Neurodevelopment and growth until 6.5 years of infants who consumed a low-energy, low-protein formula supplemented with bovine milk fat globule membranes: a randomized controlled trial

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ABSTRACT

Background: We previously reported results from a randomized controlled trial in which we found that Swedish infants consuming an experimental low-energy, low-protein formula (EF) supplemented with bovine milk fat globule membranes (MFGMs) until 6 mo of age had several positive outcomes, including better performance in the cognitive domain of Bayley Scales of Infant and Toddler Development 3rd Edition at 12 mo of age, and higher plasma cholesterol concentrations during the intervention, than infants consuming standard formula (SF).

Objectives: We aimed to evaluate neurodevelopment, growth, and plasma cholesterol status at 6 and 6.5 y of age in the same study population.

Methods: We assessed cognitive and executive functions using the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV), Brown Attention-Deficit Disorder Scales for Children and Adolescents (Brown-ADD), and Quantified Behavior (Qb) tests, and behavior using the Child Behavior Checklist (CBCL) and Teacher's Report Form (TRF), at 6.5 y of age. Anthropometrics and plasma lipids were assessed at 6 y of age.

Results: There were no differences between the EF and SF groups in any of the subscales in WISC-IV or Brown-ADD at 6.5 y of age, in the proportion of children with scores outside the normal range in the Qb test, nor in clinical or borderline indications of problems in adaptive functioning from parental and teacher's scoring using the CBCL and TRF. There were no differences between the EF and SF groups in weight, length, or head or abdominal circumferences, nor in plasma concentrations of homocysteine, lipids, insulin, or glucose.

Conclusions: Among children who as infants consumed a low-energy, low-protein formula supplemented with bovine MFGMs, there were no effects on neurodevelopment, growth, or plasma cholesterol status 6–6.5 y later. *Am J Clin Nutr* 2021;113:586–592.

Keywords: infant formula, breastfeeding, milk fat globule membranes, energy, protein, cognition, executive functions, behavior, cholesterol

Introduction

Even though exclusive breastfeeding for 6 mo is recommended by the WHO (1, 2), the global overall rate of exclusive breastfeeding for infants <6 mo of age has been estimated at only 40% (3). Because not being breastfed is associated with negative health effects even in developed countries (4), reducing the differences in health outcomes between formula-fed and breastfed infants can have considerable health effects at the population level. Higher protein and energy intake of formula-fed infants and the absence of factors essential for optimal development and growth present in human milk have been suggested to explain part of the observed differences between formula-fed and breastfed infants. The milk fat globule membrane (MFGM) is a biologically active milk fraction that historically has been discarded from infant formula when milk fat is replaced by vegetable oils (5). Different bovine MFGM concentrates are available as nutritional supplements and outcomes of supplementation of infant formulas with MFGMs have been studied in several clinical trials (6–12). We have
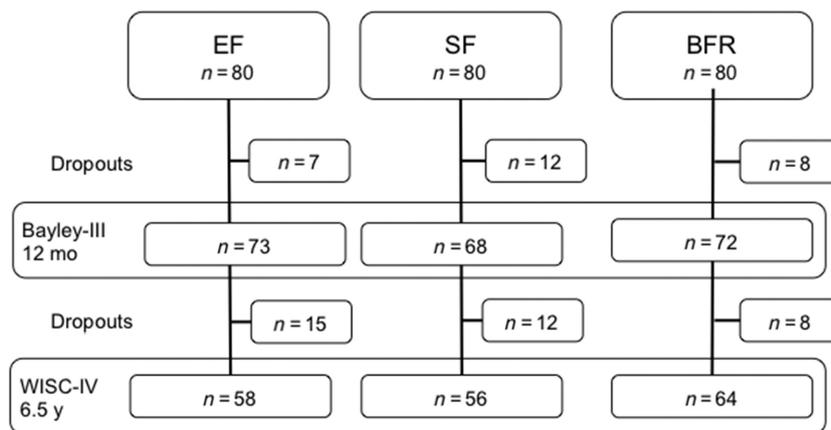
FIGURE 1 Participant flowchart from inclusion until assessment at 6.5 y of age. Bayley-III, Bayley Scales of Infant and Toddler Development 3rd Edition; BFR, breastfed reference; EF, experimental low-energy, low-protein formula; SF, standard formula; WISC-IV, Wechsler Intelligence Scale for Children 4th Edition.

