

# MFGM Lipids & Neurodevelopmental Outcomes

**Spotlight on the latest findings for MFGM Lipids and infant cognitive development.**

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This white paper describes the final outcomes of a recent Fonterra sponsored study reported by Xia et al., 2021 entitled "Neurodevelopmental Outcomes of Healthy Chinese Term Infants Fed Infant Formula Enriched in Bovine Milk Fat Globule Membrane for 12 month - A Randomized Controlled Trial"



Ingredients by

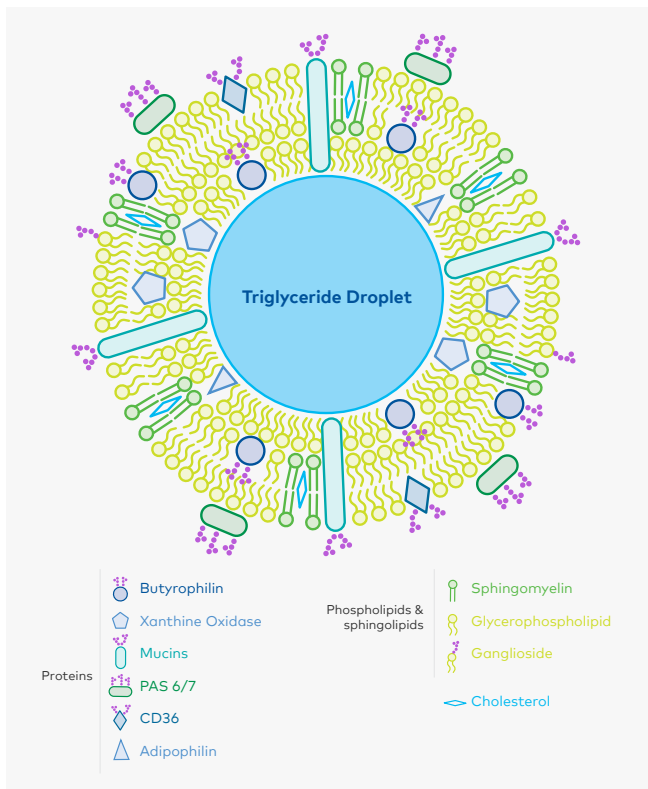


Dairy for life

# Introduction

Breastfeeding gives infants the best start in life, providing immune protection, and supporting optimal growth and development such as cognitive outcomes. Human milk provides the ideal nutrition in the first few months of life; it is the gold standard reference for the development and improvement of infant formula products, the only acceptable alternative for those who cannot or choose not to breastfeed.

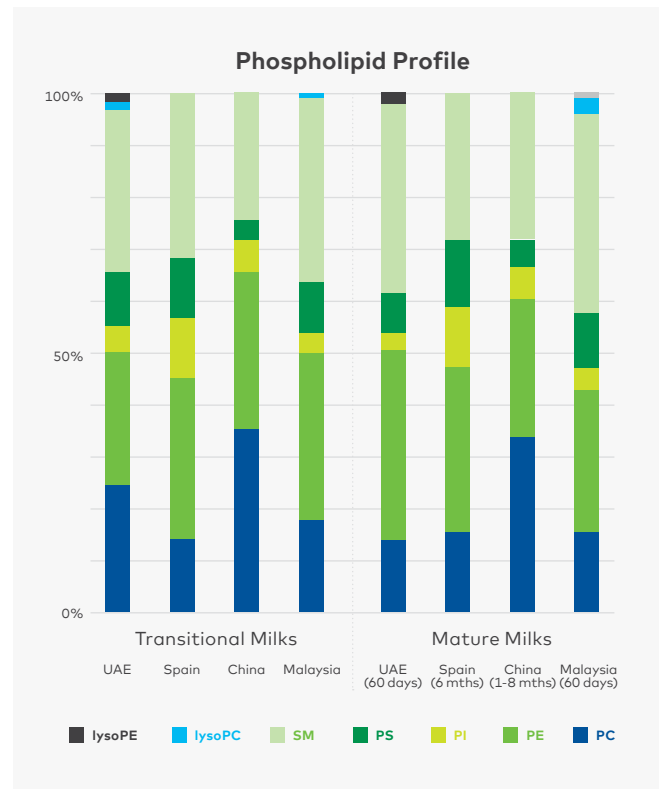
A current area of interest for human milk composition is the milkfat globule membrane (MFGM). The MFGM is found in all mammalian milks and is a trilayer of phospholipids and glycolipids (such as gangliosides), cholesterol and membrane proteins surrounding the triglyceride droplets (Figure 1).



