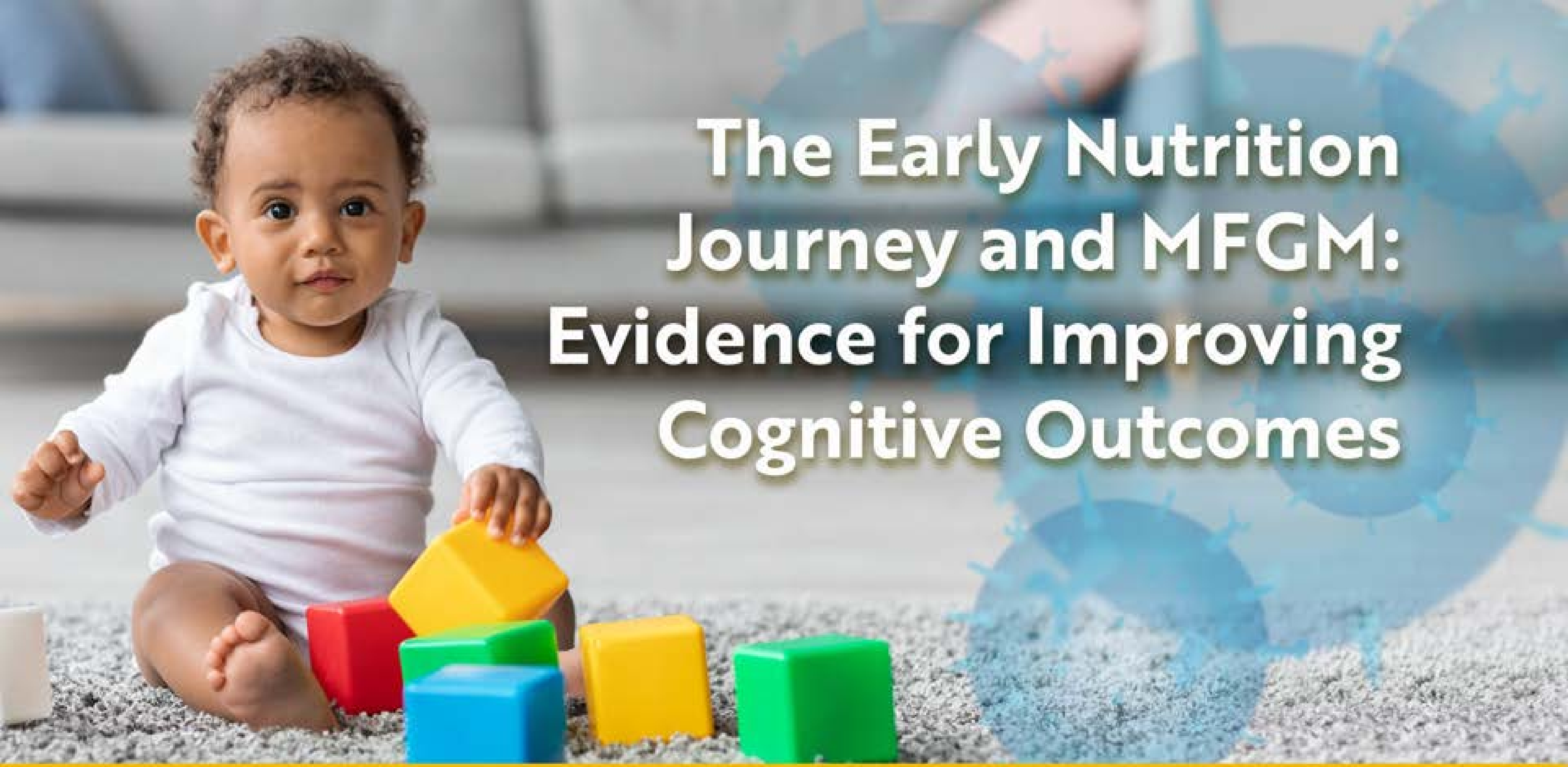
# The Early Nutrition Journey and MFGM: Evidence for Improving Cognitive Outcomes



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This activity is supported by an educational grant from Mead Johnson Nutrition.

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**John Colombo, PhD**

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**Sean Deoni, PhD**

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| *Speakers Bureau* | Mead Johnson Nutrition, Nestle Nutrition, Wyeth Nutrition |

**Rafeal Jimenez-Flores, PhD**

No relationships to disclose.

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# Learning Objectives

*By participating in this education, you will better:*

- Describe the molecular structure of MFGM as it relates to its key biological functions, including its role as a bioactive component in human milk
- Identify the clinical significance of MFGM in early life nutrition and its impact on neurodevelopment and brain structure and function
- Discuss the longitudinal benefits of early life MFGM supplementation on cognitive outcomes, measures of intelligence, and executive functioning

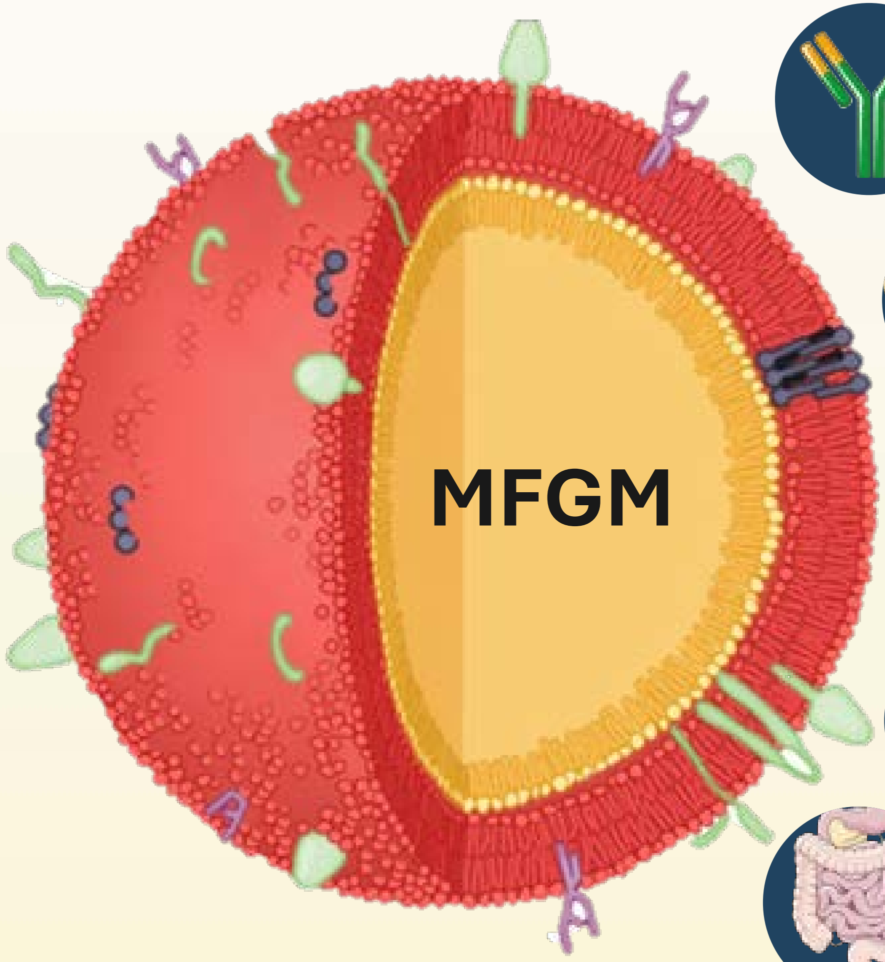
# The Early Nutrition Journey and MFGM: Evidence for Improving Cognitive Outcomes

1. **The Science and Structure of MFGM *and* Mechanisms of Action of MFGM on Health**
2. **MFGM and the Developing Brain**
3. **Supplemental MFGM and Neurodevelopmental Outcomes**

# The Science & Structure of MFGM

Rafael Jimenez-Flores, PhD

# Link Between MFGM and Human Health




- Modulation of the immune system
- Bone mineral density
- Cardiometabolic health
- Cognitive function and brain development
- Gut barrier function and microbiota

Anto L et al. *Nutrients*. 2020;12(4):1001.

# MFGM Benefits: Results From Selected International Studies

| Study (Year) | Country | Neurodevelopment | Immune System | Other |
|---|---|---|---|---|
| **Zavaleta et al (2011)** | Peru | | Less bloody diarrhea at 12 months | |
| **Gurnida et al (2012)** | Indonesia | Better coordination and performance at 6 months | | |
| **Veereman-Wauters et al (2012)** | Belgium, France, Netherlands | Better behavior in preschoolers | Fewer fever episodes at 6 weeks | |
| **Tanaka et al (2013)** | Japan | Better behavior and attention in premature infants at 18 months | | |
| **Timby et al (2014)** | Sweden | Better cognitive development scores at 12 months | | |
| **Timby N et al (2015)** | Sweden | | Lower incidence of otitis media at 6 months | |
| **Li et al (2019)** | China | Better cognitive, language, and motor functions at 12 months | Less diarrhea and IVRA | |
| **Jaramillo-Ospina et al (2022)** | Chile | | | Growth and safety |

# MFGM & Cognitive Development: Short- & Long-Term Outcomes in the Lighthouse Clinical Trial

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

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

Fei Li, MD, PhD[1], Steven S. Wu, MD[2], Carol Lynn Berseth, MD[2,3], Cheryl L. Harris, MS[2], James D. Richards, PhD[4,5], Jennifer L. Wampler, PhD[2], Weihong Zhuang, MS[2], Geoffrey Cleghorn, MD[2,6], Colin D. Rudolph, MD, PhD[2,7], Bryan Liu, MD, PhD[2,8], D. Jill Shaddy, MA[9], and John Colombo, PhD[9]

**Accelerated neurodevelopmental profile at 1 year following MFGM/lactoferrin supplementation**
(Li F et al, *J Pediatr,* 2019)

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

**Improved Neurodevelopmental Outcomes at 5.5 Years of Age in Children Who Received Bovine Milk Fat Globule Membrane and Lactoferrin in Infant Formula Through 12 Months: A Randomized Controlled Trial**

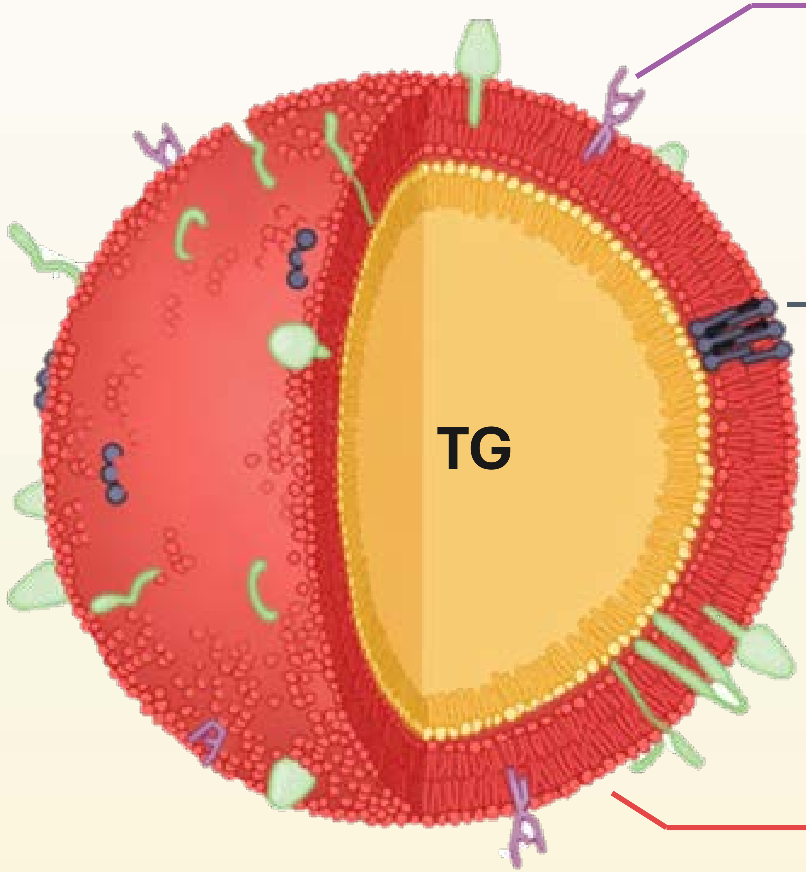
John Colombo, PhD[1], Cheryl L. Harris, MS[2], Jennifer L. Wampler, PhD[2], Weihong Zhuang, MS[2], D. Jill Shaddy, MA[3], Bryan Y. Liu, MD, PhD[4], and Steven S. Wu, MD[2,5]

