fed Breast Milk, Cow's Milk Formula, or Soy Formula

WHAT'S KNOWN ON THIS SUBJECT: Although soy protein–based infant formula is known to support physical growth equal to that of infants fed cow's milk–based formula, data are lacking on developmental status of infants fed soy formula compared with breast milk or milk formula.

WHAT THIS STUDY ADDS: Infants fed soy protein–based formula scored within normal limits on standardized developmental testing and did not differ from infants fed cow's milk–based formula. Breastfed infants have a slight advantage on cognitive development compared with formula-fed infants.

abstract

FREE

BACKGROUND AND OBJECTIVE: Although soy formula has been reported to support normal development, concerns exist regarding potential adverse developmental effects of phytochemicals associated with soy protein. This study characterized developmental status (mental, motor, and language) of breastfed (BF), milk-based formula–fed (MF), or soy protein–based formula–fed (SF) infants during the first year of life.

METHODS: Healthy infants (N = 391) were assessed longitudinally at ages 3, 6, 9, and 12 months. Development was evaluated by using the Bayley Scales of Infant Development and the Preschool Language Scale-3. Mixed effects models were used while adjusting for socioeconomic status, mother's age and IQ, gestational age, gender, birth weight, head circumference, race, age, and diet history.

RESULTS: No differences were found between formula-fed infants (MF versus SF). BF infants scored slightly higher than formula-fed infants on the Mental Developmental Index (MDI) score at ages 6 and 12 months ($P < .05$). Infants who were breastfed also had higher Psychomotor Development Index scores than SF infants at age 6 months and slightly higher Preschool Language Scale-3 scores than MF infants at ages 3 and 6 months ($P < .05$). In addition, BF infants had a lower probability to score within the lower MDI quartile compared with MF infants and a higher likelihood to score within the upper quartile for the MDI and Psychomotor Development Index compared with SF infants.

CONCLUSIONS: This unique study showed that all scores on developmental testing were within established normal ranges and that MF and SF groups did not differ significantly. Furthermore, this study demonstrated a slight advantage of BF infants on cognitive development compared with formula-fed infants. *Pediatrics* 2012;129:1134–1140

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KEY WORDS

developmental assessment, breast milk, infant nutrition, cow's milk formula, soy formula

ABBREVIATIONS

BF—breastfed
BSID—Bayley Scales of Infant Development
CI—confidence interval
MDI—Mental Developmental Index
MF—milk-based formula–fed
OR—odds ratio
PDI—Psychomotor Development Index
PLS-3—Preschool Language Scale-3
SES—socioeconomic status
SF—soy protein–based formula–fed
WASI—Wechsler Abbreviated Scale of Intelligence

Drs Badger and Casey designed the study; Drs Andres and Bellando participated in the collection of data; Dr Cleves analyzed the data; and Drs Andres, Badger, Pivik, and Cleves wrote the manuscript.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00616395).

www.pediatrics.org/cgi/doi/10.1542/peds.2011-3121

doi:10.1542/peds.2011-3121

Accepted for publication Feb 14, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *Dr Badger is a member of the Science Advisory Board of the Soy Nutrition Institute and has provided input to the NIEHS-sponsored committee that has published the NTP-CERHR report on the recommendations for potential effects of soy formula intake on reproductive health.*

FUNDING: Supported by the USDA Agriculture Research Service CRIS grants 6251-51000-007-04s and 6251-51000-006-03s.

COMPANION PAPERS: Companions to this article can be found on pages 1141 and 1166, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2011-2127 and www.pediatrics.org/cgi/doi/10.1542/peds.2012-0934.

