Improved Neurodevelopmental Outcomes Associated with Bovine Milk Fat Globule Membrane and Lactoferrin in Infant Formula: A Randomized, Controlled Trial

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Objective To evaluate neurodevelopment, growth, and health outcomes in infants receiving bovine milk fat globule membrane (MFGM) and lactoferrin in infant formula.

Study design Healthy term infants were randomized to a cow's milk-based infant formula or MFGM + LF (a similar infant formula, with an added source of bovine milk fat globule membrane [bMFGM; whey protein-lipid concentrate, 5 g/L] and bovine lactoferrin [0.6 g/L]) through 365 days of age. The Bayley Scales of Infant Development, 3rd edition cognitive composite score at day 365 was the primary outcome. Secondary outcomes included tolerance measures through day 365, additional neurodevelopmental and language outcomes, growth, and medically confirmed adverse events through day 545.

Results Of 451 infants enrolled (control, 228; MFGM + LF, 223), 291 completed study feeding and Bayley-III testing at day 365 (control, 148; MFGM + LF, 143). The mean cognitive (+8.7), language (+12.3), and motor (+12.6) scores were higher (P < .001) for the MFGM + LF group; no differences were observed at day 545. Global development scores from day 120 to day 275 and attention at day 365 were significantly improved. Few group differences in day 545 neurodevelopmental outcomes were detected, however scores of some subcategories of the MacArthur-Bates Communicative Development Inventories were higher (P < .05) in the MFGM + LF group. The overall incidence of respiratory-associated adverse events and diarrhea were significantly lower for the MFGM + LF group through day 545.

Conclusions Infants receiving formula with added bovine MFGM and bovine lactoferrin had an accelerated neurodevelopmental profile at day 365 and improved language subcategories at day 545. Formulas were associated with age-appropriate growth and significantly fewer diarrhea and respiratory-associated adverse events through 545 days of age. *(J Pediatr 2019;215:24-31).*

Trial registration Clinicaltrials.gov: NCT02274883.

Although the World Health Organization recommends exclusive breastfeeding through 6 months of age[1] and human milk is recognized as the gold standard for infant nutrition, a significant proportion of infants worldwide receive partial or exclusive formula feeding. Over the past century, changes in infant formula to better match the dynamic features of breast milk have brought the composition, functionality, and health-based outcomes closer together for infants receiving human milk or infant formula.[2] For example, lactoferrin is a relatively well-studied bioactive component[3,4] that shares approximately 70% sequence homology and comparable bioactivity with bovine lactoferrin (as reviewed[3,5]). We previously reported 0.6 g bovine lactoferrin per liter in routine infant formula was safe, well-tolerated, and associated with normal growth in healthy term infants through 365 days of age[6]; dietary bovine lactoferrin was also demonstrated to decrease invasive fungal infections in preterm infants[7] and to decrease parasite colonization[8] and vomiting and diarrhea[9] in older children.

AE	Adverse event
ASQ	Ages & Stages Questionnaire
Bayley-III	Bayley Scales of Infant Development, 3rd edition
CDI	Communicative Development Inventories
MFGM	Milk fat globule membrane
bMFGM	Bovine MFGM

Milk fat globule membrane (MFGM), is a complex protein–phospholipid trilayer that surrounds fat droplets secreted into milk.[10-13] It is highly conserved across mammalian species. Emergent research supports MFGM as a bioactive component for digestive health, immune, and central nervous system development and function (as reviewed[14]). Improved bovine fat globule separation during dairy processing has facilitated bovine MFGM (bMFGM) incorporation in infant formula to better approximate the composition of complex human milk lipids.[3,15] Early clinical studies demonstrated the safety and potential developmental and behavioral benefits of different sources of bMFGM or its components in infant formula.[16-22]

Additional clinical data based on recognized study outcomes and consistent bMFGM sources would help establish recommendations for the addition of bMFGM to infant formula. This randomized clinical trial was designed to evaluate neurodevelopmental outcomes in healthy term infants through 545 days of age (18 months) who received bMFGM and bovine lactoferrin in infant formula through 365 days of age.

Methods

Eligible infants were enrolled in this multicenter, double-blind, randomized, controlled, parallel group trial from November 2014 to October 2015 at 3 clinical sites in Fuyang, Anhui Province, China (ClinicalTrials.gov: NCT02274883). The research protocol and informed consent forms observing the Declaration of Helsinki (including October 1996 amendment) were approved by the Shanghai Nutrition Academy Medical Ethical Committee. The study complied with good clinical practices. Parents or guardians provided written informed consent before enrollment. Mothers who had decided to exclusively provide infant formula were screened for study eligibility. Participants were born at 37-42 weeks of gestation and had received infant formula feeding for ≥3 days before randomization. Infants were 10-14 days of age at randomization. Other inclusion and exclusion criteria are described in Table I (available at www.jpeds.com). Study visits corresponded to 14 (−4 days; enrollment), 30 (±3), 42 (±3), 60 (±3), 90 (±3), 120 (+5), 180 (+7), 275 (+10), 365 (+10), and 545 (±7) days of age. All developmental testing was performed by study site professionals proficient in the administration of cognitive tests. Participants were eligible to continue in the study and complete neurodevelopmental testing at days 365 and 545 even if study formula consumption was discontinued after 180 days of age.

Randomization and Study Group Allocation

Participants were randomly assigned to receive one of two staged, routine cow's milk-based study formulas (Mead Johnson Nutrition, Evansville, Indiana; Table II): a control formula or MFGM + LF, a similar formula with added whey protein-lipid concentrate (5 g/L, source of bMFGM; Lacprodan MFGM-10, Arla Foods Ingredients, Basking Ridge, New Jersey) and bovine lactoferrin (0.6 g/L; FrieslandCampina

Table II. Nutrient composition per 100 kcal (20 Calories/fl oz)*

Nutrients	Study formula (target values)			
	Stage 1		Stage 2	
	Control	MFGM + LF	Control	MFGM + LF
Total protein, g[†]	2.1	2.1	3.3	3.3
Total fat, g[‡]	5.3	5.3	4.1	4.1
Linoleic, mg	810	810	640	640
α-Linolenic acid, mg	71	71	56	56
ARA, mg	25	25	25	25
DHA, mg	17	17	17	17
Total carbohydrate, g[§]	11.2	11.2	12.8	12.8
Vitamin A, IU	280	280	300	300
Vitamin D, IU	62	62	56	56
Vitamin E, IU	1.9	1.9	1.7	1.7
Vitamin K, μg	7.2	7.2	8	8
Thiamin, μg	85	85	80	80
Riboflavin, μg	170	170	200	200
Vitamin B_6, μg	60	60	70	70
Vitamin B_{12}, μg	0.31	0.31	0.5	0.5
Niacin, μg	660	660	700	700
Folic acid, μg	18	18	16	16
Pantothenic acid, μg	570	570	650	650
Biotin, μg	2.7	2.7	3	3
Vitamin C, mg	18	18	20	20
Choline, mg	24	24	24	24
Inositol, mg	8.5	8.5	7	7
Carnitine, mg[¶]	2	2	–	–
Taurine, mg	6	6	4.3	4.3
Calcium, mg	79	79	110	110
Phosphorus, mg	48	48	65	65
Magnesium, mg	8	8	9.5	9.5
Iron, mg	1.0	1.0	1.25	1.25
Zinc, mg	0.8	0.8	0.76	0.76
Manganese, μg	18	18	17.8	17.8
Copper, μg	65	65	68	68
Iodine, μg	17	17	22	22
Selenium, μg	2.7	2.7	2.5	2.5
Sodium, mg	28	28	46	46
Potassium, mg	110	110	150	150
Chloride, mg	65	65	94	94
Total nucleotides, mg	3.1	3.1	4	4