previously reported results from a randomized controlled trial in which we found that infants consuming an experimental low-energy, low-protein formula (EF) supplemented with bovine MFGMs performed 4 scale points better in the cognitive domain of the primary outcome Bayley Scales of Infant and Toddler Development, 3rd Edition (Bayley-III) at 12 mo of age than infants consuming standard formula (SF), whereas there were no differences between the EF group and a breastfed reference (BFR) group. There were no differences in growth parameters at 6 mo of age (7). Among the secondary outcomes we found that infants consuming the EF compared with infants consuming SF had a lower incidence of infections leading to antibiotic treatment or hospitalization [particularly otitis media (8)], higher serum cholesterol concentrations more similar to the BFR group (9), and did not differ in adverse events (8). In the present long-term follow-up of the same study population we evaluated neurodevelopment, growth, and metabolism at 6 and 6.5 y of age.

Methods

From March 2008 to February 2012, 160 formula-fed infants and 80 breastfed infants were recruited as previously described (7). Inclusion criteria were <2 mo of age, gestational age at birth 37–42 wk, birth weight 2500–4500 g, absence of chronic illness, and exclusive formula-feeding or exclusive breastfeeding. The formula-fed infants were stratified for sex and randomly assigned to receive EF or SF from inclusion until 6 mo of age. Compared with the SF, the EF had a lower energy density (60 compared with 66 kcal/100 mL), a lower protein concentration (1.20 compared with 1.27 g/100 mL), and was supplemented with a bovine MFGM concentrate (Lacprodan® MFGM-10; Arla Foods Ingredients). Protein from the MFGM concentrate constituted 4% (wt:wt) of the total protein content in the EF. The intervention was blinded to the staff until all infants had finished the intervention, and to parents and examining psychologists until all children had finished the follow-up at 6.5 y of age. Breastfed infants served as a reference (BFR) group. Data on prevalence of chronic illness, medication, and allergy at 6 y of age and incidence of hospitalization and otitis between 1 and 6 y of age were collected in a parental form at 6 y of age.

Assessment of neurodevelopment

At 6.5 y of age, the Wechsler Intelligence Scale for Children 4th Edition (WISC-IV) (13) (Swedish version, Pearson Assessment) and the Quantified Behavior (Qb) test (QbTech) were performed by an experienced psychologist to assess cognitive functions and ADHD core symptoms, respectively. Two psychologists performed all testing in a clinic setting; the children were assigned to 1 of the 2 psychologists based on availability and not stratified for study group. A parental form on executive cognitive functioning, Brown Attention-Deficit Disorder Scales for Children and Adolescents (Brown-ADD) (14) (Swedish version, Pearson Assessment), was also collected. Adaptive and maladaptive behavior was assessed with the Child Behavior Checklist (CBCL) and Teacher's Report Form (TRF) for ages 6–18 y (15), and analyzed as the proportions of children reaching the cutoff levels for clinical and borderline (>97th and 93rd–97th percentiles of the normative sample, respectively) ranges of Diagnostic and Statistical Manual of Mental Disorders–oriented scales.

Assessment of growth and plasma analysis

At a study visit at 6 y of age, weight (Seca 701; Seca), height (analog stadiometer), head circumference (analog measuring tape), abdominal circumference (analog measuring tape), and blood pressure (GE Carescape V110 Monitor) were measured with 0.1-kg, 0.1-cm, 0.1-cm, 0.1-cm, and 1-mm-Hg accuracy, respectively. A venous blood sample was drawn >2 h after the latest meal. Plasma constituents were analyzed consecutively in clinical routine in the accredited laboratory at Umeå University Hospital. Insulin was analyzed by Elecsys Insulin reagent on Cobas e601 analyzers (Roche). Homocysteine was analyzed by Cobas HCYS reagents on Cobas c501/c502 analyzers (Roche); values below the detection limit were set to the lower cutoff value (5.4 mmol/L). During 2014–February 2015, glucose, total plasma cholesterol (p-Ch), HDL cholesterol, and triglycerides (TGs) were analyzed using Vitros GLU slides, CHOL slides, dHDL slides, and TRIG slides on Vitros 5.1 FS analyzers (Ortho Clinical Diagnostics Inc). During March 2015–2018, glucose, total p-Ch, HDL cholesterol, and TGs were analyzed using Cobas

GLUC3, CHOL2, HDLC3/4, and TRIGL reagents on Cobas c701 analyzers (Roche). LDL cholesterol was calculated using Friedewald's formula (16). Because the original randomization was performed in blocks of 8, the proportions of children with glucose, total p-Ch, HDL cholesterol, and TG analyzed before March 2015 were similar for the 2 randomized formula-fed groups.