Although 62% of US infants were breastfed as newborns in 2008, 73% of these were transitioned to infant formula between birth and age 6 months.[1] The American Academy of Pediatrics recommends the use of human breast milk as the ideal source of nutrition for infant feeding.[2] Milk formulas are the second choice and soy formulas the third choice.[2] Approximately 20% of formula-fed infants in the United States are fed soy protein–based formula during their first year of life.[2,3] Understanding the potential benefits or adverse effects of these early diets is important to optimize nutritional status, promote health, and prevent diseases later in life. Growth and development of soy protein–based formula–fed (SF) infants have been shown to be similar to milk-based formula–fed (MF) infants. Nevertheless, concerns have been raised about the isoflavone content of soy protein–based formula.[4] Infants fed soy protein–based formula consume significant levels of isoflavones (6–11 mg kg^{-1} body weight per day) compared with negligible levels in breastfed (BF) infants (<0.01 mg kg^{-1} body weight per day), resulting in serum and urinary isoflavone levels in the range of 0.4–1.5 μM.[5–8] These isoflavones can bind and activate estrogen receptors α and β, raising the possibility of potential estrogenic effects.[9] Numerous studies have evaluated the effects of soy protein–based formula feeding on growth (weight, length, and head circumference) compared with MF or BF infants,[10–16] but behavioral (mental, psychomotor, and language) development in SF infants compared with MF or BF infants has not yet been characterized. The objective of this study was to compare mental, psychomotor, and language development during the first year of life of BF, MF, and SF infants. We hypothesized that behavioral development would not differ between formula-fed groups but would be higher in BF infants.

METHOD

Participants

Participants were 391 infants enrolled in the *Beginnings Study* between 2002 and 2010 (www.clinicaltrials.gov, identifier NCT00616395). Infants were recruited between ages 1 and 2 months. Pregnancies were uncomplicated with no medical diagnoses (eg, diabetes or preeclampsia) or medications known to affect fetal or infant growth and development (eg, selective serotonin reuptake inhibitors or thyroid replacement). All mothers were nonsmokers, were denied alcohol use during pregnancy, and reported no use of soy products or other estrogenic compounds during pregnancy and/or lactation. Infants were term (≥37 weeks), 2.7 kg (6 lbs) to 4.1 kg (9 lbs) at birth, had no medical diagnoses, or had not been administered medications known to affect growth or development. Other exclusion criteria included change of formula after age 2 months and before age 12 months; complementary foods before 4 months; and body weight at 3 months <5 kg. Study visits were scheduled at ages 3, 6, 9, and 12 months. Consent was obtained and signed by parents or guardians before any study procedures. The study was approved by the Institutional Review Board of the University of Arkansas for Medical Sciences.

Infant Diet

Parents, following the advice of their pediatricians, made decisions about which diet to feed their infants before enrolling in the study, and those electing to formula feed chose between milk (Similac Advance or Enfamil Lipil) or soy (Similac Soy Isomil or Enfamil Prosobee) formulas. Similac formulas were manufactured by Abbott Nutrition (Columbus, OH), and Enfamil formulas were manufactured by Mead Johnson (Evansville, IN). All formulas were supplemented with docosahexaenoic acid and arachidonic acid. Thus, infants were BF, MF, or SF infants. Enrollment was performed in a diet-type paced manner (ie, for every BF infant enrolled, 1 MF and 1 SF were enrolled) to ensure equal distribution across feeding groups throughout the study period. All formula-fed infants remained on their selected formula from 2 to 12 months of age. Thus, formula-fed participants did not change feeding group during the study period. For BF infants, breastfeeding was encouraged until age 12 months. If not possible, BF infants were switched to milk formula between 6 and 12 months. Complementary foods (eg, juices, cereals, and solid foods) could be introduced after age 4 months for all 3 diet groups (BF, MF, and SF). Formula intake was assessed at each study visit by using 3 days of food records analyzed with the Nutrition Data System for Research (University of Minnesota, MN).

Anthropometrics

Anthropometric measures (recumbent weight and length) were obtained at each study visit by using standardized methods. Briefly, infant weight was measured to the nearest 0.01 kg by using a tarred scale (SECA 727; SECA Corp, Ontario, Canada) with infants wearing a diaper only. Infant length was measured to the nearest 0.1 cm by using a length board (Easy Glide Bearing Infantometer; Perspective Enterprises, Portage, MI).