ARA, Arachidonic acid; *DHA*, docosahexaenoic acid.
*Study formulas were provided as powders and could not be differentiated by smell, consistency, or any other characteristics; identical mixing instructions were provided (final product, 20 calories/fluid ounce).
†Sources of protein for control: skim milk and whey protein concentrate (WPC); and for MFGM + LF: skim milk, WPC, whey protein-lipid concentrate (5 g/L, source of bMFGM; Lacprodan MFGM-10, Arla Foods Ingredients) and bovine lactoferrin (0.6 g/L; Friesland Campina DMV).
‡Sources of fat: base blend of palm olein, soybean, coconut, and high oleic sunflower oils; fungal-derived single cell oil (source of ARA); algal-derived single cell oil (source of DHA).
§Sources of carbohydrate: lactose (stage 1, 10.6 g; stage 2, 12.1 g) and prebiotic oligosaccharides (stage 1, 0.62 g; stage 2, 0.7 g; source: blend of polydextrose [PDX, Litesse Two Polydextrose; Danisco] and galacto-oligosaccharides [GOS; DOMO Vivinal GOS; FrieslandCampina DMV] [1:1 ratio]).
¶Not added to stage 2 study formulas.

DMV, Amersfoort, the Netherlands). The amount and source of bMFGM was based on a prior infant formula study,[19] with the aim of adding sphingomyelin at a concentration within the reported human milk range.[23,24] Participants received exclusive study formula feeding through day 120. Within each study group, stage 1 formula was used up to day 180 and switched to a corresponding stage 2 formula through day 365. The study sponsor created a computer-generated, sex-stratified randomization schedule

provided in sealed consecutively numbered envelopes for each study site. Study formula was assigned by opening the next sequential envelope from the appropriate set at the study site. Study formulas, each designated by 2 unique codes known only to the sponsor, were dispensed to parents at each visit before day 365. Neither product labels nor sealed envelopes allowed direct unblinding by the study site. Blinding could be broken by study sponsor personnel in the event of a medical emergency. In this study, it was not necessary to break the study code prematurely.

Bayley Scales of Infant Development, 3rd edition Testing

The Bayley Scales of Infant Development, 3rd edition (Bayley-III; developed and validated in a US population[25]) evaluates infants and children from 1 to 42 months of age. The cognitive, language (receptive and expressive communication), and motor (fine and gross motor) domains were assessed by a trained evaluator. The social-emotional and adaptive behavior scales were assessed by parent questionnaire. Composite scores (cognitive, language, and motor) were converted from raw scores based on successful completion of items at age of testing (standardized mean, 100; range varies by scale: cognitive and social-emotional, 55-145; language, 47-153; motor, 46-154; and adaptive behavior, 40-160). The mean scores may vary based on country, age, or developmental domain (compared with US data), and normative data are not available for all populations or languages of interest.[26] The Bayley-III has been previously translated into Chinese (Mandarin), adapted for the Chinese population,[27] and used as a developmental assessment tool in two further clinical studies.[28,29] The Bayley-III (Chinese version) was completed at days 365 and 545. The primary outcome was the Bayley-III cognitive composite score at day 365.

Other Secondary Outcomes

Weight growth rate from 14 to 120 days of age was a key secondary growth and safety outcome. At study enrollment, infant birth characteristics and family demographics data were collected; parents completed a baseline recall of tolerance and stool characteristics. At all subsequent study visits through day 365, a 24-hour recall of formula intake, tolerance, and stool characteristics was collected. Anthropometric measures were recorded at all study visits. Medically confirmed adverse events (AEs) were collected through day 545 and coded according to specific AE and body system involved. In addition to the Bayley-III, the following instruments used were previously translated, revised, and adapted for use in Chinese populations: Ages & Stages Questionnaire (ASQ), MacArthur-Bates Communicative Development Inventories (CDI), and Carey Toddler Temperament Scales (TTS). The ASQ was completed at days 120, 180, and 275. The CDI, TTS, and Single Object Free Play Task were conducted at days 365 and 545. All secondary outcomes are detailed in the Appendix (available at www.jpeds.com).

Statistical Analyses

A sample size of 143 infants per group was required to detect a 5-point difference in the Bayley-III cognitive composite score (SD, 15; 80% power; $\alpha = 0.05$; 2 tailed test). We aimed to enroll approximately 450 participants to accommodate a potential attrition rate of 35%. Bayley-III composite scores were analyzed separately by ANOVA and post hoc by ANCOVA to adjust for potential confounding variables. With the exception of a one-tailed test for comparison of mean weight growth rates (per American Academy of Pediatrics Task Force on Clinical Testing of Infant Formulas[30]), all other secondary outcome comparisons were 2 tailed ($\alpha = 0.05$). Detailed statistical analysis methods for other secondary outcomes are provided in the Appendix. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

A total of 451 participants were randomized and received allocated study formula (control, n = 228; MFGM + LF, n = 223) (Figure 1; available at www.jpeds.com). No group differences were observed in birth characteristics, body weight, length, or head circumference by sex or other family demographics collected at study enrollment (Table III). For all participants, no statistically significant group differences were detected for study formula discontinuation before day 365 (P = .96). No group differences in participant characteristics or family demographics were detected for those who discontinued the study. The most common reason for study discontinuation was that the participant was lost to follow-up. A total of 292 infants completed study feeding through day 365 (control, n = 148; MFGM + LF, n = 144).

Global Developmental Status: Bayley-III Primary and Secondary Outcomes

Primary outcome Bayley-III data were available for all who completed study feeding with the exception of one participant in the MFGM + LF group (Figure 1). The Bayley-III cognitive composite mean ± SE score at day 365 was significantly higher for the MFGM + LF vs the control group (111.0 ± 0.9 vs 102.3 ± 0.9; an 8.7-point difference; P < .001) (Table IV). MFGM + LF vs control language (122.6 ± 0.9 vs 110.3 ± 0.9; a 12.3-point difference) and motor (118.3 ± 1.2 vs 105.7 ± 1.2; a 12.6-point difference) mean scores were also significantly higher (P < .001). No significant group differences were detected in social-emotional or general adaptive mean scores. Similar results persisted when adjusted for family income, parental education, and other socioenvironmental variables. Owing to study attrition after day 365 nearly 40% of participants did not undergo subsequent testing; no group differences were detected (adjusted or unadjusted) in any Bayley-III domain in participants tested at day 545 (control, n = 88; MFGM + LF, n = 95).