**Improved cognitive outcomes in multiple domains at 5.5 years following MFGM/lactoferrin supplementation**
(Colombo J et al, *J Pediatr,* 2023)

# The Science & Structure of MFGM

## What Is MFGM?

# MFGM Components




**Gangliosides[1,2]**

Examples: Glycosphingolipids containing sialic acid

Role: Involved in myelination and synaptic transmission

**Sphingolipids[1,4]**

Example: Sphingomyelin

Role: Supports myelination of nerves

**Proteins[1,5,6]**

Examples: mucin-1 (MUC1), lactadherin

Roles: Supports the immune system, antimicrobial effects

**Phospholipids[1,3]**

Example: Phosphatidylcholine

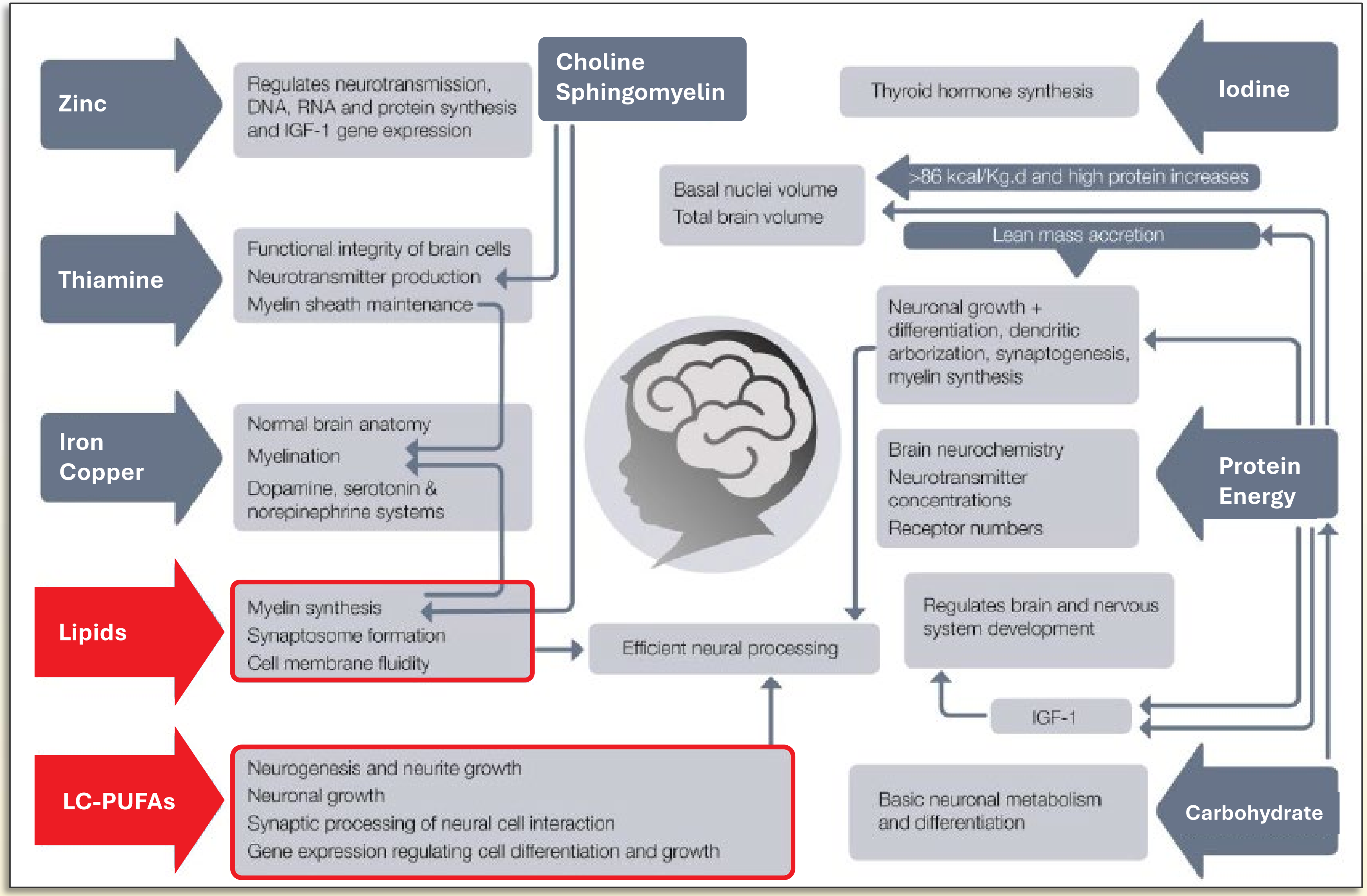
Role: Important component of cell membranes

TG, triglycerides



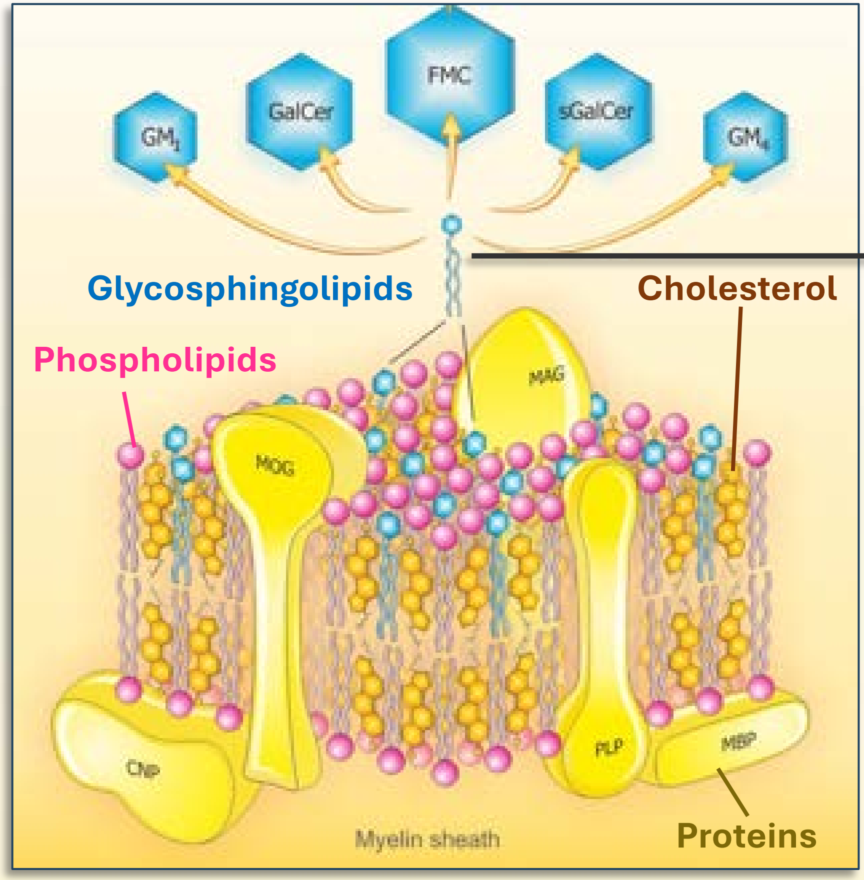
1. Dewettinck K et al. Int Dairy J. 2008;18:436-457. 2. McJarrow P et al. Nutr Rev. 2009;67:451-463. 3. Wurtman RJ. Metabolism. 2008;57(suppl 2):S6-10. 4. Quarles RH et al. In: Siegel GJ, ed. Basic Neurochemistry: Molecular, Cellular, and Medical Aspects; 2006:51-71. 5. Sheng YH et al. Mucosal Immunol. 2013;6:557-568. 6. Hettinga K et al. PLoS One. 2011;6:e19433.

# Nutrients Needed for Brain Development



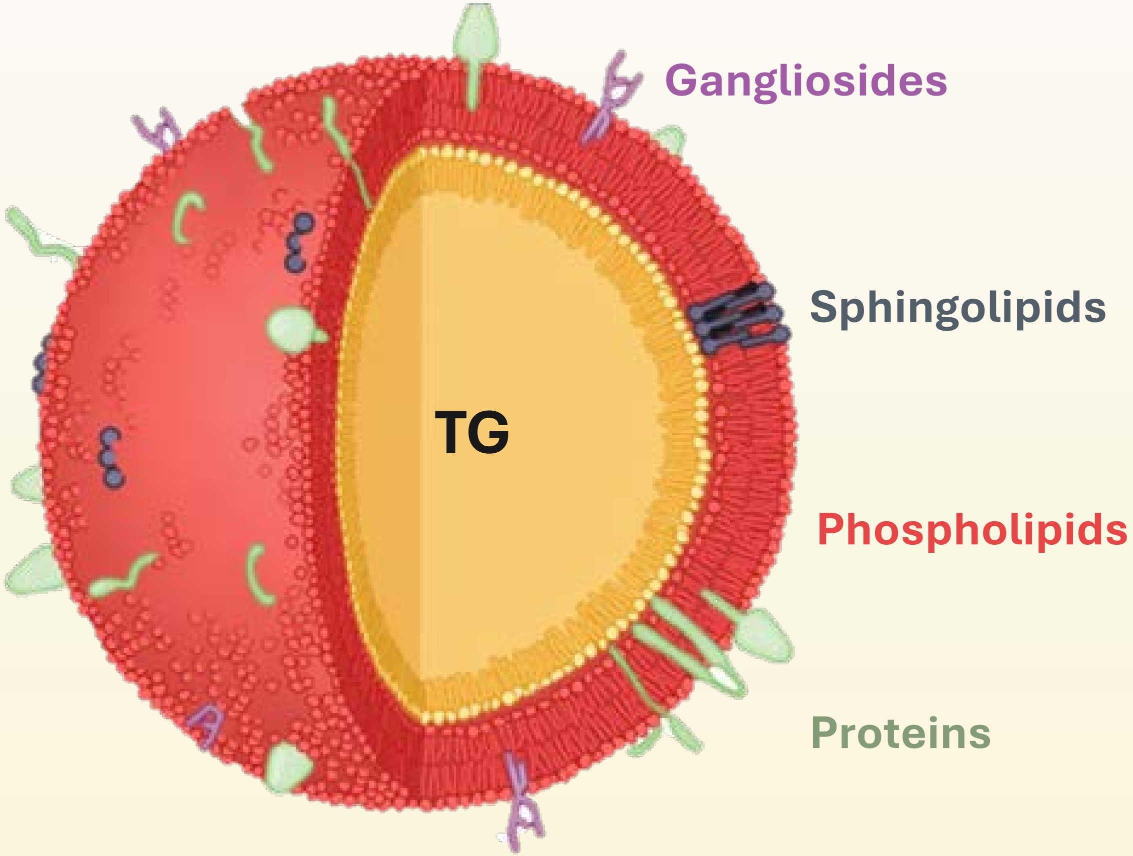
# MFGM as a Source of Nutrients for Neurodevelopment