Infant Behavioral Development

Infants were assessed with the Bayley Scales of Infant Development (BSID), second edition, from which the Mental Developmental Index (MDI) and Psychomotor Development Index (PDI) were derived.[17] Infants were also assessed with the Preschool Language Scale-3 (PLS-3) by using the expressive communication and auditory comprehension subscales.[18] Results are presented as standard scores adjusted for child's age with a mean of 100 (SD = 15), and the range for normal scores is 85–115. Delay on these measures was defined as a score below 85 and accelerated performance a score greater than 115. Both assessments were administered at each study visit by psychological examiners supervised by a licensed psychologist. All examiners were blinded to feeding group unless BF infants were fed during the testing period. Interexaminer reliability was high (interclass correlation: MDI = 0.93, PDI = 0.95, PLS-3 = 0.83).

Scale of Intelligence

The Wechsler Abbreviated Scale of Intelligence (WASI) was used to assess verbal, nonverbal, and general cognitive functioning of the participants' mothers.[19] The full-scale IQ scores were computed. The WASI was administered to mothers at the 3-month visit by psychological examiners supervised by a licensed psychologist, with established high interexaminer reliability (interclass correlation: WASI = 0.98).

Socioeconomic Status

The socioeconomic status (SES) of study participants' families was estimated by the Hollingshead Four-Factor Index of Social Status, which combines the highest level of formal parental education achieved and occupations.[20] Derived scores describe familial social strata. Scores ranged from 8 to 66, with the higher scores indicating higher theoretical social status.

Statistical Analyses

Summary statistics for continuous variables are presented as means ± SDs and as counts and percentages for categorical variables. Differences of participant characteristics measured in the interval scale were compared among the 3 feeding groups by using analysis of variance followed by Tukey–Kramer post-hoc tests. Characteristics measured in the nominal scale were compared by using Pearson's χ^2 test or Fisher's exact test.

Mixed effects models with repeated measures were used to examine the relationship between each developmental index (MDI, PDI, and PLS-3) and the 3 feeding groups over time.[21] On the basis of the empirical shape of the time trajectory of development indexes, a quadratic term for time was entered into all models as well as interactions with feeding group to permit additional flexibility of the fitted model. Likelihood ratio tests were used to determine the significance of the interactions by comparing nested models with and without interaction terms. Infant's age, gender, race, gestational age, birth weight, head circumference, and diet history, as well as mother's SES, IQ, and age, were included as covariates in all models. Because of the known relationship between weight and the PDI score, infant's weight at each assessment was also included as a time varying covariate when modeling PDI. Because of a significant feeding group by age interaction, results from models are summarized at each visit by the estimated mean (marginal linear prediction) and the corresponding δ-method computed standard errors. Marginal effects across feeding groups at each time period were compared by constructing appropriate contrasts and tested by using a Bonferroni corrected Wald test statistic.[22]

Odds ratios (OR) and corresponding 95% confidence intervals (CI) for the comparison of distributional quintiles were estimated by using repeated measures mixed effects models assuming a binomial family and logit link. These models were also adjusted for infant's age, gender, race, gestational age, head circumference, birth weight, and feeding history, as well as mother's SES, IQ, and age. Analysis was conducted by using Stataversion 12 (Stata Corporation, College Station, TX) and SAS version 9.2 (SAS Institute Inc, Cary, NC) statistical packages.

RESULTS

Of 483 potential participants, 49 (10.1%) were excluded because they did not meet inclusion criteria, and 8 (1.6%) were excluded because of a medical diagnosis (4 neurologic disorders, 3 growth disorders, and 1 vision impairment). Of the remaining 426 participants, 35 (8.2%) voluntarily withdrew or were lost to follow-up. The final cohort analyses consisted of 131 BF infants (61 girls), 131 MF infants (61 girls), and 129 SF infants (55 girls), for a total of 391 infants. Study visit compliance was high; only 10 infants (2.5%) missed 1 study visit. All other infants attended all 4 study visits at ages 3, 6, 9, and 12 months. Summarized in Table 1 are selected characteristics of cohort participants. Gestational age was similar between groups but greater in BF infants compared with MF and SF infants ($P < .05$). Birth weights were also similar between diet groups although higher in BF infants compared with SF infants ($P < .05$). Similarly, mother's IQ and SES were greater in breastfeeding mothers than mothers of MF or SF infants. There were no differences in birth length, mother's age, or mean ages of the infants at the time of their visits. There were also no statistical differences in infant's head circumference, weight, or length between diet groups across all ages.