Ethics

The study was approved by the Regional Ethical Review Board in Umeå, Sweden (Dnr 07-083M), and was conducted according to the principles in the Declaration of Helsinki. Written informed consent was obtained from all caregivers.

Statistics

A prestudy power analysis showed that a sample of 63 in each group was needed to detect a difference of 0.5 SD with 80% power at the significance level of 0.05 in the primary outcomes at 6 and 12 mo of age as previously reported (7). With an expected dropout rate of 25% between inclusion and 12 mo of age, 80 infants were included in each group (EF, SF, and BFR). Statistical calculations were performed using IBM SPSS Statistics version 26 (IBM 1989, 2019). All analyses were done on an intention-to-treat basis. Comparisons of means were done by independent-samples t test. Insulin concentrations were log transformed before calculations because they were not normally distributed, and transformed back for presentation as geometric means and 95% CIs. Homocysteine was not normally distributed due to the accretion of cases at the lower cutoff level and the distribution between groups was analyzed using the nonparametric independent-samples Mann–Whitney U test. Comparisons of proportions were done by chi-square test or, if any cell had an expected count < 5, Fisher's exact test (2-sided). Comparisons between the nonrandomized BFR group and the 2 formula-fed groups pooled together were done without adjustment for confounding factors.

Results

At 6.5 y of age, 58 (73%), 56 (70%), and 64 (80%) of the originally included infants in the EF, SF, and BFR groups, respectively, were still in the study and completed the psychological assessment with WISC-IV. **Figure 1** presents a flowchart. **Table 1** presents baseline data for children still in the study and dropouts. Based on a parental form collected at 6 y of age, there were no differences between the EF and SF groups in prevalence of chronic illness (7% compared with 10%, $P = 0.74$), prevalence of medication (12% compared with 13%, $P = 0.87$), or prevalence of allergy (35% compared with 32%, $P = 0.69$) at 6 y of age, nor in hospitalization (31% compared with 32%, $P = 0.94$) or incidence of otitis between 1 and 6 y of age (39% compared with 47%, $P = 0.43$). Because gestational age was lower for children still in the study than for dropouts in the EF group, comparisons of means were adjusted for gestational age.

There were no differences between the EF and SF groups in any of the subscales in WISC-IV or Brown-ADD at 6.5 y of age,

TABLE 1 Baseline characteristics for subjects assessed with WISC-IV at 6.5 y (in study) and dropouts[1]

	EF			SF			BFR		
	In study ($n = 58$)	Dropouts ($n = 22$)	P	In study ($n = 56$)	Dropouts ($n = 24$)	P	In study ($n = 64$)	Dropouts ($n = 16$)	P
Maternal age, y	29.9 ± 5.8	28.4 ± 5.2	0.30	29.2 ± 5.7	29.6 ± 4.6	0.79	31.5 ± 4.1	30.7 ± 3.3	0.47
Maternal education, y after 7 y of age	13.7 ± 2.9	13.2 ± 2.3	0.49	13.5 ± 2.3	13.4 ± 2.2	0.79	15.9 ± 2.6	15.0 ± 1.9	0.19
Maternal smoking	6 (10)	3 (14)	0.70	5 (9)	2 (8)	1.0	1 (2)	0 (0)	1.0
Paternal age, y	32.8 ± 6.1	32.1 ± 6.0	0.67	32.2 ± 5.8	32.1 ± 6.0	0.97	34.3 ± 4.2	32.9 ± 4.4	0.25
Paternal education, y after 7 y of age	12.4 ± 2.1	13.5 ± 2.4	0.075	12.7 ± 2.1	13.3 ± 1.9	0.27	15.2 ± 2.7	15.5 ± 3.2	0.72
Paternal smoking	9 (16)	1 (5)	0.27	5 (9)	6 (25)	0.078	2 (3)	1 (6)	0.49
Gestational age, wk	39.4 ± 1.5	40.2 ± 1.2	0.033	39.7 ± 1.3	39.7 ± 1.4	0.93	40.1 ± 1.4	39.8 ± 1.2	0.36
Birth weight, kg	3.50 ± 0.38	3.60 ± 0.45	0.35	3.47 ± 0.49	3.46 ± 0.44	0.93	3.63 ± 0.35	3.41 ± 0.44	0.036
Cesarean delivery	13 (22)	2 (9)	0.22	8 (17)	6 (25)	0.34	5 (8)	1 (6)	1.0

[1]Values are means ± SDs or n (%) unless otherwise indicated. Comparisons of means were done by independent-samples t test. Comparisons of proportions were done by chi-square test or, if any cell had an expected count < 5, Fisher's exact test (2-sided). BFR, breastfed reference; EF, experimental low-energy, low-protein formula; SF, standard formula; WISC-IV, Wechsler Intelligence Scale for Children 4th Edition.