Table III. Birth characteristics* and infant and family demographics at enrollment		
Characteristics	Control	MFGM + LF
Total no. of participants	228	223
Birth characteristics		
Weight, g	3390.5 ± 23.2	3438.2 ± 23.4
Length, cm	49.8 ± 0.1	50.0 ± 0.1
No. of males/females	134/94	131/92
Anthropometrics at enrollment		
Males		
Weight, g	3827.3 ± 34.2	3853.8 ± 34.6
Length, cm	52.0 ± 0.1	52.1 ± 0.1
Weight-for-length z-score	0.1 ± 0.1	0.1 ± 0.1
Head circumference, cm	35.5 ± 0.1	35.6 ± 0.1
Females		
Weight, g	3708.1 ± 44.9	3750.7 ± 45.5
Length, cm	51.5 ± 0.1	51.5 ± 0.1
Weight-for-length z-score	0.0 ± 0.1	0.2 ± 0.1
Head circumference, cm	35.0 ± 0.1	35.2 ± 0.1
No. family members in household	4.5 ± 0.1	4.4 ± 0.1
Maternal age at birth, y		
<25	72 (32)	62 (28)
25-29	102 (45)	108 (48)
30-35	47 (21)	43 (19)
>35	7 (3)	10 (4)
Maternal use of DHA supplements		
Regular consumption	67 (29)	71 (32)
(≥1 time/week)		
Did not consume regularly	161 (71)	152 (68)
Maternal use of prenatal vitamins		
Regular consumption	69 (30)	73 (33)
(≥1 time/week)		
Did not consume regularly	159 (70)	150 (67)
Monthly average family income, RMB		
<3000	61 (27)	67 (30)
3000-5999	119 (52)	120 (54)
6000-8000	33 (14)	22 (10)
>8000	15 (17)	14 (6)
Maternal education		
No formal education	2 (1)	3 (1)
Primary school	12 (5)	14 (6)
Junior school	135 (59)	140 (63)
High school/technical school	56 (25)	40 (18)
Associate degree	18 (8)	20 (9)
Bachelor degree	4 (2)	6 (3)
Masters (or above) degree	1 (0)	0 (0)
Paternal education		
No formal education	1 (0)	1 (0)
Primary school	19 (8)	17 (8)
Junior school	116 (51)	119 (53)
High school/technical school	66 (29)	53 (24)
Associate degree	18 (8)	24 (11)
Bachelor degree	7 (3)	9 (4)
Masters (or above) degree	1 (0)	0 (0)

RMB, renminbi.
Values are number (%) or mean ± SE.
*All participants identified as Asian.

Other Secondary Outcomes through 18 Months of Age

ASQ scores (mean ± SE) were significantly higher in the MFGM + LF vs control group at day 120 (Table V; available at www.jpeds.com). Higher scores for all 5 domains in the MFGM + LF group persisted from day 120 to day 275 and a significant overall effect was detected (Table VI; available at www.jpeds.com). CDI scores were used as a measure of language development (Table VII and Table VIII; available at www.jpeds.com). No group differences were detected at day 365; significantly higher scores were detected for the MFGM + LF vs control group at day 545 in sentence complexity (using words in longer and more grammatically correct combinations) and 2 categorical items: absent owners (naming an absent person to whom a visible object belongs) and Chinese classifiers (grammatical marker specific to Chinese language). For TTS scores, a statistically significant group difference in 1 of 9 domains (activity level) was detected at day 365 (Table IX; available at www.jpeds.com). No group differences were detected at day 545. Using the Single Object Free Play Task to measure attention, look duration (mean ± SE) at day 365 was significantly longer in the MFGM + LF vs the control group (23.9 ± 2.0 vs 18.2 ± 2.0 seconds; P = .03) (Table X; available at www.jpeds.com). No group differences were detected at day 545 (MFGM + LF, n = 29: 21.0 ± 2.4 seconds vs control, n = 27: 23.0 ± 2.5 seconds); however, data availability was low owing to limitations on data usability and study attrition. Groups were similar for look episodes at days 365 and 545.

Infant Growth

No statistically significant group differences by sex in weight growth rate from days 14 to 120 were detected (Table XI; available at www.jpeds.com). As outlined in American Academy of Pediatrics guidance, rate of weight gain is the most important consideration in clinical evaluation of infant formula with differences of >3 g/day over a 3- to 4-month period considered clinically significant.[30] No statistically significant group differences by sex were observed for weight, length, or head circumference growth rates for any measured age range, with the exception of small differences in length growth rate (0.01 cm/day) for females from day 14 to 60 or day 14 to 90. No statistically significant group differences by sex were observed for mean achieved weight or weight-for-length z-score at any measured time point up to 545 days of age; statistically significant, minor differences in achieved length and head circumference are reported in Table XII (available at www.jpeds.com). The mean achieved weight for males and females using the World Health Organization weight-for-age standard growth chart[31] plotted between the 75th and 90th percentiles throughout the study period (Figure 2 and Figure 3; available at www.jpeds.com).

Tolerance and AEs

The mean study formula intake (mL/day) increased from day 30 (approximately 800 mL/day) to 120 (approximately 930 mL/day) for both groups by sex, indicating typical intake for both groups. Group intake was similar at all time points assessed (data not shown); intake began to plateau by day 120 to 180 and decreased slightly by day 275 (approximately 900 mL/day) as parents and caregivers begin to offer complementary foods. Fussiness and amount of gas (with a minor exception at day 42) were similar at all study time points

Table IV. Bayley-III composite scores, days 365 and 545

| | Bayley-III composite score | | | | | |
| | Unadjusted | | | Adjusted* | | |
Domains	Control (n = 148)	MFGM + LF (n = 143)	*P* value	Control (n = 148)	MFGM + LF (n = 143)	*P* value
Primary outcome						
Day 365						
Cognitive	102.3 ± 0.9	111.0 ± 0.9	<.001	102.1 ± 1.0	110.8 ± 1.0	<.001
Secondary outcomes						
Language	110.3 ± 0.9	122.6 ± 0.9	<.001	109.8 ± 1.0	122.1 ± 1.0	<.001
Motor	105.7 ± 1.2	118.3 ± 1.2	<.001	104.8 ± 1.3	117.3 ± 1.3	<.001
Social-emotional	97.1 ± 1.1	97.2 ± 1.1	.95	96.8 ± 1.2	97.0 ± 1.2	.91
General adaptive	103.3 ± 1.2	105.1 ± 1.3	.30	102.7 ± 1.4	104.9 ± 1.4	.21
	Control (n = 88)	MFGM + LF (n = 95)	*P* value	Control (n = 88)	MFGM + LF (n = 95)	*P* value
Day 545						
Cognitive	110.5 ± 1.1	111.8 ± 1.0	.39	111.1 ± 1.2	112.1 ± 1.1	.50
Language	116.9 ± 0.8	117.0 ± 0.7	.93	117.0 ± 0.9	117.2 ± 0.8	.83
Motor	131.8 ± 1.0	132.5 ± 1.0	.60	132.3 ± 1.2	132.9 ± 1.1	.70
Social-emotional	98.4 ± 1.9	97.3 ± 1.8	.67	97.9 ± 2.1	97.0 ± 2.0	.73
General adaptive	108.5 ± 1.9	109.1 ± 1.9	.83	108.7 ± 2.2	109.1 ± 2.1	.90

Values are mean ± SE.
*ANCOVA model included the following adjustments for sex, birth weight, family income, number of family members living in the household, father education, mother education, mother's age when participant was born, maternal DHA supplement use during last 12 weeks of pregnancy, maternal prenatal vitamin use during last 12 weeks of pregnancy, and exposure to smoking at study enrollment.

(Table XIII and Table XIV; available at www.jpeds.com). No differences in mean stool frequency (number per day) or stool consistency were detected at any time point assessed (Table XV; available at www.jpeds.com).

The overall incidence of AEs categorized by respiratory and gastrointestinal system, including the specific incidences of upper respiratory tract infections, cough, and diarrhea, were significantly lower for the MFGM + LF group than for the control group (Table XVI). Episodes of respiratory and diarrhea events were also significantly lower. No group difference in the incidence of constipation was detected. No group differences in the skin system, including eczema, were detected. No group difference was detected in the number of participants for whom at least one medically confirmed AE was reported (control, 208, 91%; MFGM + LF, 198, 89%; *P* = .43). No serious AEs were reported.