The mean age for introducing the study formula ranged from 2.7 to 3.1 weeks for MF and SF infants, respectively. Details on the diet history of formula-fed infants are presented in Table 2. Fewer infants (33%) were exclusively fed soy protein–based formula from birth, compared with 50% who were exclusively fed milk-based formula from birth. All of the remaining MF infants were breastfed until switched to milk-based formula. SF infants were either fed breast milk

TABLE 1 Cohort Characteristics

	BF	MF	SF
N	131	131	129
Race (%)			
Caucasian	120 (91)	112 (86)	112 (87)
African American	5 (4)	8 (6)	13 (10)
Other	6 (5)	11 (8)	4 (3)
Gender (%)			
Girls	61 (46.6)	61 (46.6)	55 (42.6)
Boys	70 (53.4)	70 (53.4)	74 (57.4)
Gestational age (wk)	39.5 (1.2)[a]	39.1 (1.0)[b]	39.2 (1.0)[b]
Parity	2.0 (0.9)	2.0 (0.9)	2.2 (0.8)
Birth wt (kg)	3.58 (0.34)[a]	3.51 (0.39)	3.45 (0.37)[b]
Birth length (cm)	51.6 (2.2)	51.3 (2.5)	51.2 (2.2)
Mother's age (y)	29.0 (4.3)	29.6 (4.5)	29.9 (4.5)
Mother's full-scale IQ	109.8 (10.0)[a]	106.0 (8.9)[b]	103.8 (10.5)[b]
SES	49.8 (11.0)[a]	45.6 (10.6)[b]	45.9 (10.8)[b]
Infant's age (d)			
3-mo visit	92.3 (4.7)	91.8 (4.0)	91.8 (5.0)
6-mo visit	183.7 (4.6)	183.7 (4.1)	184.0 (4.4)
9-mo visit	274.1 (4.2)	274.7 (5.3)	274.4 (4.2)
12-mo visit	366.8 (4.9)	367.0 (8.9)	365.9 (5.0)
Head circumference (cm)			
3 mo	40.7 (1.2)	40.7 (1.1)	40.7 (1.1)
6 mo	43.5 (1.3)	43.6 (0.2)	43.8 (1.3)
9 mo	45.2 (1.3)	45.3 (1.2)	45.5 (1.4)
12 mo	46.4 (1.3)	46.5 (1.2)	46.6 (1.5)
Infant's wt (kg)			
3 mo	6.2 (0.7)	6.1 (0.6)	6.0 (0.5)
6 mo	7.7 (0.9)	8.0 (0.8)	7.9 (0.8)
9 mo	8.6 (0.9)	9.1 (1.0)	9.1 (0.9)
12 mo	9.5 (1.0)	10.0 (1.0)	10.0 (1.0)
Infant's length (cm)			
3 mo	60.5 (2.0)	60.1 (2.2)	60.0 (2.0)
6 mo	66.2 (2.4)	66.7 (2.3)	66.6 (2.2)
9 mo	70.0 (2.3)	71.2 (2.6)	71.0 (2.4)
12 mo	74.0 (0.4)	74.8 (2.3)	74.9 (2.5)

Values are either percentages (%) or means (SD). Means with different superscript letters differ ($P < .05$).

or milk formula before being fed soy protein–based formula because of perceived intolerance. All formula-fed infants remained on their formula until age 12 months, at which point cow's milk was introduced. Breastfeeding mothers were encouraged to breastfeed for 12 months, and 53% (*N* = 70) did. Ten percent (*N* = 13) of mothers started mixed feeding after age 6 months and continued until age 12 months. The remaining infants (*N* = 48) were fed breast milk until at least age 6 months and then were fed milk-based formula. Ten percent (*N* = 13) were breastfed until age 6 months, 21% (*N* = 27) were breastfed until age 8 months, and 6% (*N* = 8) were breastfed until age 10 months. Mean formula intake (kilocalories per day ± SD) was not statistically different between MF and SF infants at 3, 6, 9, and 12 months (595 ± 116 vs 629 ± 126; 758 ± 137 vs 737 ± 148; 877 ± 225 vs 682 ± 190; and 1005 ± 260 vs 1007 ± 261, respectively).