**Figure 1. Schematic of the milk fat globule membrane surround the triglyceride droplet**  
Adapted from Singh and Gallier, 2017

Recent studies on the phospholipid and ganglioside content of human milk gives us a better understanding of the MFGM composition, how it varies across lactation and between different populations, and the relative profiles of the individual phospholipid species (Figure 2). This information gives mean values for human milk composition and can be compared with standard infant formula to estimate the gap for MFGM components.

Infant formula has lower levels of MFGM components than human milk as the dairy fat is replaced by vegetable oil. Supplementation with MFGM ingredients can help to more closely match the levels of key MFGM components such as gangliosides and phospholipids to human milk, and research is now suggesting that this may have some benefits for the formula fed infant such as improved cognitive outcomes and protection against infection when compared to standard formula (Rueda et al., 2007, Gurnida et al., 2012, Poppitt et al., 2014).



**Figure 2. Relative proportions of human breastmilk phospholipids from the MFGM across lactation for different population groups**  
(McJarow et al., 2019).

## PREVIOUS WORK ON MFGM INGREDIENTS AND BRAIN DEVELOPMENT IN INFANTS

A number of studies have been published that show the potential benefit of MFGM containing ingredients on infant cognitive development (Table 1). These MFGM ingredients, typically sourced from cheese whey or cream, have been used in infant feeding studies and are reported to be well tolerated and to support normal infant growth and development (Gurnida et al., 2012, Billeaud et al., 2014, Li et al., 2019).

Phospholipids and gangliosides are also found in high concentrations in the human brain making up to 35% of total lipid (O'Brien, J. S., & Sampson, E. L., 1965). These complex lipids play important roles in neurological development, cognitive function and memory formation and regulating the immune system of the growing infant (McJarow et al., 2009, Brink et al., 2020). A recent study also suggests that intake of human milk MFGM components is associated with increased head circumference (George et al., 2021).



**Table 1.** Summary of infant intervention studies using MFGM supplemented infant and follow-on formula on cognition and behavioural outcomes.

Author	Age + Duration	MFGM Test Product add dose	Composition in intervention	MFGM main result
Gurnida 2012	Infants 2-8wks old until 6 mo of age	Cream-based	9 mg/100g Ganglioside, (revised ~17mg/100g with modern methods) 235mg/100g Phospholipids	Higher hand and eye coordination and performance, higher total score (general IQ), (Griffiths scale)
Tanaka 2013	Preterm infants to~8-10 wks of age, follow up 18mo	Cream-based	200mg/100g Phospholipids (20% sphingomyelin)	At 18 months, improved neurobehavioral development. Higher scores for behaviour, sustained attention scores (Bayley-II)
Veereman 2012	Toddlers 2.5-6 yrs for 4mo	Cream-based, 2.5%	500 g/day Phospholipids	Less behavior problems (Achenbach)
Timby 2014	Infants <8wks until 6mo, follow-up 12mo	Whey-based	70mg/100ml Phospholipids (~500mg/100g)	Higher cognitive score (Bayley-III)
Nieto-Ruiz 2019	Infants <2mo until 18mo, follow up at 2.5 and 4 years	Whey-based, (10% of total protein,wt:wt)	~100mg/100g Phospholipids, +probiotic/LCPUFA	Brain maturation/visual function, improved (Cortical VEPs) at 18months, behavior improvement at 2.5 years, language improvement at 4 years
Li 2019	Infants 3 wks-4mo until 12 mo	Whey-based, 3.88g/100g	adds ~230mg/100g Phospholipids, + Lactoferrin 0.6 g/L	Lower incidences of diarrhea + respiratory events; higher cognitive, language, + motor scores (Bayley III), and attention
Xia 2021	Infants 2wks until 12 months of age	Cream-based, ~4g/100g	18mg/100g Gangliosides, 520mg/100g Phospholipids	At 12 months significant improvement in general adaptive and social emotional scores (Bayley-III), short term memory. Improved attention at 6 mo.