Discussion

The current randomized, double-blinded trial demonstrated an accelerated neurodevelopmental profile by 12 months of age in infants receiving bioactive bMFGM components and bovine lactoferrin in infant formula at concentrations similar to human milk. The mean Bayley-III cognitive scores at 12 months of age were higher by 8.7 points and language and motor scores by approximately 12 points for infants in the MFGM + LF group than those in the control group. Differences persisted after adjustment for potentially confounding socioeconomic and environmental variables. These findings are in line with a prior study demonstrating significantly higher mean Bayley-III cognitive scores for infants receiving formula with added bMFGM (vs without).[19]

Although the reported group difference was lower than observed in the current study (approximately 4 vs 9 points), the feeding period was also shorter (6 vs 12 months) in the previous study. Although our study did not include a breastfed comparison group, the magnitude of difference for the mean cognitive score between MFGM + LF and control groups was comparable with the previously reported comparison of formula-fed to breastfed infants.[19]

In addition, although the mean Bayley-III cognitive, language, and motor scores in this study were higher for both groups relative to US norms (100 ± 15), the control group mean scores seemed to be relatively comparable with scores previously reported for neurotypical infants and toddlers in 6 districts of Shanghai (n = 457) using the Chinese adaptation of the Bayley-III (cognitive, 104.62 ± 11.40; language, 105.96 ± 12.43; and motor, 106.27 ± 13.39).[27] Similar observations of higher scores in ≥1 Bayley-III subscales for populations worldwide compared with US reference data are well-described,[26,32,33] reinforcing the need for population-specific norms.

Rapid acceleration in expressive language[34,35] and increased attentional engagement[36] from 12 to 18 months of age is well-documented. In the current study, infants receiving bMFGM and bovine lactoferrin scored higher in selected communicative measures, including the Bayley-III language domain at 12 months of age. Both groups followed a pattern of longitudinal vocabulary growth over 12-18 months of age. The observation that few group differences in neurodevelopmental outcomes were detected at 18 months could indicate that the control group caught up developmentally and the earlier advantages observed in the MFGM + LF group were not sustained. However, scores for 3 subcategories of the CDI were significantly higher in

Table XVI. Medically confirmed Adverse Events classified by body system and event category

AE Incidence

Body System and Category	Study Group	n (%)	P
Respiratory	Control	193 (85)	.02
	MFGM + LF	168 (75)	
Upper respiratory tract infection	Control	177 (78)	.02
	MFGM + LF	151 (68)	
Cough	Control	92 (40)	.02
	MFGM + LF	66 (30)	
Gastrointestinal	Control	157 (69)	.02
	MFGM + LF	130 (58)	
Diarrhea	Control	156 (68)	.003
	MFGM + LF	121 (54)	
Constipation	Control	27 (12)	.45
	MFGM + LF	21 (9)	
Metabolic and Nutrition			
Lack of Appetite	Control	36 (16)	.35
	MFGM + LF	28 (13)	
Skin	Control	31 (14)	.31
	MFGM + LF	23 (10)	
Diaper Rash	Control	18 (8)	.58
	MFGM + LF	14 (6)	
Eczema	Control	9 (4)	.80
	MFGM + LF	7 (3)	
Viral Skin Rash	Control	7 (3)	.54
	MFGM + LF	4 (2)	

AE Episodes	Study Group	Number of Episodes, n (%)						
		None	1	2	3	4	5	P
Respiratory*	Control	35 (15)	54 (24)	58 (25)	54 (24)	25 (11)	2 (1)	<.001
	MFGM + LF	55 (25)	66 (30)	62 (28)	32 (14)	8 (4)	0 (0)	
Diarrhea	Control	72 (32)	112 (49)	43 (19)	1 (0)	0 (0)	0 (0)	.005
	MFGM + LF	102 (46)	91 (41)	27 (12)	3 (1)	0 (0)	0 (0)	

*Respiratory includes: episodes of URI and Cough

the MFGM + LF group at 18 months of age. One explanation could include differences in mode of administration (eg, Bayley-III by direct observation vs parent-reported CDI) or in testing content that may be sensitive to different components of development. Another potential explanation lies in the concept of "developmental cascades," defined as cumulative change in one domain that influences distal outcomes over time or shifts in other domains.[37] In a study of the nutrient docosahexaenoic acid and development of attention in infants and toddlers, for example, a transition of neurodevelopmental effects from the first to second year of age was observed.[36,38] Along the same lines, the MFGM + LF group demonstrated accelerated neurodevelopment by 12 months characterized in part by significantly longer attentional engagement and higher selected Bayley-III scores. Whereas the differences in these outcome measures did not persist at 18 months, improvements in several aspects of language at 18 months may be suggestive of a developmental cascade.

Addition of whey lipid-protein concentrate (5 g/L, source of bMFGM) and bovine lactoferrin (0.6 g/L) in routine infant formula was safe, well-tolerated, and associated with age-appropriate growth and fewer gastrointestinal and respiratory AEs through 18 months of age. Previously, in term infants randomized to a formula enriched with the same source of bMFGM (vs a control) through 4 months of age, a post hoc analysis of AEs suggested a low but increased, incidence of eczema.[18] Subsequently, no group differences in reported eczema were detected in infants receiving bMFGM-enriched formula (same source as current study but slightly higher concentration [approximately 6 g/L vs 5 g/L]) through 6 months of age.[19] In the current study, bMFGM and bovine lactoferrin in infant formula were not associated with increased risk of eczema or any other AEs within the skin system through 18 months of age. A decreased risk of diarrhea in infants and young children[9,39,40] and lower respiratory infection rates in infants[41] and children with recurrent respiratory infections[42] receiving dietary bovine lactoferrin has been demonstrated previously. Clinical evidence of lower incidence of diarrhea[21] and otitis media[20] in infants receiving dietary bMFGM are also consistent with preclinical data supporting antipathogenic effects. Consequently, we hypothesize that the decrease in AEs in the present trial may be attributable to both nutritional components.

We note several limitations of the present study. One is that a breastfed reference group was not enrolled. Such a reference group certainly helps to gauge the degree to which formula-fed infants approach optimal levels of outcome; however, the confounding of variables inherent in the use of a breastfeeding reference group does not allow for direct comparison and would not directly bear on the demonstration of the relative efficacy of the formulas evaluated in this

study. Another potential limitation is the inability to distinguish with certainty between individual effects of MFGM and lactoferrin, although we note that a growing body of clinical evidence to date has demonstrated neurodevelopmental or behavioral effects of MFGM and its components, whereas clinical evidence for lactoferrin in these domains is absent. Finally, data availability at 18 months was low owing to study attrition and limitations on data usability.

Overall, the addition of bMFGM and bovine lactoferrin in an infant formula was associated with a significantly accelerated neurodevelopmental profile, including higher ASQ scores from 4 to 9 months of age, higher mean Bayley-III cognitive, language, and motor scores, and longer sustained attention at 12 months, and higher scores for some language domains (CDI) at 18 months of age. The current study is also the first to demonstrate safety, tolerance, and association with typical growth, and a significantly lower incidence of gastrointestinal- and respiratory-associated AEs through 18 months of age in infants receiving bMFGM components and bovine lactoferrin in infant formula at concentrations similar to human milk. Therefore, dietary bMFGM and bovine lactoferrin together may not only provide a better approximation of the bioactive composition of human milk, but also contribute to beneficial cognitive, gastrointestinal, and respiratory health outcomes. As noted, the field of MFGM research is rapidly emerging and the data in our study add to this knowledge base. More data will certainly be needed to evaluate neurodevelopmental outcomes in older children to help establish how the nutritive effects of MFGM may be manifested longitudinally using a developmental systems approach. ∎

Data Statement

Data sharing statement available at www.jpeds.com.