TABLE 2 Diet History of Formula-Fed Infants Before Age 2 Months

	MF	SF
Exclusively formula fed at birth, *N* (%)	65 (50)	43 (33)
Exclusively formula fed by age 2 wk, *N* (%)	18 (14)	16 (12)
Exclusively formula fed by age 4 wk, *N* (%)	21 (16)	42 (32)
Exclusively formula fed by age 6 wk, *N* (%)	15 (11)	21 (16)
Exclusively formula fed by age 8 wk, *N* (%)	12 (9)	9 (7)

Fitted regression models for which estimated means and standard errors are presented in Tables 3, 4, and 5 were used to estimate feeding group differences at each age. There were no significant differences between MF and SF infants at any age for each behavioral measure. In addition, estimated mean scores for all 3 behavioral measures were within the published normal ranges (Fig 1). Also, the areas under the curve were similar for all infants (BF, MF, and SF; $P > .05$) for all 3 behavioral measures (data not shown).

The MDI of the BSID measures performance in the areas of sensory perception, knowledge, memory, problem solving, and early language with tasks adapted to each age group. Small but statistically significant effects of early diet on the MDI scores were seen for infants 6 months or older. BF infants had significantly higher scores than SF infants at ages 6, 9, and 12 months and significantly higher scores than MF infants at ages 9 and 12 months (Table 3). Although these effects reached statistical significance, the MDI scores were within the expected normal range, and the differences were very small (average difference = 2.09 points).

The PDI of the BSID assesses the child's level of fine and gross motor development with tasks adapted to each age group. Significant effects of early diet on the PDI scores were transient. SF infants had significantly lower PDI scores compared with BF infants, although the effect was very small again (−2.69 points) and seen at age 6 months only (Table 4). No other diet effect was observed for the PDI.

Although the PLS-3 evaluates the receptive and expressive language skills in infants, it also measures behaviors considered as language precursors. For PLS-3, only MF infants had significantly lower scores compared with BF infants at ages 3 and 6 months (−3.09 and −2.18 points, respectively; Table 5), although the differences were very small, and both groups were well within the normal range.

TABLE 3 MDI Scores Estimated From Fitted Mixed Models

	3 mo	6 mo	9 mo	12 mo
BF	103.08 (0.57)	108.56 (0.44)[a]	108.67 (0.44)[a]	103.81 (0.57)[a]
MF	102.61 (0.58)	107.31 (0.45)[ab]	106.56 (0.45)[b]	100.86 (0.59)[b]
SF	101.31 (0.59)	106.67 (0.46)[b]	106.49 (0.46)[b]	101.31 (0.60)[b]
P value	.2745	.0205	.0006	.0010

Adjusted for SES, mother's age, mother's IQ, gestational age, child's race, child's gender, child's age, birth wt, head circumference, and diet history. Modeled estimated means (SEM) with different superscript letters differ ($P < .05$).

TABLE 4 PDI Scores Estimated From Fitted Mixed Models

	3 mo	6 mo	9 mo	12 mo
BF	98.66 (0.84)[a]	103.57 (0.70)[a]	103.31 (0.70)	98.26 (0.85)
MF	97.27 (0.86)[ab]	102.07 (0.72)[ab]	101.68 (0.72)	96.64 (0.87)
SF	95.18 (0.88)[b]	100.64 (0.73)[b]	100.87 (0.73)	96.37 (0.89)
P value	.0484	.0397	.1418	.8838

Adjusted for SES, mother's age, mother's IQ, gestational age, child's race, child's gender, child's age, birth wt, head circumference, and diet history. Modeled estimated means (SEM) with different superscript letters differ ($P < .05$). PDI was also adjusted for child's weight.

TABLE 5 PLS-3 Scores Estimated From Fitted Mixed Models

	3 mo	6 mo	9 mo	12 mo
BF	98.98 (0.63)[a]	104.87 (0.48)[a]	104.55 (0.48)	98.26 (0.64)
MF	95.89 (0.65)[b]	102.69 (0.49)[b]	103.23 (0.49)	97.82 (0.66)
SF	97.40 (0.66)[ab]	103.80 (0.50)[ab]	103.92 (0.50)	98.03 (0.67)
P value	.0069	.0101	.4625	1.0000

Adjusted for SES, mother's age, mother's IQ, gestational age, child's race, child's gender, child's age, birth wt, head circumference, and diet history. Modeled estimated means (SEM) with different superscript letters differ ($P < .05$).