TABLE 2 Psychological assessment at 6.5 y of age[1]

Test	EF	SF	P value EF vs. SF	BFR
WISC-IV				
Full Scale IQ	93.8 ± 11.2	92.5 ± 11.5	0.55[2]	98.7 ± 9.4
Verbal Comprehension	98.0 ± 8.5	98.5 ± 10.0	0.69[2]	102.4 ± 8.2
Perceptual Reasoning	98.7 ± 13.4	96.3 ± 12.7	0.26[2]	103.5 ± 12.4
Working Memory	87.1 ± 11.0	85.7 ± 12.2	0.57[2]	91.4 ± 9.0
Processing Speed	94.3 ± 13.7	93.0 ± 11.4	0.52[2]	93.7 ± 11.4
Brown-ADD				
ADD inattention	46.5 ± 8.1	46.4 ± 7.9	0.83	45.5 ± 6.3
ADD combined	46.8 ± 7.9	46.6 ± 7.8	0.79[2]	45.4 ± 6.1
Qb test outside normal range (−1.4 to 1.4)				
High activity score	9 (17)	13 (26)	0.24	20 (32)
Low activity score	2 (3)	0	0.50	1 (2)
High inattention score	9 (17)	13 (26)	0.24	14 (22)
Low inattention score	1 (2)	3 (6)	0.35	2 (3)
High impulsivity score	6 (11)	2 (4)	0.27	8 (13)
Low impulsivity score	4 (7)	6 (12)	0.52	5 (8)

[1] WISC-IV: EF, $n = 58$; SF, $n = 56$; BFR, $n = 64$; Brown-ADD: EF, $n = 59$; SF, $n = 57$; BFR, $n = 64$; Qb: EF, $n = 54$; SF, $n = 50$; BFR, $n = 63$. Values are means ± SDs or n (%) unless otherwise indicated. Comparisons of means were done by independent-samples t test. Comparisons of proportions were done by chi-square test or, if any cell had an expected count < 5, Fisher's exact test (2-sided). ADD, Attention-Deficit Disorder; BFR, breastfed reference; Brown-ADD, Brown Attention-Deficit Disorder Scales for Children and Adolescents; EF, experimental low-energy, low-protein formula; Qb, Quantified Behavior; SF, standard formula; WISC-IV, Wechsler Intelligence Scale for Children 4th Edition.

[2] Adjusted for gestational age.

nor were there any differences in the proportion of children with scores outside the normal range in the Qb test (**Table 2**). The BFR group had higher scores in full scale IQ, verbal comprehension, perceptual reasoning, and working memory from WISC-IV than the EF and SF groups pooled together (**Supplemental Table 1**). The proportion of children with indicated problems from parental scoring of adaptive and maladaptive functioning using the CBCL did not differ between the EF and SF groups (**Table 3**), nor did the proportion of children with indicated problems from teachers' scoring using the TRF (**Table 4**). The proportion of children with a borderline indication of affective problems in the CBCL was

lower in the BFR group than in the EF and SF groups pooled together, whereas there were no differences between the BFR and formula-fed groups in any of the other problem areas of the CBCL or in any of the problem areas of the TRF (Supplemental Table 1).

At 6 y of age, there were no differences between the EF and SF groups in weight, height, or head or abdominal circumferences (**Table 5**), nor in plasma concentrations of homocysteine, lipids, insulin, or glucose (**Table 6**). The BFR group had larger head circumference than the EF and SF groups pooled together but did not differ in any of the other anthropometric

TABLE 3 Parental scoring of adaptive and maladaptive functioning using the Child Behavior Checklist at 6.5 y of age[1]