**Myelin Sheath[1]**




Myelin
↓
Sphingomyelin
↓
Ceramide
↓
Fatty acids
↓
Ketone bodies

**MFGM[2]**







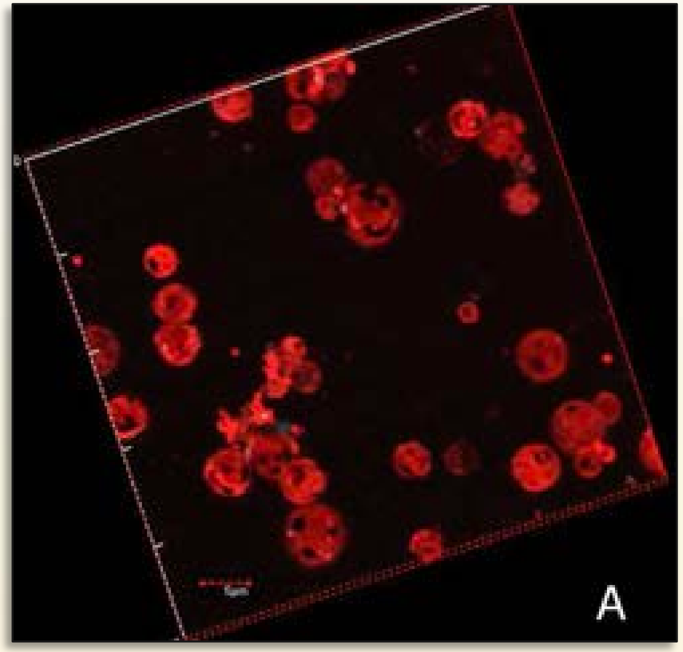

**1.** Podbielska M et al. Brain Sci. 2013;3(3):1282-1324. **2.** Dewettinck K et al. *Int Dairy J.* 2008;18:436-457.

# The Science & Structure of MFGM

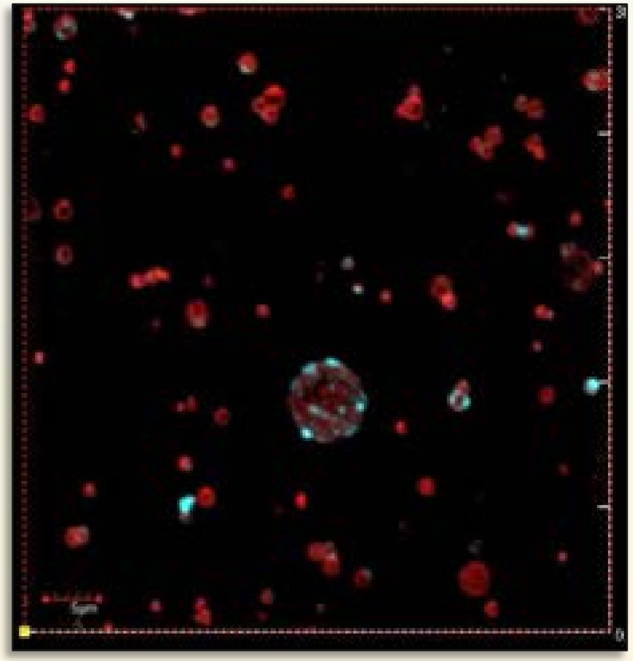
## MFGM Production & Manufacturing

# Effects of Processing on MFGM

MFGM From Raw Cream




MFGM From Pasteurized Cream



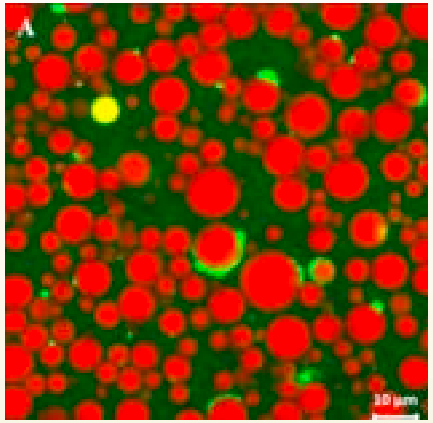
**With homogenization and pasteurization, fewer large fat globules, higher amounts of proteins (blue)**

Gallier S et al. *J Agric Food Chem*. 2010;58(7):4250-4257.

# Differences Between Lipids in Human Milk and Standard Infant Formula

**Confocal Microscopy Images of Fat Droplets Showing Lipids (Red) and Proteins (Green)[1]**

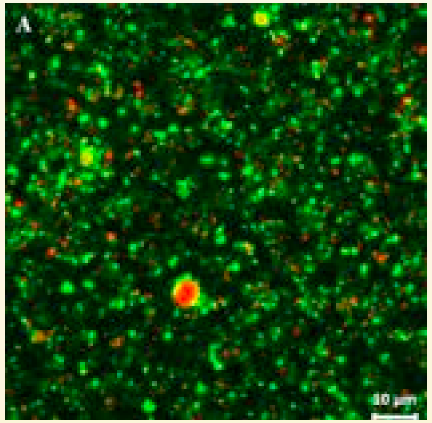
**Human milk**



### Characteristics of Human Milk Fat Droplets[2]

- High sphingomyelin content
- Dynamic across lactation stages
- Large fat globules (~5 µm)
- Phospholipid bilayer membrane

**Standard infant formula**



### Characteristics of Standard Infant Formula Fat Droplets[2]

- High phospholipid content
- High phosphatidylcholine content
- Small fat globules (~0.2 µm)
- No phospholipid bilayer membrane



1. Gallier S et al. *Colloids Surf B Biointerfaces*. 2015;136:329-339. Images used under a Creative Commons license (CC BY). © 2015, the Authors.
2. Wei W et al. *J Agric Food Chem*. 2019;67(50):13922-13928.

# Mechanisms of Action of MFGM on Health

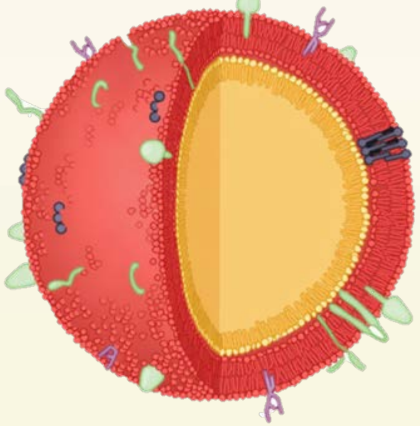
## The Gut Microbiome

# Maternal & Environmental Factors, MFGM Composition, & Effects on the Infant Gut

- Maternal body composition
- Gestation period
- Lactation period
- Genetics
- Environmental factors (eg, infection)
- Infant sex
- Maternal diet

→

**MFGM in breast milk**



Fatty acids, phospholipids, glycosphingolipids, proteins, and other molecules

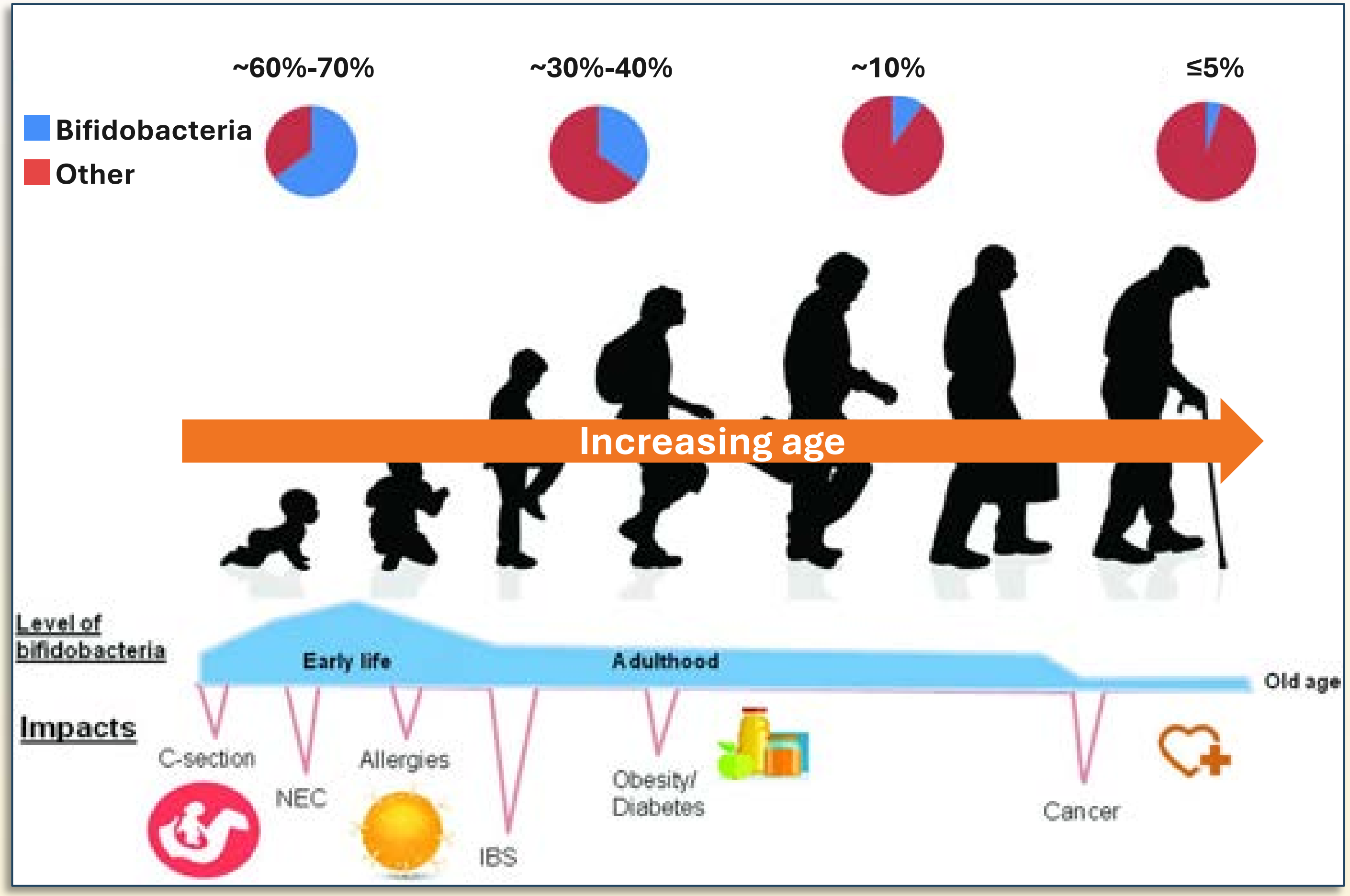
→

**Breastfed Infants**

- Structural development (eg, intestinal mucosa/vasculature)
- Intestinal immune maturation
- Establishment of the early gut microbiota

Lee H et al. *Front Pediatr*. 2018;6:313.