Similar results were found when missing data were imputed for 41 participants (mother's age: 2.5% missing; SES: 8.2%). Analogous results were also obtained when the model was applied only to the formula-fed infants who were exclusively on their formula of interest by age 2 weeks. For MDI, significant differences were lost at age 6 months, and BF = SF at ages 9 and 12 months. PDI lost significant differences at 3 months, and BF = MF at 9 months; and PLS-3 results showed an additional significant difference at 9 months where BF = SF > MF. Finally, results were unchanged when BF infants who were mixed fed after age 6 months were excluded from the statistical model, suggesting that our results are reflective of infants who would have been exclusively breastfed or formula fed from birth to age 12 months.

Because of the low incidence of clinically delayed scores (<85) or clinically accelerated scores (>115) across the age groups in our cohort (4 delayed and 4 accelerated), OR for the lower quintile (<20%) and upper quintile (>80%) compared with the middle quintiles (20%–80%) were estimated by using mixed effects models for binary outcomes with repeated measures. The quintile analysis found no significant effect of diet on PLS-3 and no significant difference between SF and MF infants on any of the 3 developmental measurements. However, BF infants had a lower chance to score within the lower quintile for MDI compared with MF (OR = 0.50, 95% CI = 0.31–0.81). In addition, BF infants had a greater chance to score within the higher quartile on MDI and PDI compared with SF infants (OR = 2.29 and 2.64, 95% CI = 1.09–4.80 and 1.25–5.58, respectively).

DISCUSSION

In this study, we prospectively characterized the development during the first year of life in 391 BF, MF, or SF infants. It is the first study comparing mental, psychomotor, and language development between all 3 diet groups by using anthropometric measures as well as previously validated measures of infant development (BSID and PLS-3). In our cohort, standardized mental, psychomotor, and language development scores were very similar among the 3 feeding groups, with averages falling within the clinically normal limits.[17,18,23]

In the current study, we focused on the developmental status of SF relative to MF infants because of concerns related to high levels of potentially estrogenic soy isoflavones that could affect central nervous system development. On the basis of more than 25 years of soy protein–based formula use in the United States without any peer review journal reports of adverse effects, we hypothesized that MF and SF infants would score similarly on standardized behavioral testing. No significant differences were observed in scores of the MDI, PDI, or PLS-3 between MF and SF groups throughout the first year of life. Thus, our results confirmed the hypothesis. Our findings are also in agreement with studies suggesting similar electroencephalographic activities demonstrating comparable cognitive development between MF and SF infants.[24,25] These results concur with 2 studies showing normal neurodevelopment of SF infants compared with MF infants, although actual testing results were not reported.[14,26] The follow-up of the infants in our study to age 6 years will help us determine whether diet effects will emerge later in life or further support our hypothesis. In a large retrospective study of SF or MF infants, the percentage of men or women (N = 811) who achieved some level of college or trade school education did not differ across feeding groups, potentially showing no differences in cognitive achievement between the feeding groups.[27]