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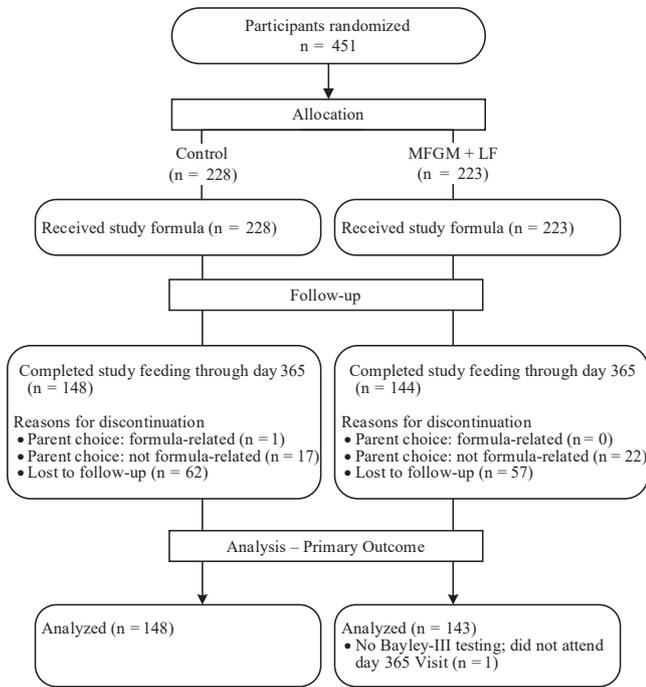
Figure 1. Study allocation.
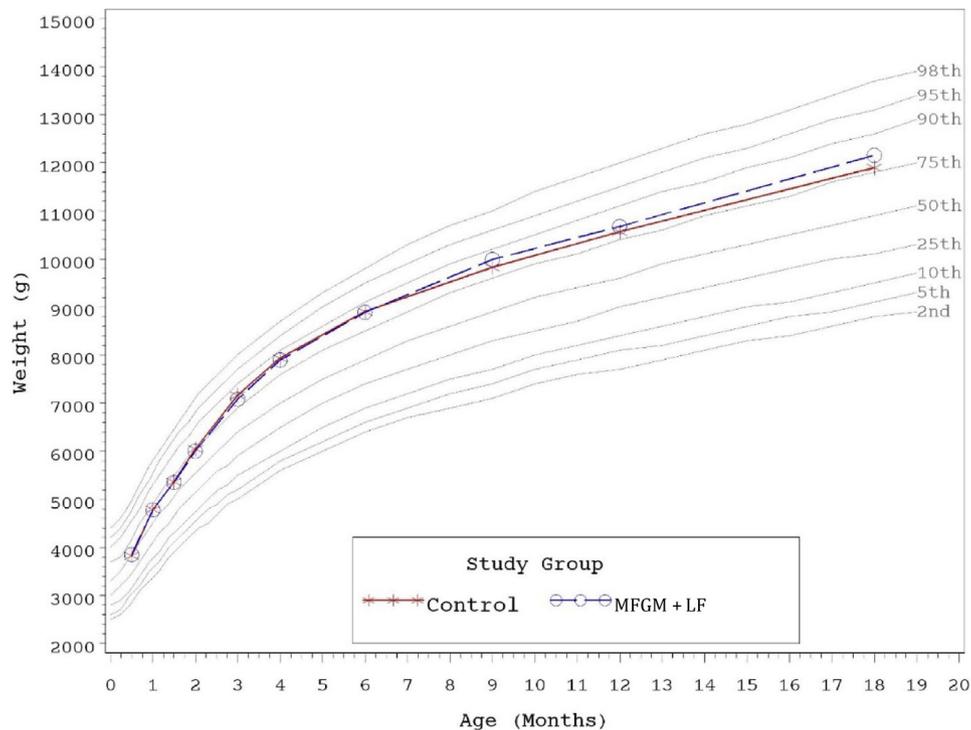
Figure 2. Mean achieved weight for male participants with World Health Organization reference percentiles (2nd to 98th) through 18 months (14-545 days) of age. Control, stars; MFGM + LF, circles.
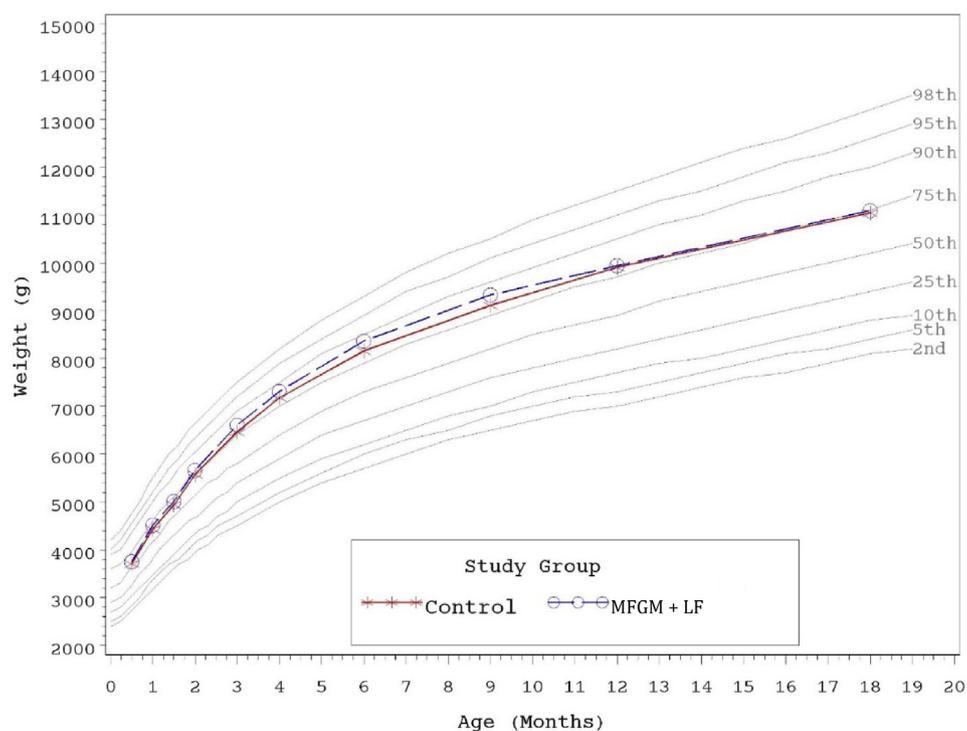
Figure 3. Mean achieved weight for female participants with World Health Organization reference percentiles (2nd to 98th) through 18 months (14-545 days) of age. Control, stars; MFGM + LF, circles.