# Bifidobacteria Populations Decline With Age




- Predominant genus in the gut microbiome of healthy breastfed infants
- May be beneficial for health across age ranges

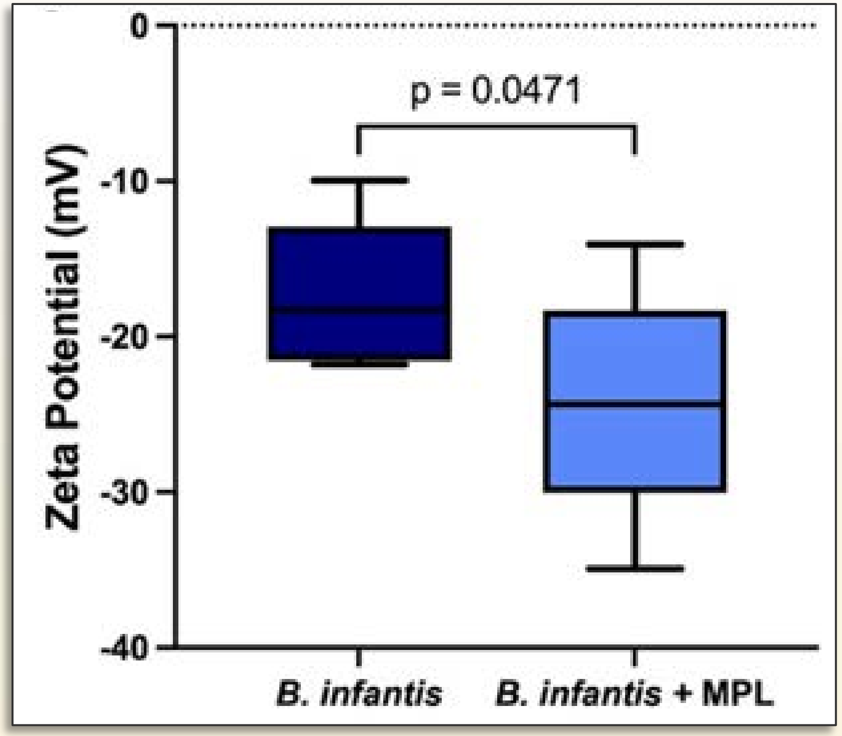
**How can we promote Bifidobacteria persistence?**



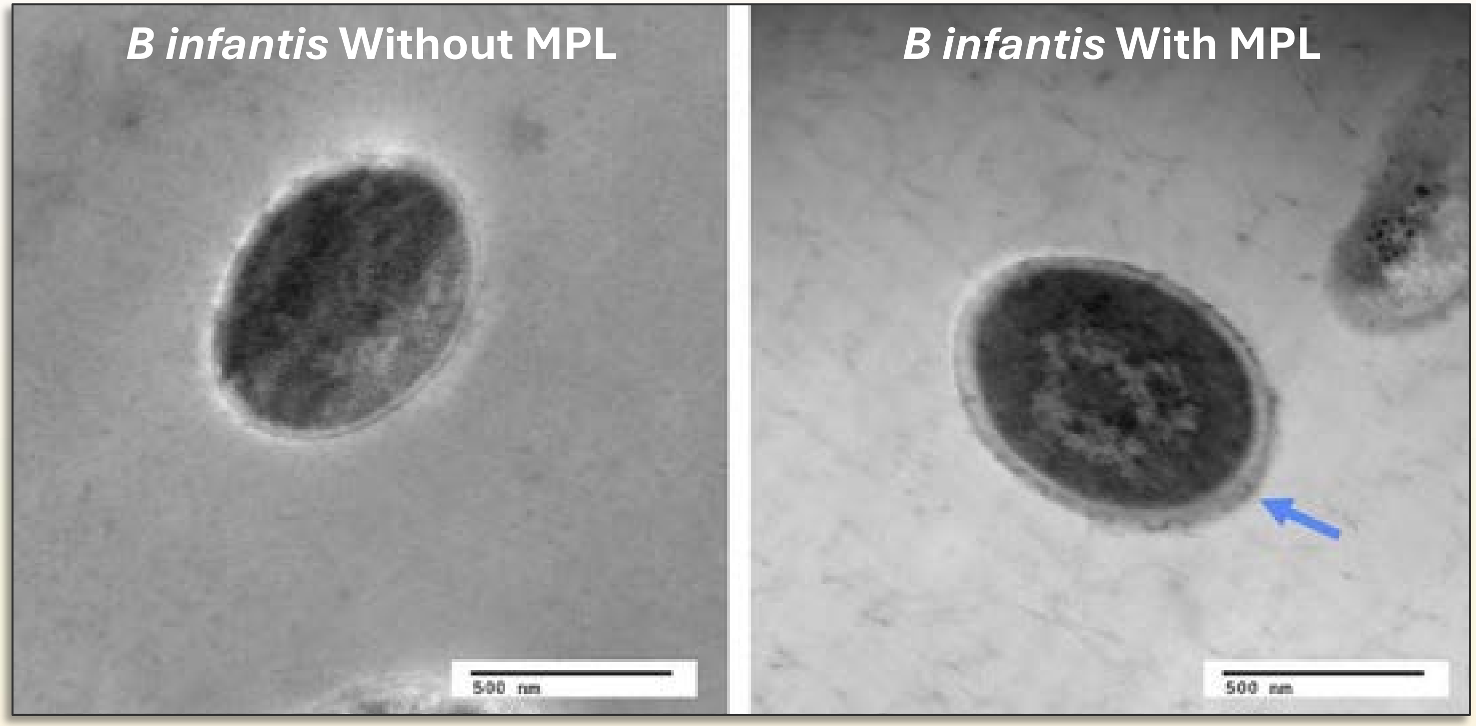


Arboleya S et al. *Front Microbiol*. 2016;7:1204.

# Milk Phospholipid Protection of *Bifidobacterium longum* ssp *infantis* During In Vitro Digestion




Decreased surface charge of *B infantis* with milk phospholipids

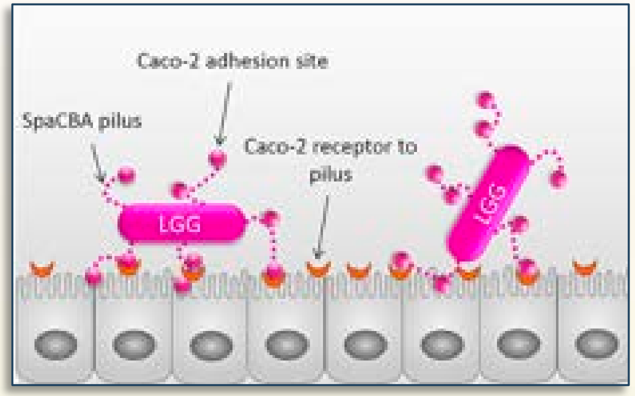



Thicker outer surface layer due to increase in bound polysaccharides in the presence of milk phospholipids

MPL, milk phospholipid

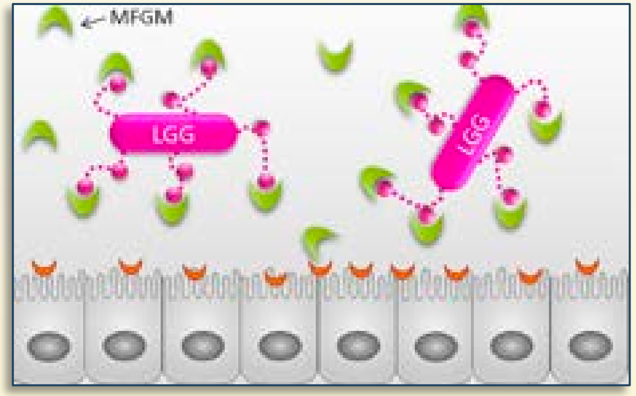
# MFGM Modifies LAB Surface and Adhesive Properties

### LGG in the GI Tract Without MFGM[1]



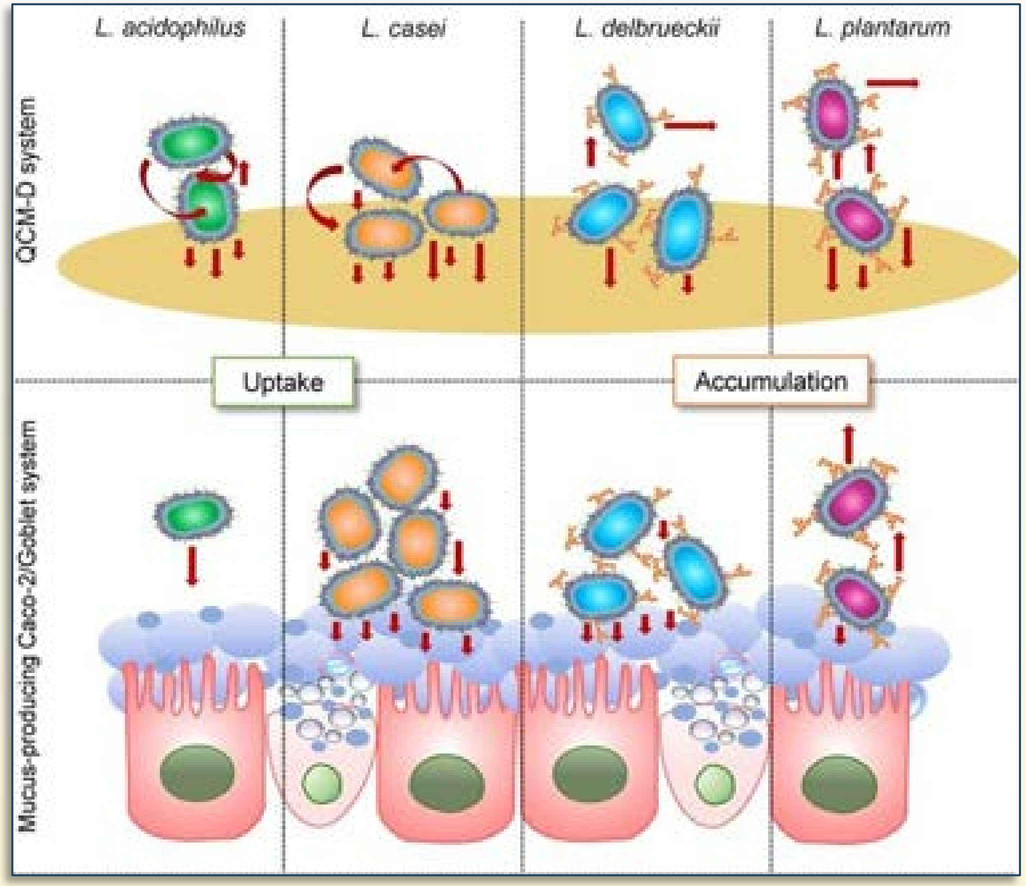

Bacterial adhesion to Caco-2 TC7 intestinal cells

### LGG in the GI Tract With MFGM[1]




Inhibition of bacterial adhesion to Caco-2 TC7 intestinal cells

### Differential Adhesion Behavior After Treatment With MFGM[2]




Strain-dependent effects of milk phospholipids on bacterial surface properties and subsequent adhesion

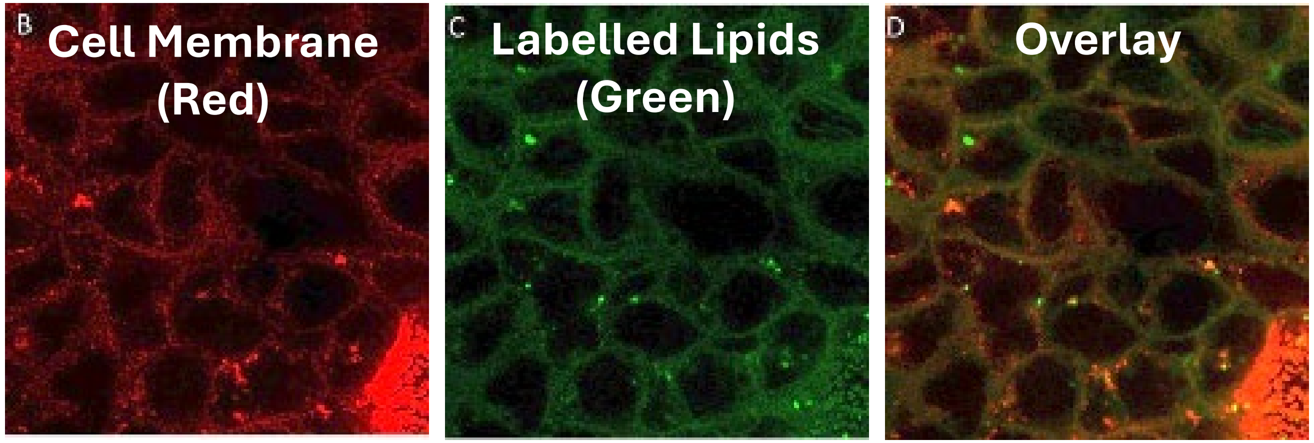
LAB, lactic acid–producing bacteria; LGG, *Lactobacillus rhamnosus* GG; QCM-D, quartz crystal microbalance with dissipation monitoring.