	EF ($n = 53$)	SF ($n = 53$)	P value EF vs. SF	BFR ($n = 62$)
Parental scoring indicating clinically relevant problems				
Affective	2 (4)	1 (2)	1.0	0 (0)
Anxiety	1 (2)	0 (0)	1.0	1 (2)
Somatic	1 (2)	3 (6)	0.62	0 (0)
Attention deficit/hyperactivity	4 (8)	2 (4)	0.68	0 (0)
Oppositional defiant	3 (6)	2 (4)	1.0	1 (2)
Conduct	4 (8)	0 (0)	0.12	1 (2)
Parental scoring indicating borderline level of problems				
Affective	9 (17)	3 (6)	0.12	1 (2)
Anxiety	5 (9)	3 (6)	0.72	6 (10)
Somatic	3 (6)	5 (9)	0.72	3 (5)
Attention deficit/hyperactivity	6 (11)	3 (6)	0.49	1 (2)
Oppositional defiant	6 (11)	4 (8)	0.74	3 (5)
Conduct	7 (13)	2 (4)	0.16	2 (3)

[1] Values are n (%) unless otherwise indicated. Comparisons of proportions were done by chi-square test or, if any cell had an expected count < 5, Fisher's exact test (2-sided). BFR, breastfed reference; EF, experimental low-energy, low-protein formula; SF, standard formula.

TABLE 4 Teachers' scoring of adaptive and maladaptive functioning using the Teacher's Report Form at 6.5 y of age[1]

	EF (*n* = 33)	SF (*n* = 34)	*P* value EF vs. SF	BFR (*n* = 44)
Teachers' scoring indicating clinically relevant problems				
Affective	0	0	Constant	0
Anxiety	0	1 (3)	1.0	0
Somatic	0	0	Constant	0
Attention deficit/hyperactivity	0	0	Constant	0
Oppositional defiant	4 (12)	1 (3)	0.20	0
Conduct	1 (3)	0	0.49	0
Teachers' scoring indicating borderline level of problems				
Affective	0	1 (3)	1.0	1 (2)
Anxiety	2 (6)	3 (9)	1.0	3 (7)
Somatic	2 (6)	0	0.24	0
Attention deficit/hyperactivity	1 (3)	2 (6)	1.0	0
Oppositional defiant	6 (18)	3 (9)	0.31	1 (2)
Conduct	4 (12)	2 (6)	0.43	0

[1] Values are *n* (%) unless otherwise indicated. Comparisons of proportions were done by chi-square test or, if any cell had an expected count < 5, Fisher's exact test (2-sided). BFR, breastfed reference; EF, experimental low-energy, low-protein formula; SF, standard formula.

Discussion

In the present long-term follow-up of infants consuming a low-energy, low-protein formula supplemented with a bovine MFGM concentrate, we found no effect of the intervention on cognitive or executive functioning at 6.5 y of age. The BFR group performed better than the formula-fed groups in several subscales of the WISC-IV, well in line with previous studies comparing previously breastfed and formula-fed infants without adjusting for differences in socioeconomic or genetic background variables (17). We have previously reported from the same study population that infants consuming EF until 6 mo of age performed better at cognitive testing at 12 mo of age (7), a finding supported by a recent study on a formula supplemented with a combination of a bovine MFGM concentrate and bovine lactoferrin (11), although in that study it was not possible to decide how much of the effect was due to MFGM and how much to lactoferrin. We speculate that the positive effect could be mediated by MFGM components involved in neurodevelopment (18). During the intervention, we found significant effects of the EF on lipid composition in the blood and red cell membrane

lipidome (19), blood metabolome (20), fecal microbiome and metabolome (21), and oral microbiome (22) and were therefore interested to ascertain whether there are any long-term effects when assessed at the age of starting school.

One possible explanation of our findings is that, in the time period between 12 mo and 6.5 y of age, environmental factors other than early nutrition and genetic factors influence neurodevelopment, which is likely why the previously found differences between the EF and SF groups did not persist. It should also be noted that the original study was powered to detect a difference between the groups of 0.5 SDs corresponding to 7.5 points in WISC-IV. The difference in cognitive score found in Bayley-III at 12 mo of age was 4.0 points, which was statistically significant due to the narrow distribution in the study population compared to the reference population. In the present follow-up study, the distribution of WISC-IV-scores was more similar to the reference group's distribution and the study was underpowered to detect a 4.0-point difference. It could also be discussed at what ages and by what methods follow-up of neurodevelopment should be done to evaluate effects of early infant nutrition. The development of cognitive and executive functions is complex and can be measured by different methods throughout life. We chose to use the WISC-IV, Brown-ADD, and QB test at 6.5 y because these tests are often used in clinical practice in Sweden, have

TABLE 5 Anthropometry and blood pressure at 6 y of age[1]