Table I. Participant inclusion and exclusion criteria	
Inclusion criteria	**Exclusion criteria**
10-14 days of age at randomization, inclusive (day of birth is considered day 0)	History of underlying metabolic or chronic disease; congenital malformation; or any other condition which, in the opinion of the investigator, is likely to interfere with: the ability of the infant to ingest food, the normal growth and development of the infant, or the evaluation of the infant
Exclusively formula fed for at least 3 days before randomization	Evidence of feeding difficulties or formula intolerance, such as vomiting or poor intake, at time of randomization (at investigator discretion)
Singleton birth	Weight at visit 1 is <95% of birth weight [(weight at visit 1 ÷ birth weight) × 100 < 95%]
Gestational age of 37-42 weeks (36 weeks and 6 days is considered 36 weeks gestational age)	Infant is immunocompromised (according to a doctor's diagnosis of immunodeficiency such as combined immunodeficiencies, DiGeorge syndrome, Wiskott-Aldrich syndrome, severe congenital neutropenia and secondary immunodeficiencies linked to HIV infection, Down syndrome or others), and children with known head, brain disease, or injury such as microcephaly or macrocephaly
Birth weight of 2500-4000 g	
Signed informed consent obtained for infant's participation in the study	
Parent or guardian of infant agrees not to enroll infant in another interventional clinical research study while participating in this study	

Table V. ASQ domain scores, days 120, 180, and 275

Domains	Day 120			Day 180			Day 275		
	Control (n = 187)	MFGM + LF (n = 187)	P value	Control (n = 185)	MFGM + LF (n = 183)	P value	Control (n = 167)	MFGM + LF (n = 166)	P value
Communication	49.0 ± 0.5	51.3 ± 0.5	.003	50.7 ± 0.5	51.4 ± 0.5	.353	51.4 ± 0.6	52.4 ± 0.6	.227
Gross motor	49.6 ± 0.5	52.2 ± 0.5	<.001	48.4 ± 0.6	49.4 ± 0.6	.255	46.1 ± 0.8	47.0 ± 0.8	.437
Fine motor	46.6 ± 0.6	49.5 ± 0.6	.002	52.0 ± 0.6	52.9 ± 0.6	.262	53.4 ± 0.5	54.5 ± 0.5	.099
Problem solving	49.6 ± 0.6	52.0 ± 0.6	.002	49.4 ± 0.6	51.0 ± 0.6	.060	51.8 ± 0.6	52.6 ± 0.6	.294
Personal/social	46.5 ± 0.5	50.2 ± 0.5	<.001	47.0 ± 0.6	48.4 ± 0.6	.124	50.0 ± 0.6	50.8 ± 0.7	.351

Values are mean ± SE.

Table VI. ASQ domain scores from day 120 to 275, repeated measures analysis

Domains	Day 120		Day 180		Day 275		P value for age*study group interaction	P value for study group
	Control n = 187	MFGM + LF n = 187	Control n = 185	MFGM + LF n = 183	Control n = 167	MFGM + LF n = 166		
Communication	49.1 ± 0.5	51.4 ± 0.5	50.8 ± 0.5	51.5 ± 0.5	51.5 ± 0.6	52.5 ± 0.6	.238	.010
Gross motor	49.7 ± 0.6	52.3 ± 0.6	48.6 ± 0.6	49.5 ± 0.6	46.2 ± 0.7	47.1 ± 0.7	.299	.010
Fine motor	46.6 ± 0.6	49.5 ± 0.6	52.0 ± 0.6	52.9 ± 0.6	53.4 ± 0.6	54.6 ± 0.6	.130	.002
Problem solving	49.7 ± 0.6	52.1 ± 0.6	49.5 ± 0.6	51.1 ± 0.6	51.9 ± 0.6	52.7 ± 0.6	.408	.003
Personal/social	46.5 ± 0.6	50.2 ± 0.6	47.1 ± 0.6	48.4 ± 0.6	50.0 ± 0.6	51.0 ± 0.6	.032	<.001

Values are mean ± SE.

Table VII. CDI words and gestures, day 365			
Parent responses	**Control (n = 148)**	**MFGM + LF (n = 143)**	***P* value**
First sign of understanding			
Responds when name is called			
Yes	146 (99)	139 (97)	.441
No	2 (1)	4 (3)	
Responds to "no no"			
Yes	130 (88)	130 (91)	.450
No	18 (12)	13 (9)	
Responds to "there is mommy/daddy"			
Yes	144 (97)	138 (97)	.746
No	4 (3)	5 (3)	
Starting to talk			
Point/make sound when want object			
Never	3 (2)	4 (3)	.803
Sometimes	48 (32)	42 (29)	
Often	97 (66)	97 (68)	
Say "want" or "take"			
Never	48 (32)	45 (31)	.453
Sometimes	58 (39)	49 (34)	
Often	42 (28)	49 (34)	
Imitation			
Never	54 (36)	56 (39)	.314
Sometimes	65 (44)	68 (48)	
Often	29 (20)	19 (13)	
Labeling			
Never	92 (62)	74 (52)	.119
Sometimes	38 (26)	50 (35)	
Often	18 (12)	19 (13)	
Summary scores			
Early gestures	13.3 ± 0.4	13.5 ± 0.4	.822
Later gestures	15.6 ± 0.6	16.4 ± 0.6	.353
Total actions and gestures	28.9 ± 0.8	30.0 ± 0.9	.396
Phrases understood	20.7 ± 0.5	21.3 ± 0.5	.363
Words understood	202.3 ± 7.7	201.5 ± 7.9	.940
Words produced	12.2 ± 1.7	12.6 ± 1.7	.872

Values are number (%) or mean ± SE.

Table VIII. CDI words and sentences, day 545			
Parent responses	**Control (n = 88)**	**MFGM + LF (n = 95)**	***P* value**
How children use words			
Absent object (comprehension)			
Not yet	8 (9)	11 (12)	.629
Sometimes	39 (44)	32 (34)	
Often	41 (47)	52 (55)	
Absent owner			
Not yet	22 (25)	11 (12)	.032
Sometimes	40 (45)	47 (49)	
Often	26 (30)	37 (39)	
Absent object (production)			
Not yet	44 (50)	38 (40)	.179
Sometimes	31 (35)	38 (40)	
Often	13 (15)	19 (20)	
Past			
Not yet	47 (53)	49 (52)	.434
Sometimes	33 (38)	31 (33)	
Often	8 (9)	15 (16)	
Future			
Not yet	67 (76)	68 (72)	.269
Sometimes	16 (18)	16 (17)	
Often	5 (6)	11 (12)	
Sentences			
Combining verbs			
Not yet	46 (52)	47 (49)	.480
Sometimes	38 (43)	40 (42)	
Often	4 (5)	8 (8)	
Possessive			
Not yet	39 (44)	32 (34)	.149
Sometimes	38 (43)	47 (49)	
Often	11 (13)	16 (17)	
Chinese classifiers			
Not yet	63 (72)	57 (60)	.035
Sometimes	23 (26)	29 (31)	
Often	2 (2)	9 (9)	
Past tense			
Not yet	67 (76)	60 (63)	.071
Sometimes	16 (18)	26 (27)	
Often	5 (6)	9 (9)	
Combining			
Not yet	36 (41)	44 (46)	.649
Sometimes	46 (52)	35 (37)	
Often	6 (7)	16 (17)	
Summary scores			
Words produced	255.1 ± 21.0	254.1 ± 20.4	.973
[Sentence] complexity	20.1 ± 1.7	24.9 ± 1.6	.041

Values are number (%) or mean ± SE.

Table IX. TTS domain scores, days 365 and 545

Domains	Day 365			Day 545		
	Control (n = 148)	MFGM + LF (n = 143)	P value	Control (n = 88)	MFGM + LF (n = 95)	P value
Activity level	3.6 ± 0.04	3.7 ± 0.04	.029	3.8 ± 0.05	3.8 ± 0.04	.540
Regularity	3.0 ± 0.04	2.9 ± 0.04	.130	3.0 ± 0.06	3.0 ± 0.06	.812
Approach/withdrawal	3.1 ± 0.06	3.2 ± 0.06	.851	3.2 ± 0.06	3.2 ± 0.06	.483
Adaptability	3.4 ± 0.04	3.5 ± 0.04	.145	3.4 ± 0.05	3.4 ± 0.05	.911
Intensity	3.8 ± 0.05	3.9 ± 0.05	.572	4.1 ± 0.06	4.0 ± 0.05	.266
Mood	3.2 ± 0.04	3.2 ± 0.04	.535	3.4 ± 0.06	3.3 ± 0.06	.510
Persistence	3.7 ± 0.04	3.8 ± 0.04	.376	3.6 ± 0.06	3.6 ± 0.06	.872
Distractibility	4.1 ± 0.04	4.0 ± 0.04	.530	3.9 ± 0.05	3.9 ± 0.05	.297
Sensory threshold	3.5 ± 0.04	3.5 ± 0.05	.494	3.4 ± 0.05	3.4 ± 0.05	.980

TTS, Carey Toddler Temperament Scale.
Values are number mean ± SE.