**1.** Guerin J et al. *Colloids Surf B Biointerfaces*. 2018;167:44-53. **2.** Ortega-Anaya J et al. *Food Res Int*. 2021;146:110471.

# MFGM Phospholipids and the Intestinal Epithelial Barrier

**Caco-2 Cells After Incubation With Labelled MFGM**




**Evidence of fusion between the intestinal cell plasma membrane and the phospholipids in MFGM**

**After incubation with MFGM, Caco-2 cells had significant changes in lipid composition:**

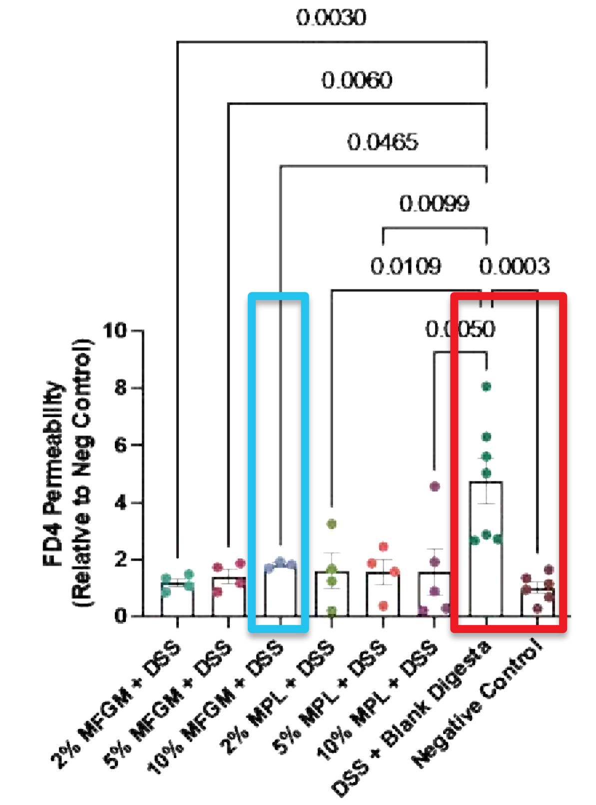
- ↑ Triacylglycerols (TAG)
- ↑ Phosphatidylcholine
- ↓ Cholesterol esters

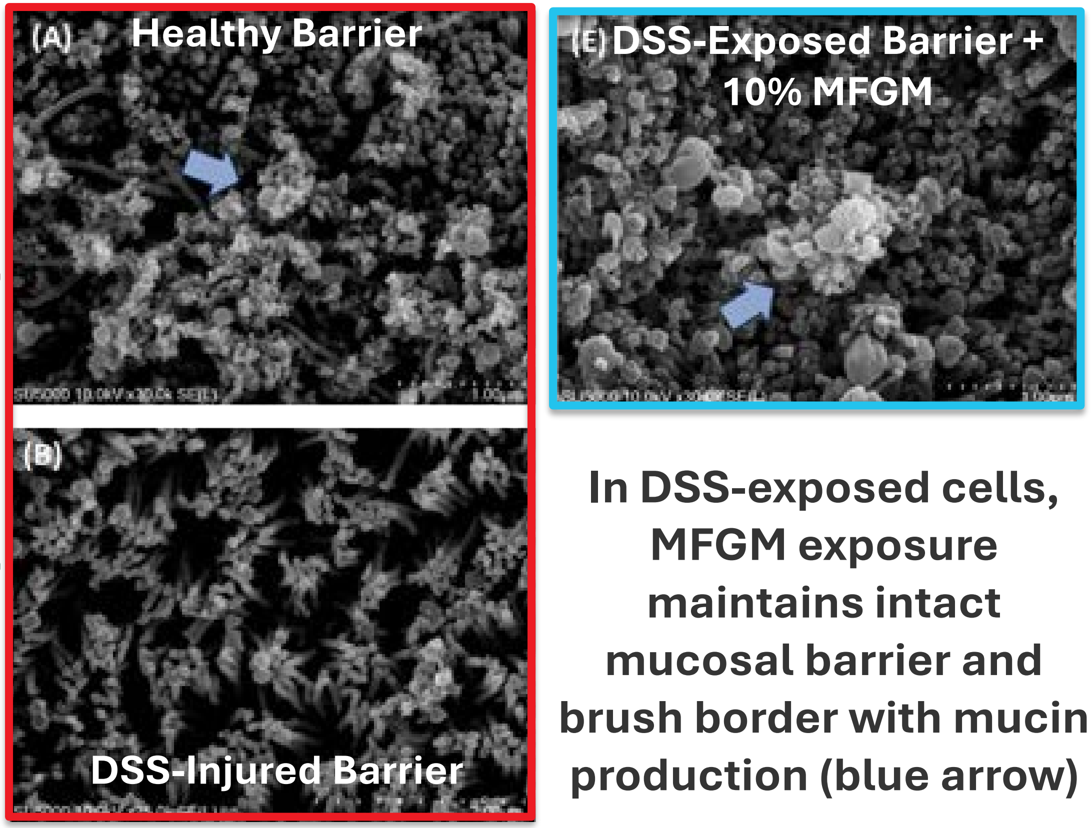




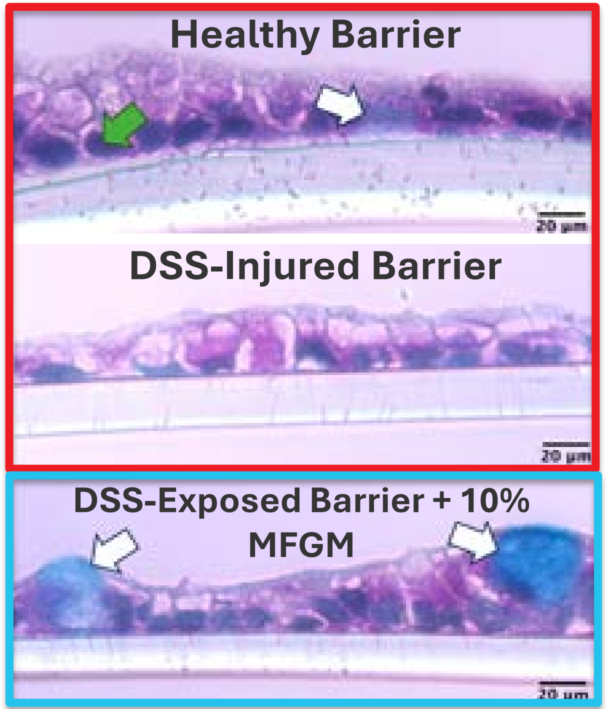
Martínez-Sánchez V et al. *Food Res Int.* 2023;173(Pt 1):113330.

# MFGM Facilitates Maintenance of the Intestinal Barrier Integrity




In DSS-exposed cells, MFGM exposure maintains intact mucosal barrier and brush border with mucin production (blue arrow)




Restored acidic mucin production (blue stain, white arrow) with MFGM

DSS, dextran sodium sulfate



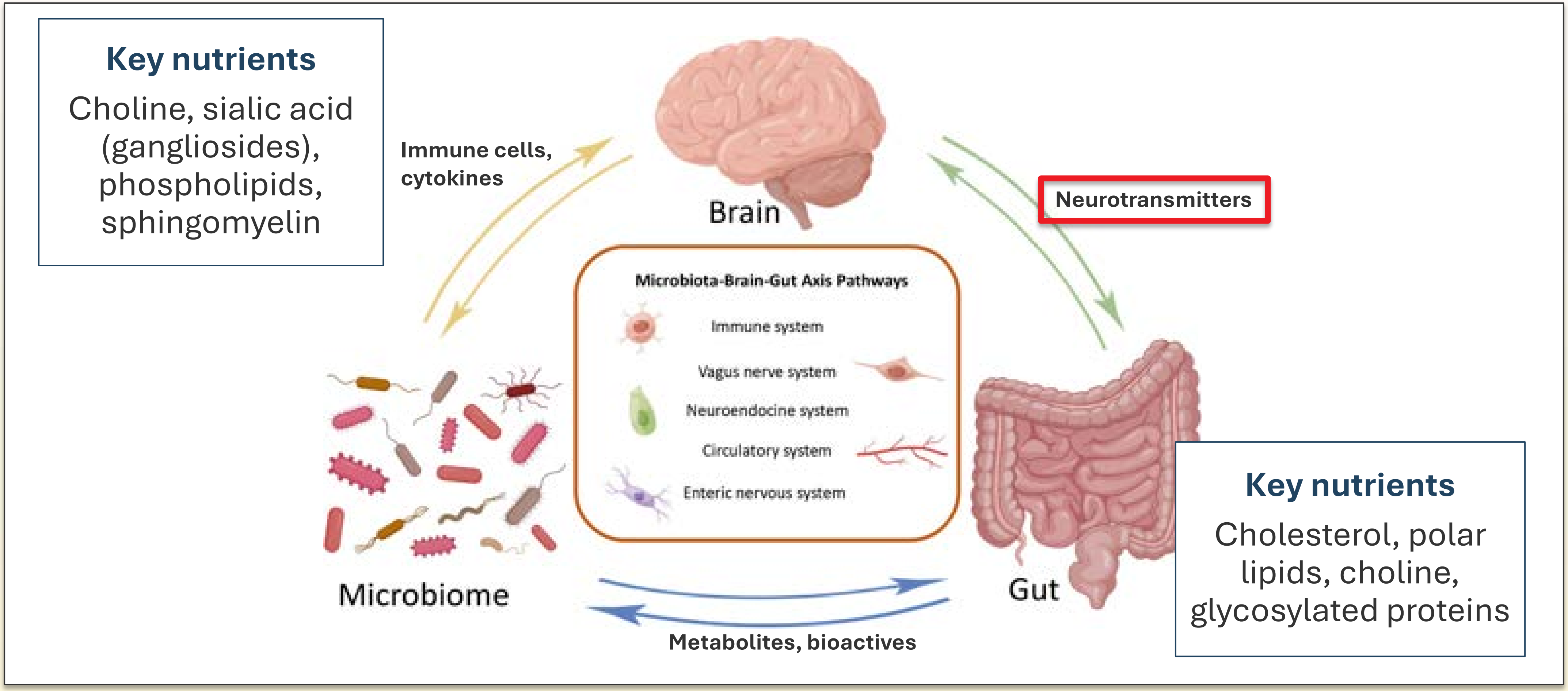


Kosmerl E et al. *Nutrients*. 2024;16(7):954.