	EF (*n* = 60)	SF (*n* = 62)	*P* value EF vs. SF[2]	BFR (*n* = 64)
Length, cm	119.0 ± 4.8	117.6 ± 5.0	0.14	116.9 ± 4.2
Weight, kg	22.9 ± 3.7	22.6 ± 3.8	0.62	22.2 ± 2.7
Head circumference, cm	51.7 ± 1.6	51.5 ± 1.5	0.46	52.1 ± 1.3
Abdominal circumference, cm	54.9 ± 5.0	54.5 ± 5.2	0.72	54.1 ± 3.4
Systolic blood pressure, mm Hg	103.5 ± 8.0	105.1 ± 8.0	0.26	105.3 ± 8.6
Diastolic blood pressure, mm Hg	60.7 ± 6.1	62.3 ± 6.8	0.14	60.9 ± 6.7

[1] Values are mean ± SDs unless otherwise indicated. Comparisons of means were done by independent-samples *t* test. BFR, breastfed reference; EF, experimental low-energy, low-protein formula; SF, standard formula.
[2] Adjusted for gestational age.

TABLE 6 Plasma analysis at 6 y of age[1]

	EF ($n = 58$)	SF ($n = 56$)	P value EF vs. SF[2]	BFR ($n = 63$)
Homocysteine,[3] mmol/L	5.8 (7.8)	5.6 (7.9)	0.24	5.8 (7.2)
Cholesterol, mmol/L	4.05 ± 0.70	4.13 ± 0.65	0.60	4.10 ± 0.65
HDL cholesterol, mmol/L	1.44 ± 0.32	1.51 ± 0.28	0.19	1.47 ± 0.30
LDL cholesterol, mmol/L	2.35 ± 0.62	2.38 ± 0.60	0.85	2.37 ± 0.61
Triglycerides, mmol/L	0.59 ± 0.16	0.53 ± 0.17	0.089	0.58 ± 0.22
Insulin,[4] mU/L	4.2 (3.7, 4.8)	4.6 (3.9, 5.3)	0.56	4.4 (4.0, 5.0)
Glucose, mmol/L	4.7 ± 0.5	4.7 ± 0.4	0.72	4.6 ± 0.4

[1] Values are means ± SDs unless otherwise indicated. Comparison of mean homocysteine was done by independent-samples Mann–Whitney U test; comparisons of the other means were done by independent-samples t test. BFR, breastfed reference; EF, experimental low-energy, low-protein formula; SF, standard formula.

[2] Adjusted for gestational age except homocysteine.

[3] Not normally distributed, lower cutoff 5.4 mmol/L; values are medians (90th percentiles).

[4] Not normally distributed; values are geometric means (95% CIs).

a high predictive value for future school achievements, and are used to identify children with special needs for school support. We used the CBCL and TRF for parental and teacher's scoring to assess adaptive functioning, and it should be noted that there was a high dropout rate for the TRF. A follow-up period beyond school age is needed to elucidate whether the intervention groups will differ in academic achievements in the future.

There was no difference in anthropometric measures or blood pressure at 6 y of age, an expected finding because the groups did not differ in these variables during the intervention or at follow-up until 12 mo of age. We have previously reported that the formula-fed infants completely compensated for the lower protein and energy densities in the EF than in the SF by regulating their volume of intake (7), resulting in similar protein and energy intakes. Further, there were no differences in blood lipids, including plasma cholesterol concentrations. During the intervention until 6 mo of age, the EF group gradually reached higher cholesterol concentrations than the SF group, approaching the same concentration as the BFR group (9). Whether this effect on early cholesterol concentrations has any programming effect on later cholesterol metabolism, as suggested by earlier observational studies on breastfed and formula-fed infants (23), would need a longer follow-up time until adolescence or adult life, and probably a larger sample size, to evaluate.

We conclude that the intervention with a low-energy, low-protein formula with MFGM supplementation was safe, because we did not find any severe adverse events in any of the study groups until 6.5 y of age, the EF group did not differ from the SF group in prevalence of chronic illness, medication, or allergy at 6 y of age, nor in hospitalization or incidence of otitis between 1 and 6 y of age, and the EF group did not differ from the SF group in any of the anthropometric, biochemical, or neurodevelopmental outcomes at 6–6.5 y of age.

To our knowledge, this is the first long-term follow-up on MFGM supplementation to infant formula. Health benefits in the population of the positive short-term effects previously reported need to be examined in other sufficiently powered, high-quality randomized controlled trials with well-characterized MFGM fractions.

Data Availability

Data described in the article, code book, and analytic code will be made available in deidentified form upon request.

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