## DEEP DIVE ON RECENT MFGM INFANT STUDY:

### “Neurodevelopmental Outcomes of Healthy Chinese Term Infants Fed Infant Formula Enriched in Bovine Milk Fat Globule Membrane for 12 month - A Randomized Controlled Trial”

A recently published paper (Xia et al., 2021) reports the outcomes from a study on the neurodevelopment and growth of healthy term Chinese infants fed MFGM-enriched formula, over 12 months. The Bayley Scale of Infant and Toddler Development, 3rd edition (Bayley-III) was used to assess the neurodevelopment primary outcomes of the infants at 12 months. The secondary outcomes measured were growth, neurodevelopment at 6 month, attention and short-term memory at 6 and 12 months, and serum ganglioside at 4 months.

#### Participants and study formula

Infants were recruited up to 2 weeks of age into the study from four hospital sites in the Fuzhou region, China, between Jan 2016 and October 2016. The infants were randomized into 2 study formula groups; MFGM-supplemented infant formula or a standard formula (control). A breast-feeding group was also recruited into the study as a reference group.

Study formulas were infant formula for 0-6 months and follow-on formula for 6-12 months (Table 2). The MFGM-supplemented formula contained a minimum ganglioside concentration of 18.2 mg/100g formula, with the MFGM sourced from SureStart™ MFGM Lipid 100 (NZMP, Fonterra). The standard formula was manufactured with the same macro- and micronutrient composition but without fortification, with an endogenous ganglioside concentration of 10.6 mg/100g.



**Table 2.** Compositions of the infant and follow-on formulae enriched in MFGM (MF) and the control infant and follow-on formulae (SF).

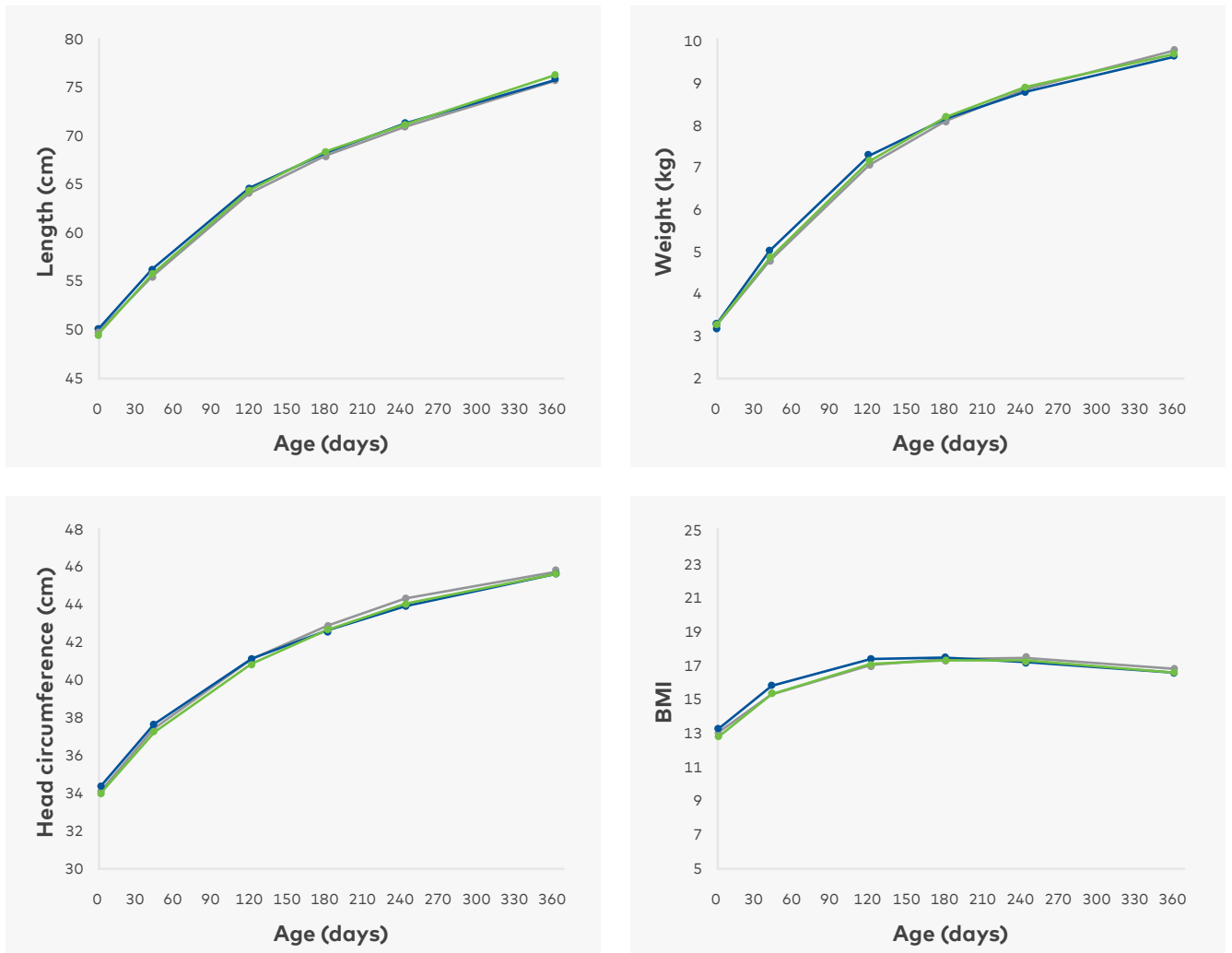
Nutrient per 100 mL	MF IF	SF IF	MF FO	SF FO
Energy (kcal)	67	67	68	68
Proteins (g)	1.7	1.7	2.2	2.2
Carbohydrate (lactose; g)	7.4	7.4	7.8	7.8
Lipids (g)	3.4	3.4	3.2	3.2
MFGM components:				
Phospholipids (mg)	71.5	39.4	75.5	36.5
Phosphatidylcholine (mg)	20.6	11.0	21.3	10.3
Phosphatidylethanolamine (mg)	19.1	9.6	20.4	9.1
Phosphatidylinositol (mg)	6.9	4.5	6.9	3.9
Phosphatidylserine (mg)	6.7	3.3	7.2	3.2
Sphingomyelin (mg)	12.8	6.3	13.3	5.9
Gangliosides (mg) <sup>1</sup>	2.5	1.4	2.7	1.5