# Mechanisms of Action of MFGM on Health

## The Gut-Brain Axis

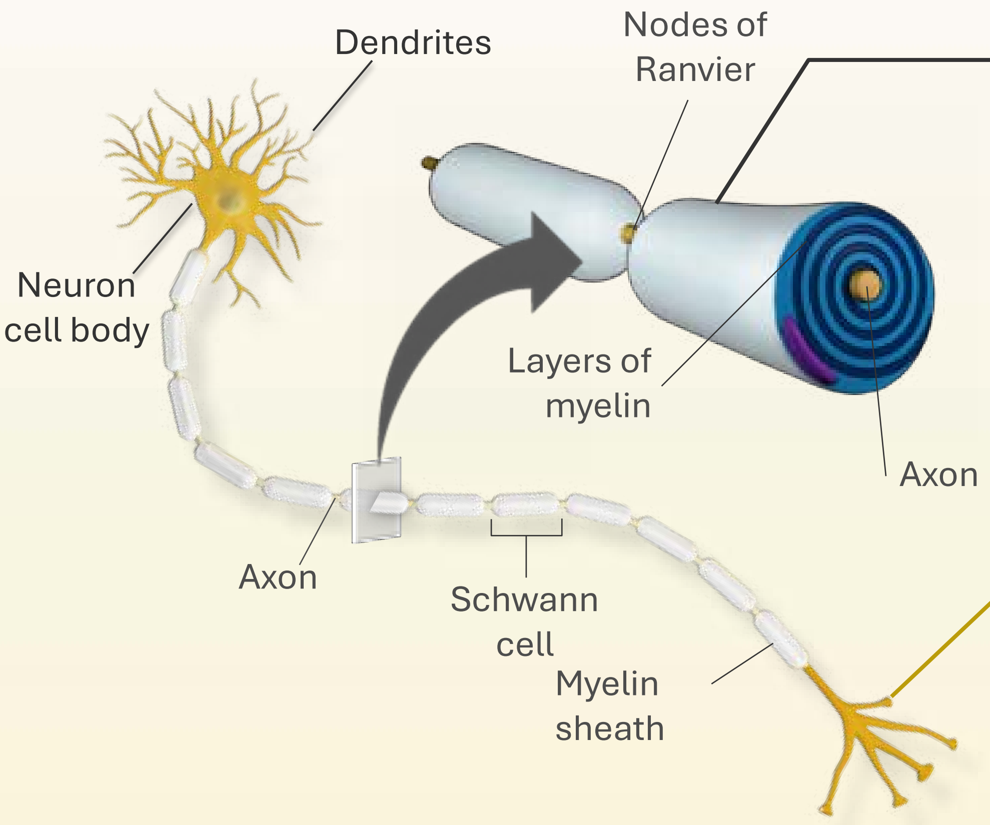
# The Gut-Brain Axis: Mediating the Effects of MFGM






**1.** Brink LR, Lönnerdal B. *J Nutr Biochem.* 2020;85:108465. **2.** Yuan C et al. *Front Cell Infect Microbiol.* 2023;13:1282431.

# MFGM Components Support Nerve Myelination and Synaptic Transmission



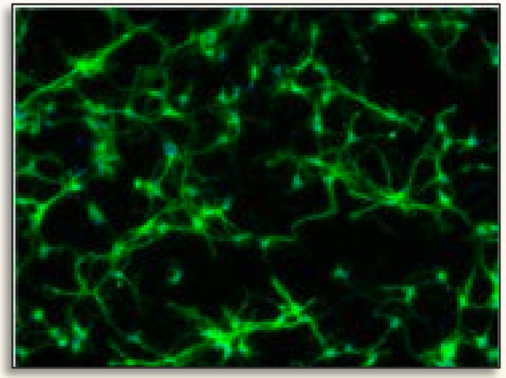

**Sphingomyelin[1] and gangliosides[2]**
Support myelination, required for fast conduction of action potentials down the axon[3]

**Gangliosides[2] and DHA[4]**
Act at the synapse to support synaptic transmission and long-term potentiation

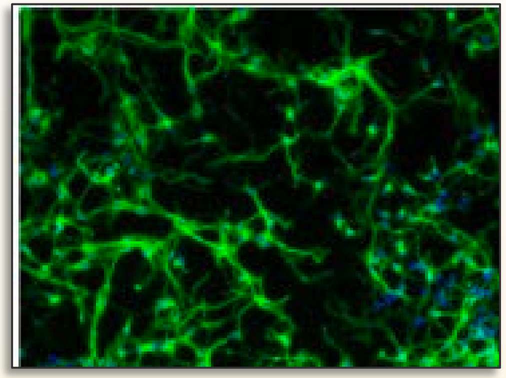


1. Quarles RH et al. In: Siegal GJ, ed. Basic Neurochemistry: Molecular, Cellular, and Medical Aspects; 2006:51-71. 2. Palmano K et al. Nutrients. 2015;7:3891-3913. 3. Squire LR et al, eds. Fundamental Neuroscience. 2nd ed; 2003. 4. Wurtman RJ. Metabolism. 2008;57(suppl 2):S6-S10.

# Dairy Phospholipids Support Cortical Neuron Growth & Stimulation

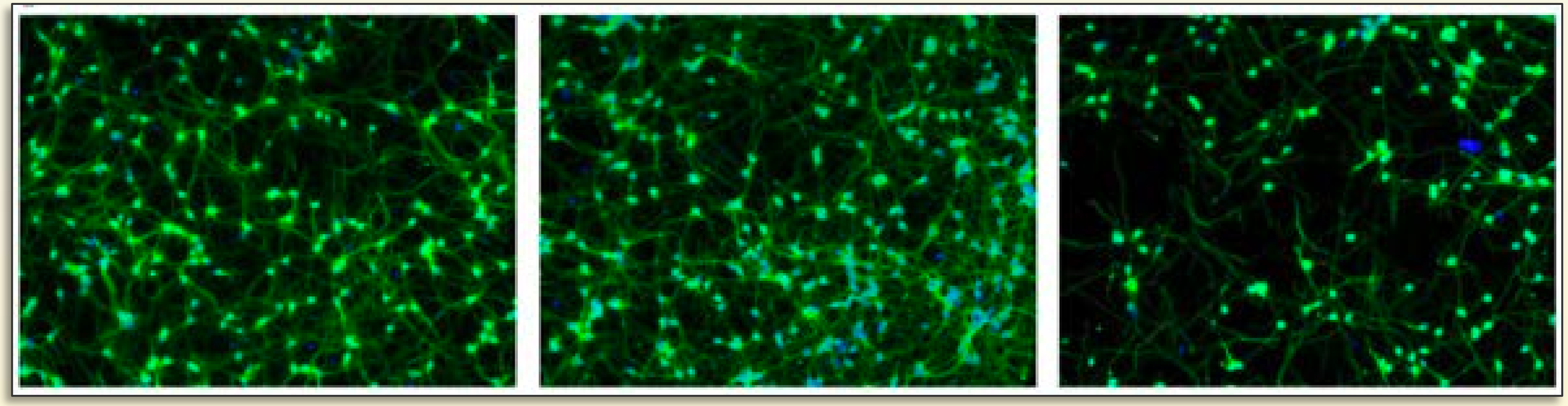


**Untreated neurons**
Negative control



**FCS-treated neurons**
Positive control

**Increasing phospholid extract concentration**



**Cortical neuron outgrowth increases after incubation with phospholipid extract**

FCS, fetal calf serum



Barry KM et al. *J Functional Foods*. 2018;40:60-67.

# Key Takeaways

- MFGM is a complex structure enveloped by a lipid trilayer containing bioactive lipids, proteins, and carbohydrates
- MFGM has an important role in the health outcomes of the developing infant
- MFGM and its lipid constituents:
  - Fortify the mucosal barrier to protect against intestinal barrier disruption through mucin regulation
  - Facilitate healthy gut microbiota
  - Play a role in the gut-brain axis, likely via the intestinal neuronal system

# Gracias!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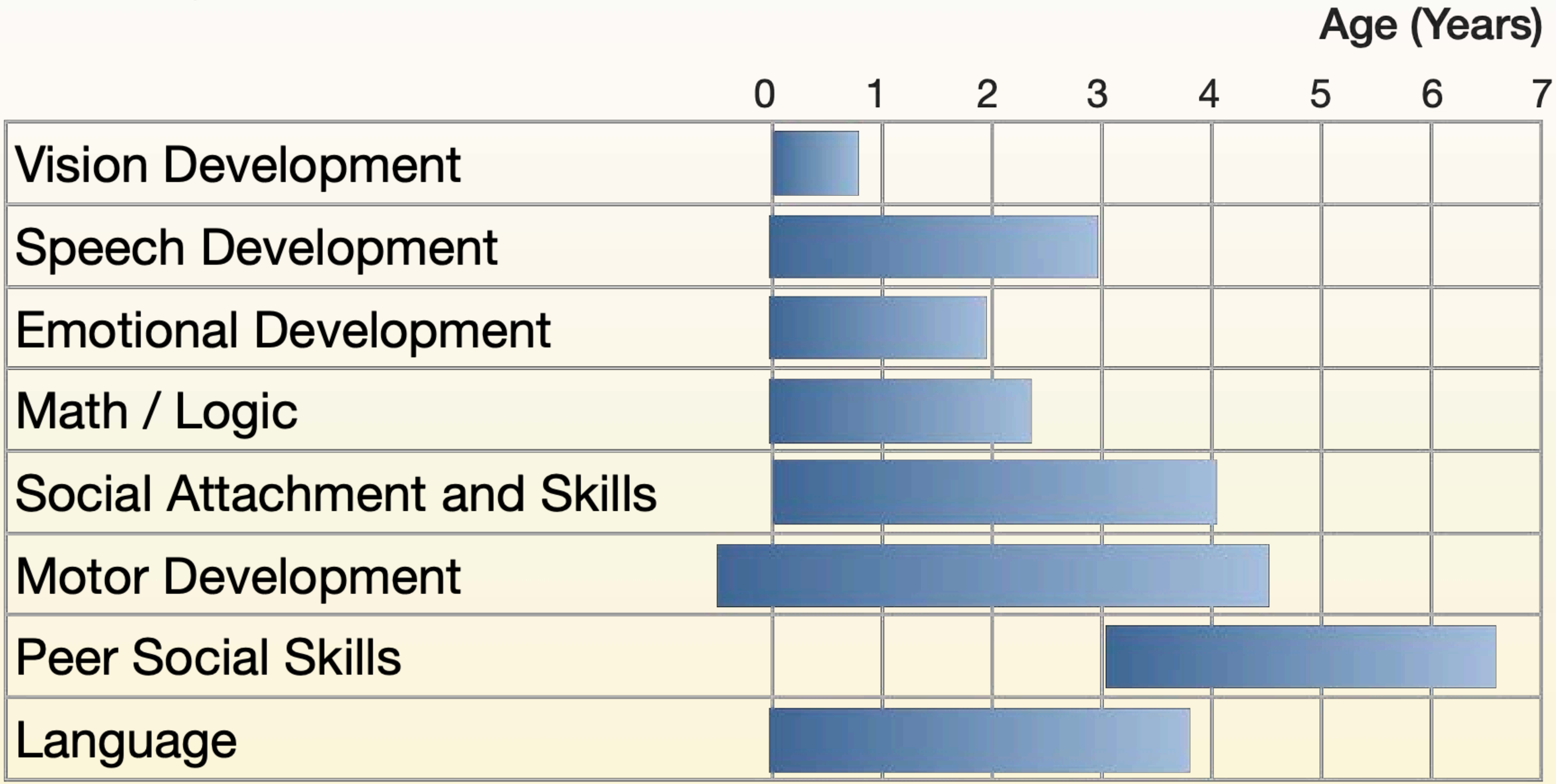
# MFGM & the Developing Brain