Table X. Five-minute single object free play, days 365 and 545

Characteristics	Day 365			Day 545		
	Control (n = 86)	MFGM + LF (n = 84)	P value	Control (n = 27)	MFGM + LF (n = 29)	P value
Look duration						
Longest	62.7 ± 4.5	68.4 ± 4.4	.344	74.5 ± 6.9	66.9 ± 6.8	.363
Total	232.5 ± 4.4	241.8 ± 4.3	.118	246.6 ± 5.1	242.0 ± 5.1	.457
Mean	18.2 ± 2.0	23.9 ± 2.0	.033	23.0 ± 2.5	21.0 ± 2.4	.519
Look episodes	15.8 ± 0.6	14.4 ± 0.6	.780	13.3 ± 1.1	14.5 ± 1.1	.951

Values are mean ± SE.

Table XI. Weight, length, and HC growth rates from day 14 to 30, 42, 60, 90, and 120

Days	Group (n)	Growth rate		
		Weight, g/d	Length, cm/d	HC, cm/d
Male				
30	Control (127)	50.5 ± 1.7	0.15 ± 0.006	0.08 ± 0.003
	MFGM + LF (129)	48.6 ± 1.7	0.14 ± 0.006	0.08 ± 0.003
42	Control (123)	49.0 ± 1.3	0.15 ± 0.004	0.08 ± 0.002
	MFGM + LF (122)	47.8 ± 1.3	0.14 ± 0.004	0.08 ± 0.002
60	Control (116)	45.3 ± 0.9	0.14 ± 0.003	0.07 ± 0.002
	MFGM + LF (118)	43.6 ± 0.9	0.14 ± 0.003	0.07 ± 0.002
90	Control (115)	41.4 ± 0.8	0.13 ± 0.002	0.06 ± 0.001
	MFGM + LF (114)	40.1 ± 0.8	0.13 ± 0.002	0.06 ± 0.001
120	Control (111)	37.1 ± 0.6	0.11 ± 0.002	0.05 ± 0.001
	MFGM + LF (111)	36.5 ± 0.6	0.12 ± 0.002	0.05 ± 0.001
Female				
30	Control (91)	38.1 ± 1.6	0.12 ± 0.006	0.07 ± 0.004
	MFGM + LF (89)	39.2 ± 1.7	0.13 ± 0.006	0.08 ± 0.004
42	Control (88)	39.2 ± 1.2	0.13 ± 0.005	0.07 ± 0.003
	MFGM + LF (88)	40.1 ± 1.2	0.14 ± 0.005	0.08 ± 0.003
60	Control (80)	37.8 ± 1.0	0.12 ± 0.003*	0.06 ± 0.002
	MFGM + LF (81)	39.0 ± 1.0	0.13 ± 0.003	0.07 ± 0.002
90	Control (79)	34.4 ± 0.8	0.11 ± 0.002*	0.05 ± 0.001
	MFGM + LF (78)	35.9 ± 0.8	0.12 ± 0.002	0.06 ± 0.001
120	Control (77)	31.6 ± 0.7	0.10 ± 0.002	0.05 ± 0.001
	MFGM + LF (76)	32.7 ± 0.7	0.11 ± 0.002	0.05 ± 0.001

Values are mean ± SE.
HC, Head circumference.
*Control vs MFGM + LF, $P < .05$.

Table XII. Achieved weight, length, weight-for-length z-scores, and HC at days 30, 42, 60, 90, 120, 275, 365, and 545

Days	Group (n)	Weight, g	Length, cm	Weight-for-length z-score	HC, cm
Male					
30	Control (127)	4787 ± 45	54.8 ± 0.2	0.7 ± 0.1	37.1 ± 0.1
	MFGM + LF (129)	4783 ± 45	54.8 ± 0.2	0.7 ± 0.1	37.2 ± 0.1
42	Control (123)	5369 ± 49	56.7 ± 0.2	0.7 ± 0.1	38.0 ± 0.1
	MFGM + LF (122)	5355 ± 49	56.6 ± 0.2	0.7 ± 0.1	38.0 ± 0.1
60	Control (116)	6048 ± 48	59.0 ± 0.2	0.7 ± 0.1	39.0 ± 0.1
	MFGM + LF (117)	6004 ± 48	58.9 ± 0.2	0.6 ± 0.1	39.0 ± 0.1
90	Control (115)	7168 ± 72	62.0 ± 0.2	1.1 ± 0.1	40.4 ± 0.1
	MFGM + LF (112)	7086 ± 73	62.2 ± 0.2	0.8 ± 0.1	40.5 ± 0.1
120	Control (108)	7941 ± 78	64.7 ± 0.2	1.1 ± 0.1	41.7 ± 0.1
	MFGM + LF (109)	7897 ± 78	64.8 ± 0.2	1.0 ± 0.1	41.7 ± 0.1
180	Control (111)	8905 ± 83	68.2 ± 0.2	1.2 ± 0.1	43.4 ± 0.1
	MFGM + LF (109)	8889 ± 84	68.3 ± 0.2	1.2 ± 0.1	43.5 ± 0.1
275	Control (103)	9824 ± 94	72.5 ± 0.2	1.1 ± 0.1	45.1 ± 0.1
	MFGM + LF (99)	9988 ± 97	72.5 ± 0.2	1.2 ± 0.1	45.3 ± 0.1
365	Control (93)	10 568 ± 101	76.2 ± 0.2	1.0 ± 0.1	46.3 ± 0.1
	MFGM + LF (85)	10 675 ± 108	76.1 ± 0.3	1.1 ± 0.1	46.5 ± 0.1
545	Control (53)	11 900 ± 162	82.5 ± 0.4	0.9 ± 0.1	47.5 ± 0.2
	MFGM + LF (55)	12 157 ± 164	83.0 ± 0.4	1.1 ± 0.1	47.9 ± 0.2
Female					
30	Control (91)	4433 ± 52	53.8 ± 0.2	0.4 ± 0.1	36.3 ± 0.1*
	MFGM + LF (89)	4516 ± 53	54.0 ± 0.2	0.5 ± 0.1	36.7 ± 0.1
42	Control (88)	4943 ± 57	55.4 ± 0.2	0.6 ± 0.1	37.2 ± 0.1*
	MFGM + LF (88)	5012 ± 57	55.8 ± 0.2	0.5 ± 0.1	37.6 ± 0.1
60	Control (80)	5577 ± 65	57.3 ± 0.2	0.8 ± 0.1	38.0 ± 0.1*
	MFGM + LF (80)	5664 ± 65	57.9 ± 0.2	0.7 ± 0.1	38.5 ± 0.1
90	Control (78)	6465 ± 78	60.2 ± 0.2*	0.9 ± 0.1	39.3 ± 0.1*
	MFGM + LF (77)	6607 ± 79	60.9 ± 0.2	0.9 ± 0.1	39.7 ± 0.1
120	Control (74)	7178 ± 89	62.9 ± 0.2	0.9 ± 0.1	40.5 ± 0.1
	MFGM + LF (74)	7310 ± 89	63.2 ± 0.2	1.0 ± 0.1	40.8 ± 0.1
180	Control (74)	8155 ± 100	65.9 ± 0.2*	1.2 ± 0.1	42.2 ± 0.2*
	MFGM + LF (74)	8365 ± 100	66.8 ± 0.2	1.2 ± 0.1	42.7 ± 0.2
275	Control (69)	9110 ± 109	70.2 ± 0.3*	1.1 ± 0.1	43.9 ± 0.2*
	MFGM + LF (71)	9327 ± 107	71.1 ± 0.3	1.1 ± 0.1	44.3 ± 0.2
365	Control (55)	9908 ± 127	74.2 ± 0.3	1.0 ± 0.1	45.1 ± 0.2
	MFGM + LF (60)	9939 ± 122	74.9 ± 0.3	0.9 ± 0.1	45.3 ± 0.2
545	Control (35)	11 049 ± 173	80.7 ± 0.4	0.8 ± 0.1	45.9 ± 0.2
	MFGM + LF (40)	11 093 ± 160	81.0 ± 0.4	0.8 ± 0.1	46.3 ± 0.2

Values are mean ± SE.
*Control vs MFGM + LF, P < .05.