Although all 3 diet groups scored within the established norms in the behavioral

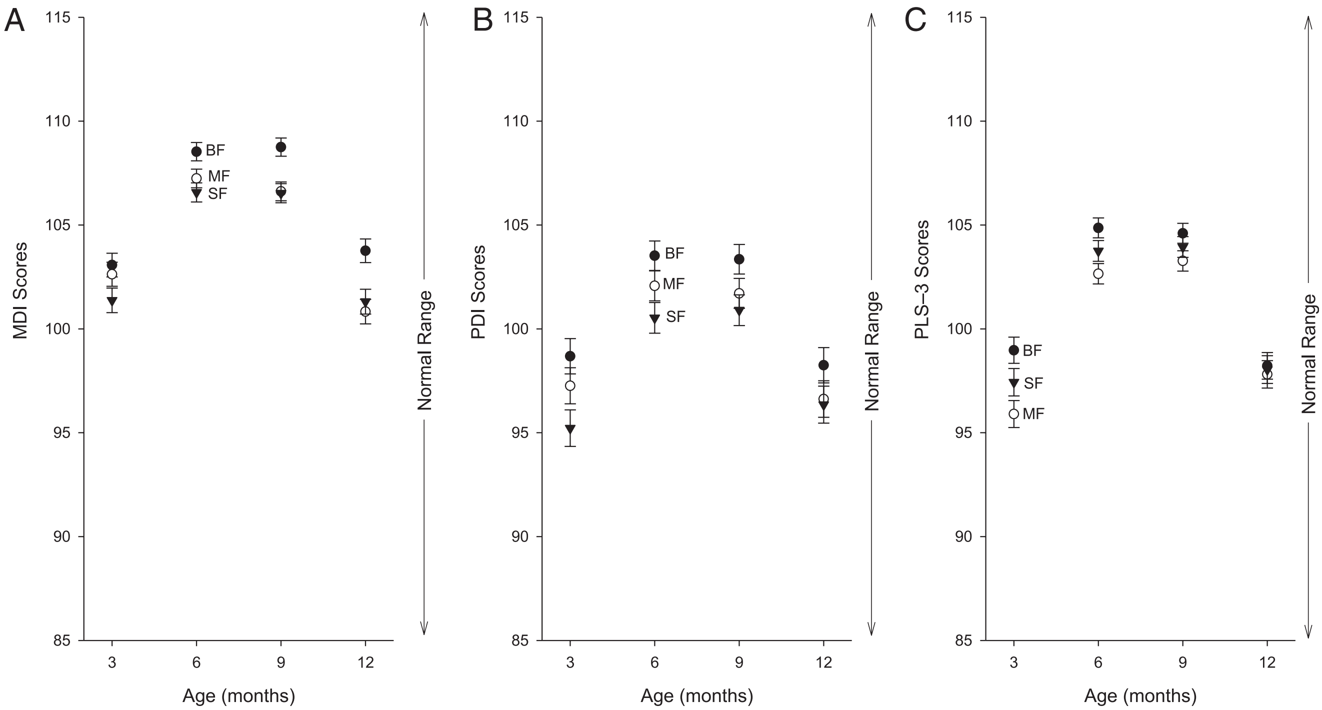

FIGURE 1
Behavioral standardized scores for BF (solid circles), MF (open circles), and SF (inverted triangles) infants during the first year of life. Estimated means and SEM are presented.

testing, BF infants scored slightly better than formula-fed infants with (1) higher MDI score than MF and SF infants between ages 6 and 12 months, (2) higher PDI scores than SF infants at age 6 months, and (3) higher PLS-3 scores than MF infants at ages 3 and 6 months. In addition, BF infants had a lower chance to score on the lower quartile of the MDI compared with MF infants and a higher chance to score within the upper quartile for MDI and PDI compared with SF infants. These results are consistent with a large body of literature demonstrating advantages of breastfeeding on cognitive function later in life.[28–37] However, it is important to point out that developmental test scores of all 3 diets groups were within the standardized norms, and differences between BF infants and formula-fed effects were quite small in magnitude and thus difficult to interpret in terms of potential clinical relevance. Previous studies have shown lesser advantages when taking into consideration confounding factors or segregating for variables such as being small for gestational age.[38–40] Here, results were similar after adjusting for confounding factors and controlling for other variables of concern. Thus, our results demonstrate a potential beneficial effect of breastfeeding on cognitive function.

This study is strengthened by the large sample size of carefully characterized infants at 4 time points during the first year of life. The results are, however, limited by the observational characteristics of the study, which reflect the infant feeding practices of our community. In addition, lower predictive validity of the BSID second edition assessment during infancy for cognitive function of children at school age warrants a follow-up of these children at school age.[41–43]

In summary, in this unique study, we established that SF infants perform within normal limits and similarly to MF infants in the areas of mental, psychomotor, and language development. Our results also suggest a slight potential advantage of cognitive development for BF infants.

ACKNOWLEDGMENTS

The authors are grateful to the infants and families who participated in this study and to Dr Janet Gilchrist for assistance in the data collection.

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Pediatrics 2012;129;1134
DOI: 10.1542/peds.2011-3121 originally published online May 28, 2012;