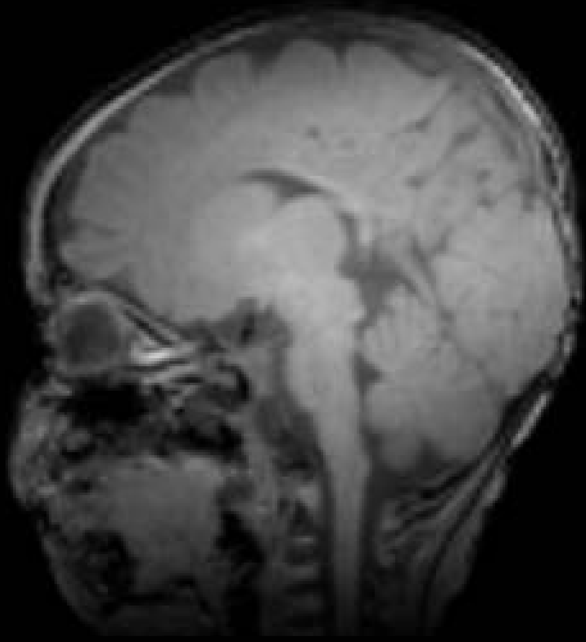
## Early Brain Development

Sean Deoni, PhD

# Early Cognitive and Behavioral Development



# Early Brain Development



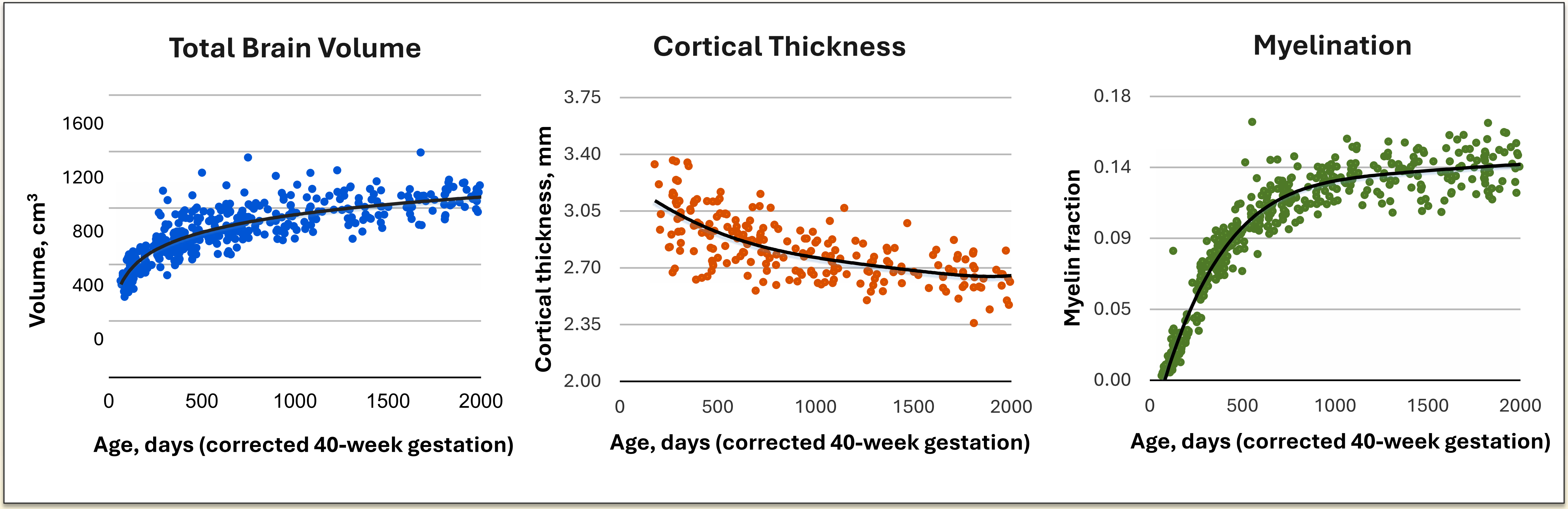
3 months

12 months

24 months

Images courtesy of Sean Deoni, PhD.

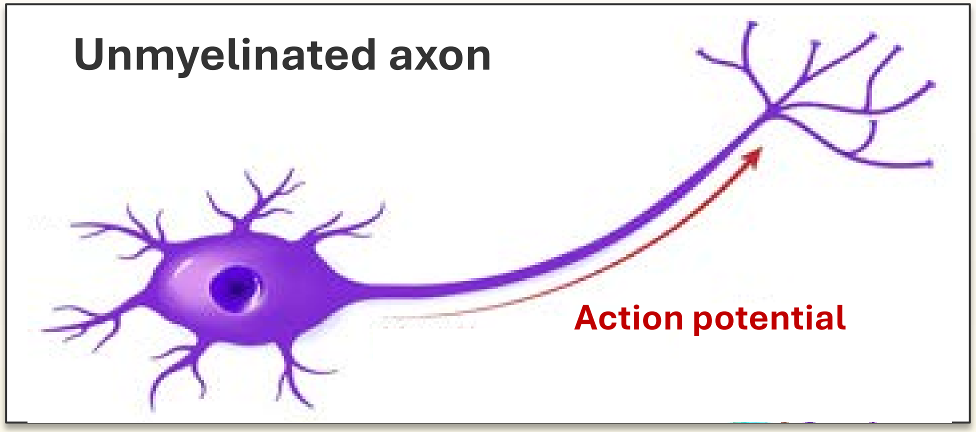
# Measures of Neurodevelopment With Age

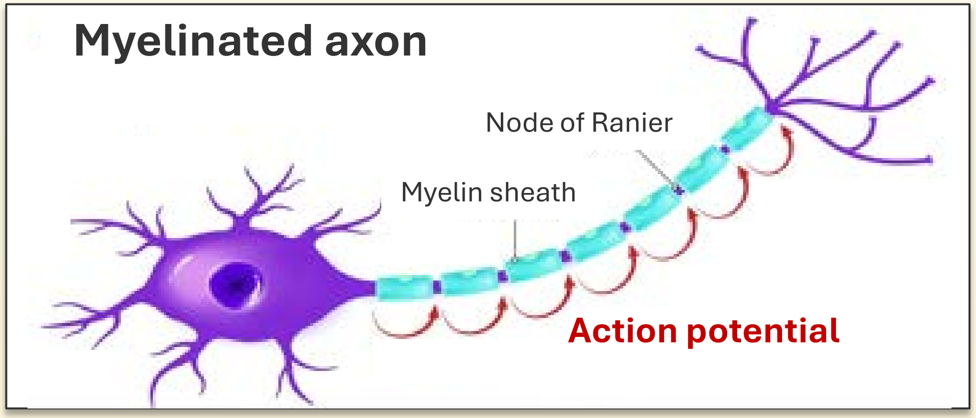





Graphs courtesy of Sean Deoni, PhD.

# Myelination in the Developing Brain



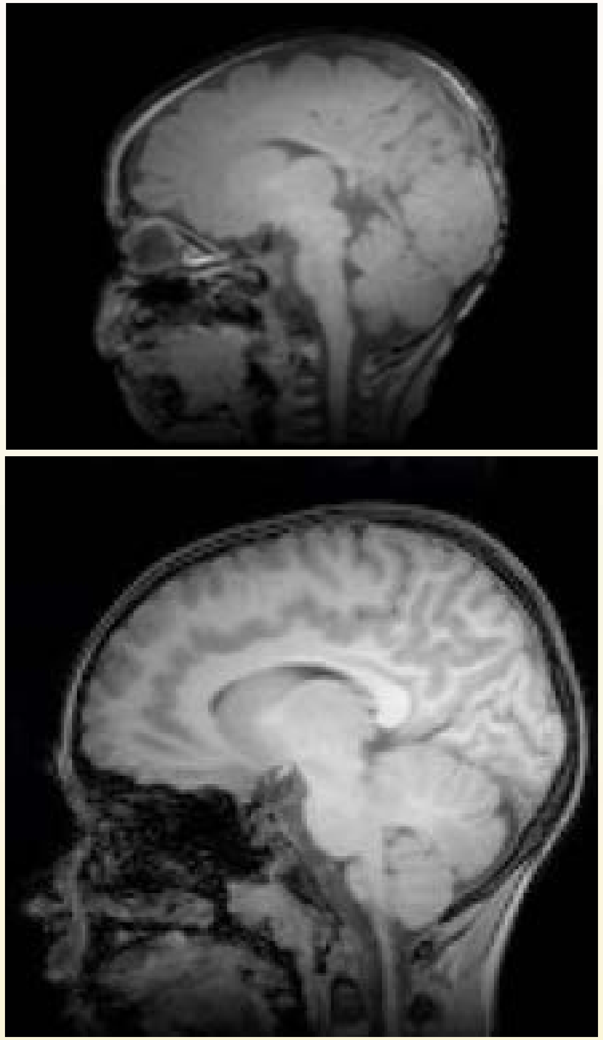



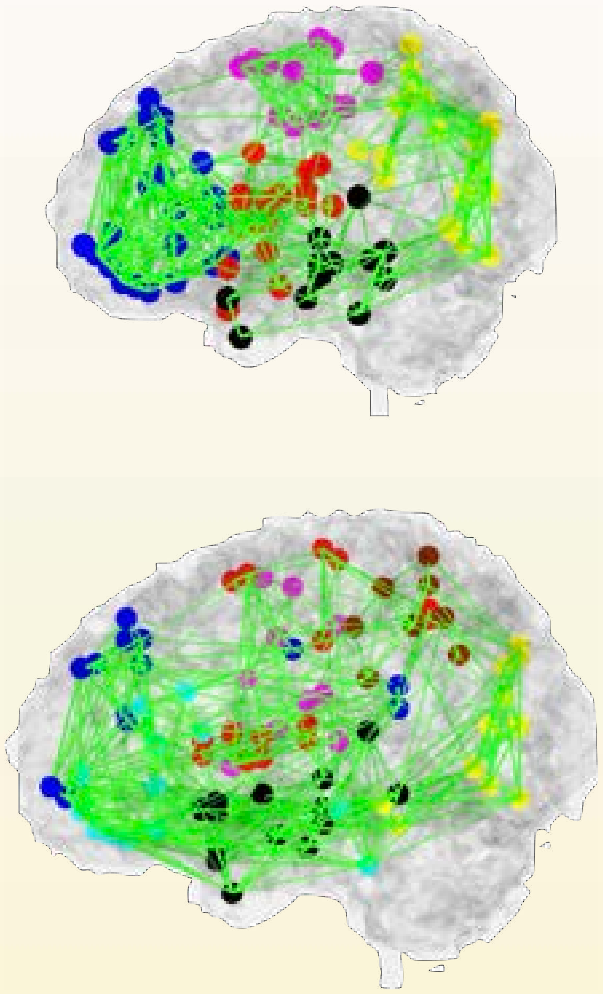

**Myelin protects the axon, speeds information transfer, and facilitates brain connectivity & function**



Stadelmann C et al. *Physiol Rev*. 2019;99(3):1381-1431.

# Myelination in the Developing Brain





Simplistic behaviors and primary cognitive abilities

Complex behaviors and coordinated cognitive skills

Stadelmann C et al. *Physiol Rev*. 2019;99(3):1381-1431.

# MFGM & the Developing Brain

## Nutrition, Human Milk, & Neurodevelopment

# Nutritional Needs for the Developing Brain

| Lipids & Fatty Acids | Minerals | Vitamins | Micronutrients |
|---|---|---|---|
| **LC-PUFAs (eg, DHA, ARA)**<br>• Promote healthy neural growth and development<br>• Regulate membrane function<br>• Involved in lipid biosynthesis and myelination<br>• ~20% of the fatty acid content of the brain<br>**Phospholipids (eg, phosphatidylcholine)**<br>• ~10% of the lipid weight of myelin<br>**Sphingolipids (eg, sphingomyelin)**<br>• Critical components of the myelin sheath<br>**Cholesterol**<br>• Essential constituent of myelin<br>• Necessary for myelin membrane synthesis | **Iron**<br>• Utilized by oligodendrocytes (myelin-producing cells)<br>**Zinc**<br>• Helps bind myelin basic proteins to the myelin membrane | **B12**<br>• Helps convert L-methylmalonyl coenzyme A into succinylcholine coenzyme A<br>• Required for synthesis of myelin phospholipids<br>**Vitamin K**<br>• Can increase sulfatides, which are incorporated into the myelin sheath to maintain structure and function | **Choline**<br>• Promotes oligodendrocytes and their precursors, influencing myelination and remyelination |