Table XIII. Fussiness at days 14, 30, 42, 60, 90, 120, 180, and 365*

Days	Group	Not at all	Slightly	Moderately	Very	Extremely	P value
14	Control	53 (23)	131 (57)	44 (19)	0 (0)	0 (0)	.863
	MFGM + LF	54 (24)	125 (56)	41 (18)	3 (1)	0 (0)	
30	Control	27 (12)	147 (67)	41 (19)	3 (1)	0 (0)	.886
	MFGM + LF	30 (14)	143 (66)	43 (20)	2 (1)	0 (0)	
42	Control	29 (14)	141 (67)	39 (19)	1 (0)	0 (0)	.929
	MFGM + LF	25 (12)	149 (71)	34 (16)	2 (1)	0 (0)	
60	Control	36 (18)	128 (65)	30 (15)	2 (1)	0 (0)	.186
	MFGM + LF	26 (13)	136 (69)	30 (15)	5 (3)	0 (0)	
90	Control	45 (23)	130 (67)	18 (9)	0 (0)	0 (0)	.486
	MFGM + LF	42 (22)	125 (66)	21 (11)	1 (1)	0 (0)	
120	Control	59 (32)	116 (64)	7 (4)	0 (0)	0 (0)	.969
	MFGM + LF	63 (34)	112 (61)	7 (4)	1 (1)	0 (0)	
180	Control	67 (36)	113 (61)	5 (3)	0 (0)	0 (0)	.253
	MFGM + LF	78 (43)	100 (55)	5 (3)	0 (0)	0 (0)	
275	Control	90 (52)	80 (47)	2 (1)	0 (0)	0 (0)	.934
	MFGM + LF	91 (54)	75 (44)	4 (2)	0 (0)	0 (0)	
365	Control	82 (55)	65 (44)	1 (1)	0 (0)	0 (0)	.830
	MFGM + LF	82 (57)	59 (41)	2 (1)	0 (0)	0 (0)	

Values are number (%).
*Twenty-four-hour recall at study visits.

Table XIV. Gassiness at days 14, 30, 42, 60, 90, 120, 180, and 365*

Days	Group	None at all	Slight amount	Moderate amount	Excessive amount	P value
14	Control	0 (0)	56 (25)	168 (74)	4 (2)	.164
	MFGM + LF	0 (0)	70 (31)	148 (66)	5 (2)	
30	Control	0 (0)	21 (10)	191 (88)	6 (3)	.808
	MFGM + LF	0 (0)	23 (11)	189 (87)	6 (3)	
42	Control	0 (0)	16 (8)	189 (90)	5 (2)	.045
	MFGM + LF	0 (0)	28 (13)	179 (85)	3 (1)	
60	Control	0 (0)	27 (14)	166 (85)	3 (2)	.161
	MFGM + LF	0 (0)	16 (8)	180 (91)	1 (1)	
90	Control	0 (0)	38 (20)	155 (80)	0 (0)	.218
	MFGM + LF	0 (0)	30 (16)	157 (83)	2 (1)	
120	Control	0 (0)	56 (31)	125 (69)	1 (1)	.168
	MFGM + LF	0 (0)	44 (24)	139 (76)	0 (0)	
180	Control	1 (1)	61 (33)	122 (66)	1 (1)	.138
	MFGM + LF	0 (0)	48 (26)	135 (74)	0 (0)	
275	Control	6 (3)	62 (36)	104 (60)	0 (0)	.920
	MFGM + LF	1 (1)	73 (43)	95 (56)	1 (1)	
365	Control	3 (2)	74 (50)	71 (48)	0 (0)	.715
	MFGM + LF	1 (1)	79 (55)	63 (44)	0 (0)	

Values are number (%).
*Twenty-four-hour recall at study visits.

Table XV. Stool characteristics at days 14, 30, 42, 60, 90, 120, 180, and 365*

Days	Group (n)	Stool frequency	P value	Stool consistency					P value
				Hard	Formed	Soft	Unformed or seedy	Watery	
14	Control (228)	2.6 ± 0.1	.659	3 (1)	19 (8)	143 (63)	61 (27)	2 (1)	.481
	MFGM + LF (223)	2.6 ± 0.1		5 (2)	15 (7)	150 (67)	51 (23)	2 (1)	
30	Control (218)	2.0 ± 0.1	.905	1 (0)	34 (16)	145 (67)	38 (17)	0 (0)	.466
	MFGM + LF (218)	2.0 ± 0.1		2 (1)	34 (16)	152 (70)	30 (14)	0 (0)	
42	Control (210)	1.6 ± 0.1	.682	0 (0)	32 (15)	147 (70)	31 (15)	0 (0)	.118
	MFGM + LF (210)	1.6 ± 0.1		1 (0)	38 (18)	148 (70)	23 (11)	0 (0)	
60	Control (196)	1.4 ± 0.1	.505	0 (0)	33 (17)	148 (76)	15 (8)	0 (0)	.197
	MFGM + LF (196)	1.4 ± 0.1		1 (1)	47 (24)	131 (66)	18 (9)	0 (0)	
90	Control (193)	1.3 ± 0.0	.643	0 (0)	51 (26)	134 (69)	8 (4)	0 (0)	.516
	MFGM + LF (189)	1.3 ± 0.0		1 (1)	50 (26)	134 (71)	4 (2)	0 (0)	
120	Control (182)	1.2 ± 0.0	.648	0 (0)	52 (29)	123 (68)	6 (3)	0 (0)	.585
	MFGM + LF (183)	1.2 ± 0.0		1 (1)	54 (30)	125 (68)	3 (2)	0 (0)	
180	Control (185)	1.3 ± 0.0	.319	2 (1)	69 (38)	111 (60)	1 (1)	1 (1)	.370
	MFGM + LF (182)	1.2 ± 0.0		0 (0)	80 (44)	102 (56)	1 (1)	0 (0)	
275	Control (172)	1.2 ± 0.0	.777	2 (1)	109 (63)	59 (34)	2 (1)	0 (0)	.756
	MFGM + LF (170)	1.2 ± 0.0		1 (1)	114 (67)	52 (31)	3 (2)	0 (0)	
365	Control (148)	1.1 ± 0.0	.669	2 (1)	120 (81)	26 (18)	0 (0)	0 (0)	.560
	MFGM + LF (143)	1.2 ± 0.0		4 (3)	110 (77)	28 (20)	1 (1)	0 (0)	

Values are number (%) or mean ± SE.
*Twenty-four-hour recall at study visits.