<sup>1</sup>Measured as GD3 as described in Fong et al., 2011

# Results

## GROWTH AND DEVELOPMENT

The study showed that the MFGM-supplemented infant formula supported normal growth over the 12 months assessment period for weight, length, head circumference, and BMI (Figure 3) with no significant differences between groups for all 3 growth measures. There was no indication of adverse events, and the MFGM-supplemented formula was well tolerated by the infants in the study.



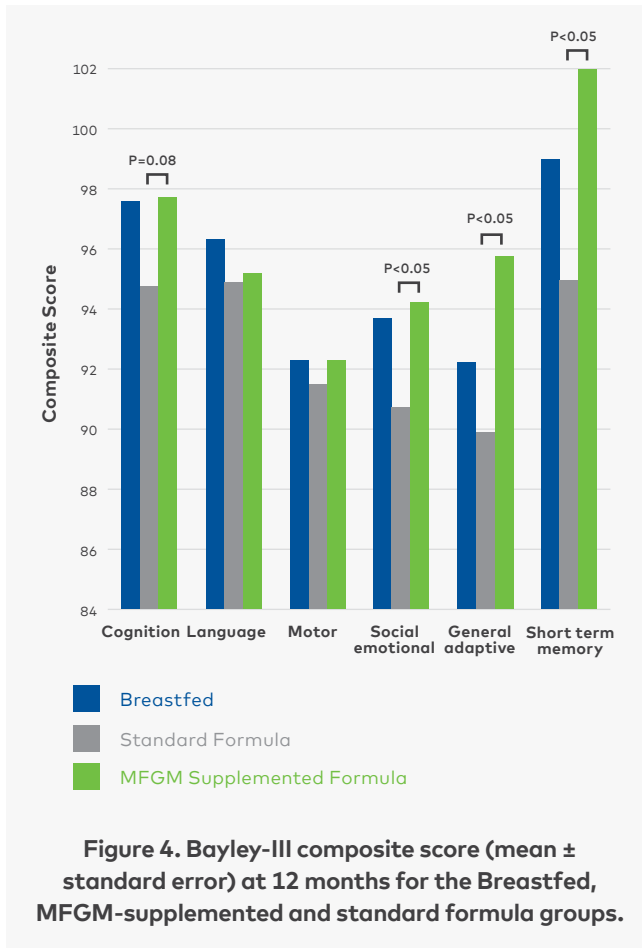
● Breastfed    ● MFGM Supplemented Formula    ● Standard Formula

**Figure 3. Growth data (weight gain, length gain, head circumference gain, and BMI) over the 12 month feeding period with MFGM supplemented infant formula, compared with control formula and a breastfed group.**

## BAYLEYS-III COGNITIVE OUTCOMES

At 12 months, the Bayley's III social emotional and general adaptive behavior composite scores were significantly higher for the infants on the MFGM-supplemented infant formula compared to infants on standard formula ( $p=0.048$  and  $p=0.004$  respectively, Figure 4). The cognitive composite score for infants in the MFGM-supplemented group were also higher when compared to infants in the control group but this was not statistically significant ( $p=0.08$ , Figure 4). No significant difference was reported for the motor or language domains between the two groups.

The study showed that the breast-fed infant group generally performed better in the Bayley-III cognitive outcomes than the two formula groups at both 6 and 12 months. The Bayley-III cognitive outcome for the infants in the MFGM-supplemented group was closer to that of the breast-fed infant group than the standard formula fed group. These findings were consistent with similar studies that reported that MFGM-supplemented infant formula improves some measures of infant cognition to be more similar to that of the breast-fed infant (Table 1).



## Short-Term Memory

The Chinese attention and short-term memory test results from the Bayley-III cognitive assessment were also analyzed using a test method validated for Chinese children. Short term memory data from the Bayley-III cognitive test (48 subtests) were used to assess the infants at both 6 and 12 months of age.

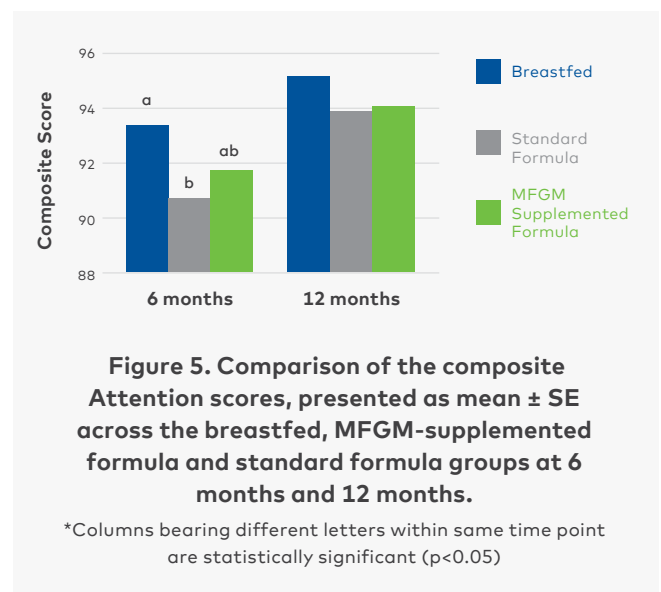
The short-term memory score reported for the MFGM-supplemented group was significantly higher than the standard formula group at 12 months old ( $p=0.008$ , Figure 4), but not at 6 months ( $98.14 \pm 0.70$  vs  $98.97 \pm 0.65$  respectively,  $p=0.94$ ).

## Attention

Attention data from the Bayley-III cognitive test (28 subtests) were used to assess the infants at both 6 and 12 months of age. While the composite attention score reported was higher in the MFGM-supplemented group than the standard formula group at both 6 and 12 months, they were not significantly different ( $p>0.05$ , Figure 5). The score for the MFGM-supplemented group was not significantly different to the BFR group at 6 months.

The attention composite scores for the standard formula group was significantly lower than the breast-fed infant group at 6 months ( $p=0.02$ ) but the difference was not significant at 12 months ( $p=0.24$ , Figure 5).

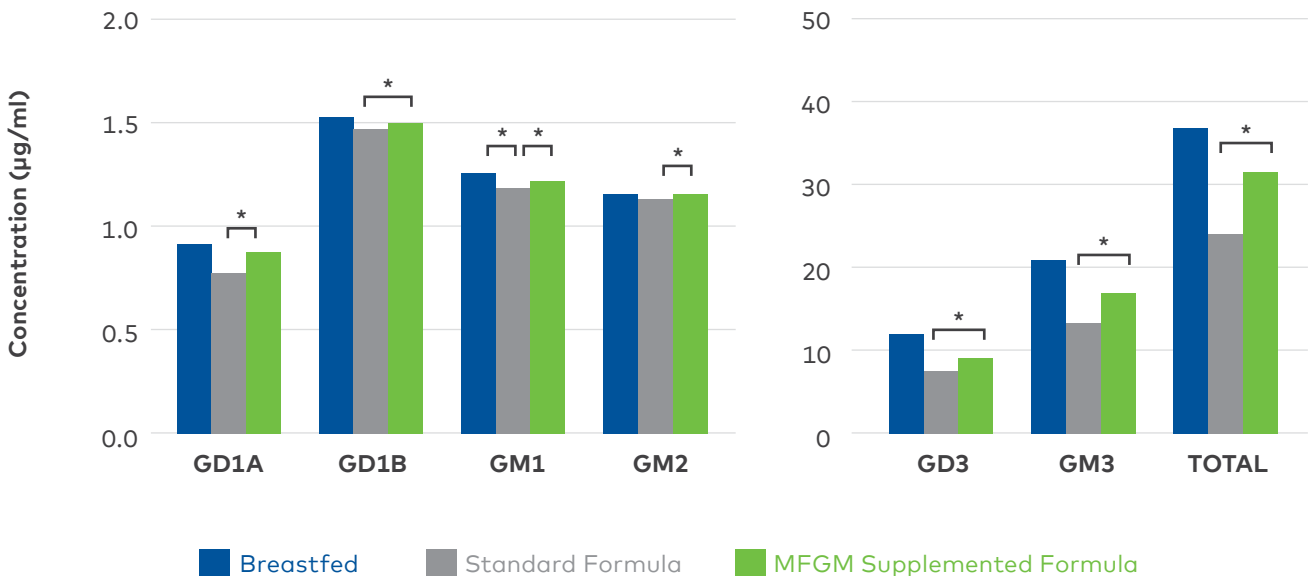
Both the attention and short-term memory results from the study showed MFGM supplementation allowed the attention and short-term memory to approach the level of the breast-fed group.



## GANGLIOSIDES CHANGES IN THE INFANT BLOOD

Serum samples were taken at 4 months from a subsample of infants, before complementary foods were introduced, and the ganglioside levels were measured. The total serum gangliosides were measured as the sum of the six major gangliosides (GD1a, GD1b, GD3, GM1, GM2, and GM3) detected, with GM3 being the major ganglioside reported. The study reported that infants on the MFGM-supplemented formula had a serum GM3, GD3, GM1, GD1a, GD1b and total ganglioside concentrations that were significantly higher than the standard formula group ( $p < 0.001$ , Figure 6).

All ganglioside concentrations reported in the study for the breast-fed infant group were significantly higher than standard formula group but not different from the MFGM-supplemented group. This suggests that the MFGM enrichment of the infant formula may increase serum ganglioside concentration in the formula fed infant to be more similar to that of the breast-fed infant, potentially linked to the observed improvements in cognitive development.



**Figure 6. Composition of the serum ganglioside concentration (mean  $\pm$  standard error) in the breastfed (n=41), MFGM-supplemented (n=26) and Standard formula (n=24) groups at 4 months of age.**

Significant difference is indicated by asterisk, \*  $p < 0.05$ , \*\*  $p < 0.01$ .

# Conclusions

The supplementation of infant formula with SureStart™ MFGM Lipid 100, to more closely match the levels of gangliosides and phospholipids in breastmilk, in the first 12 months of life:

- supports adequate growth and is well tolerated.
- improves some measures of the cognitive development in infancy using the validated Bayley-III assessment (notably social emotional scores, general adaptive behaviour, attention and short-term memory, with a trend toward cognition) when compared with infants fed a standard formula.
- Increases serum gangliosides concentration to be more similar to breast fed infants.

The mechanisms involved in how increased intake of MFGM improves cognitive outcomes is unclear. MFGM is a source of gangliosides and important phospholipids such as sphingomyelin. Gangliosides are important for the growth of neurons, are involved in synaptic connections, and memory formation, and high concentrations are measured in human brain and breastmilk. Phospholipids make up about 20% of the brain, and are involved in cell membrane structure, function and myelination. MFGM components also influence signalling between the gut and the brain. Future research will help to confirm the impact of MFGM supplementation on cognition and to elucidate the underlying mechanisms (Ambrozej et al., 2021).

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