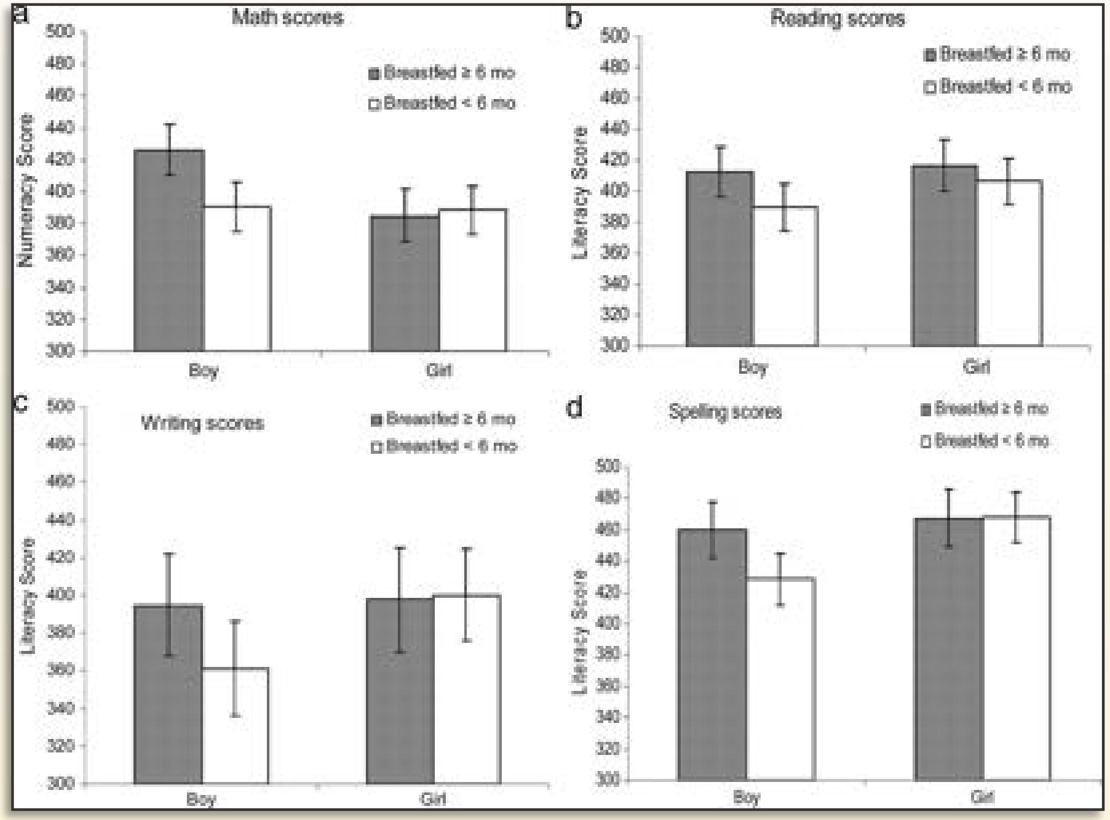
**Breastmilk provides all of these nutrients – with the exception of iron – at the right time and in the ideal amount.**

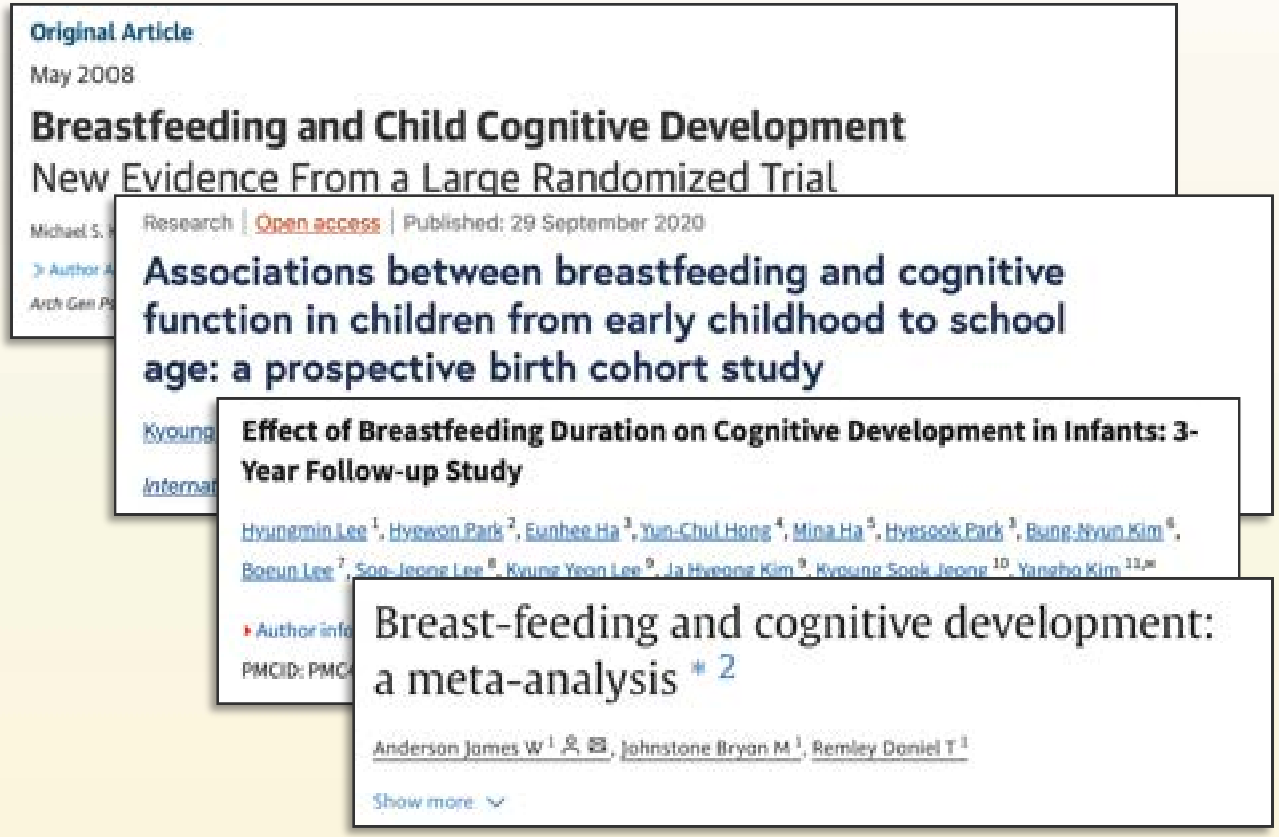


**1.** Cormack BE et al. *Nutrients*. 2019;11(9):2019. **2.** Georgieff MK. *Am J Clin Nutr*. 2007;85(2):614S-620S. **3.** Costello SE et al. *Nutr Rev*. 2021;79(12):1293-1306.

# Breastfeeding & Child Neurodevelopment

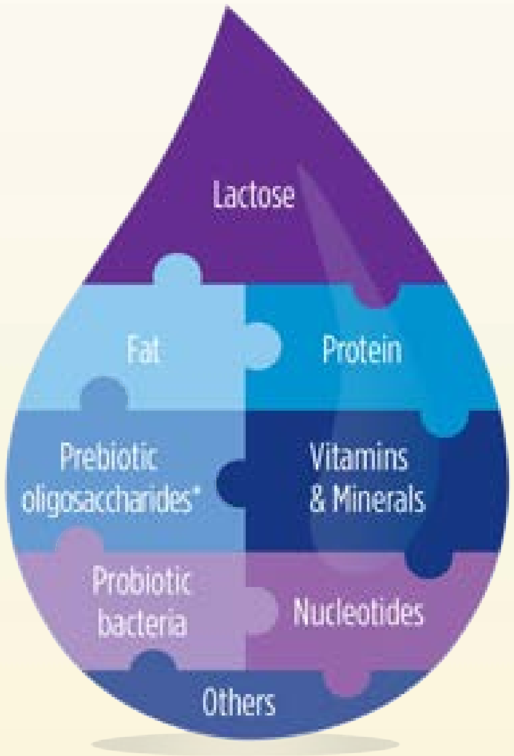
Studies consistently show improved cognitive development and academic outcomes in individuals who were breastfed as infants; enhanced as a function of breastfeeding duration.



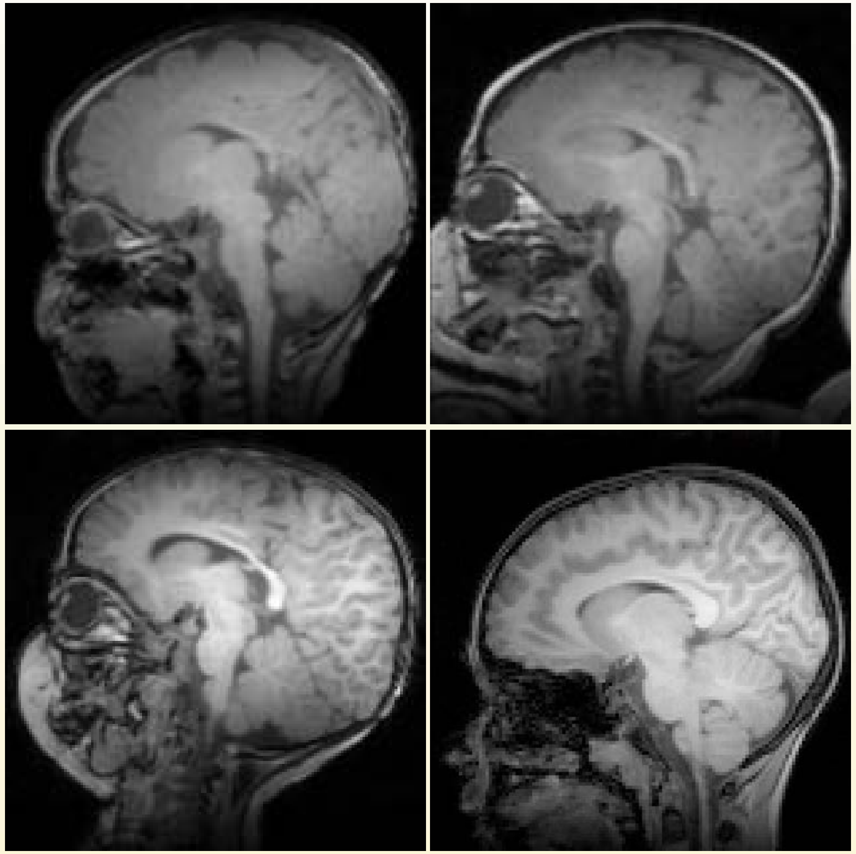



# Potential Underlying Biological Mechanism

**Human Milk Nutrients**

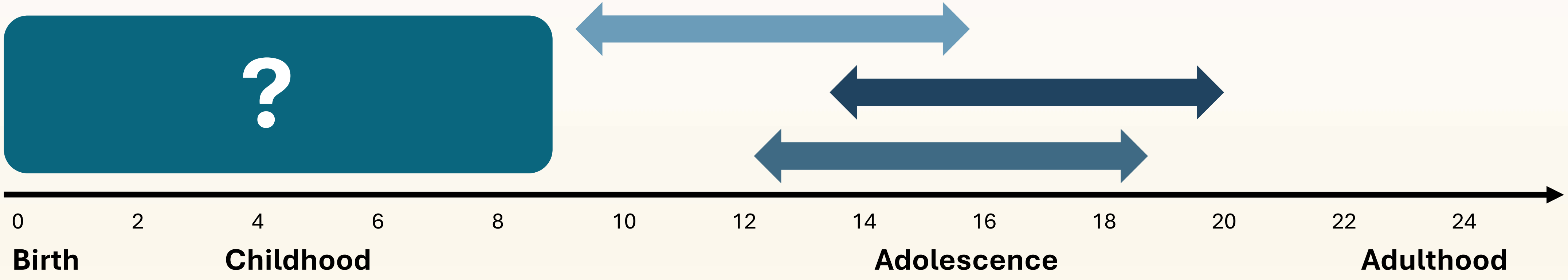



**Brain Development**



**Cognitive Development**

# Nutrition & Early Neurodevelopment




**Duration of breastfeeding associated with:[1]**
- Cortical thickness in the superior and inferior parietal lobes
- Performance IQ

**Percentage of breast milk in diet associated with:[2]**
- Verbal IQ
- White matter volume

**Relative to formula-fed infants, breastfed infants had:[3]**
- Higher IQ scores
- Larger total gray matter, and subcortical gray matter volumes

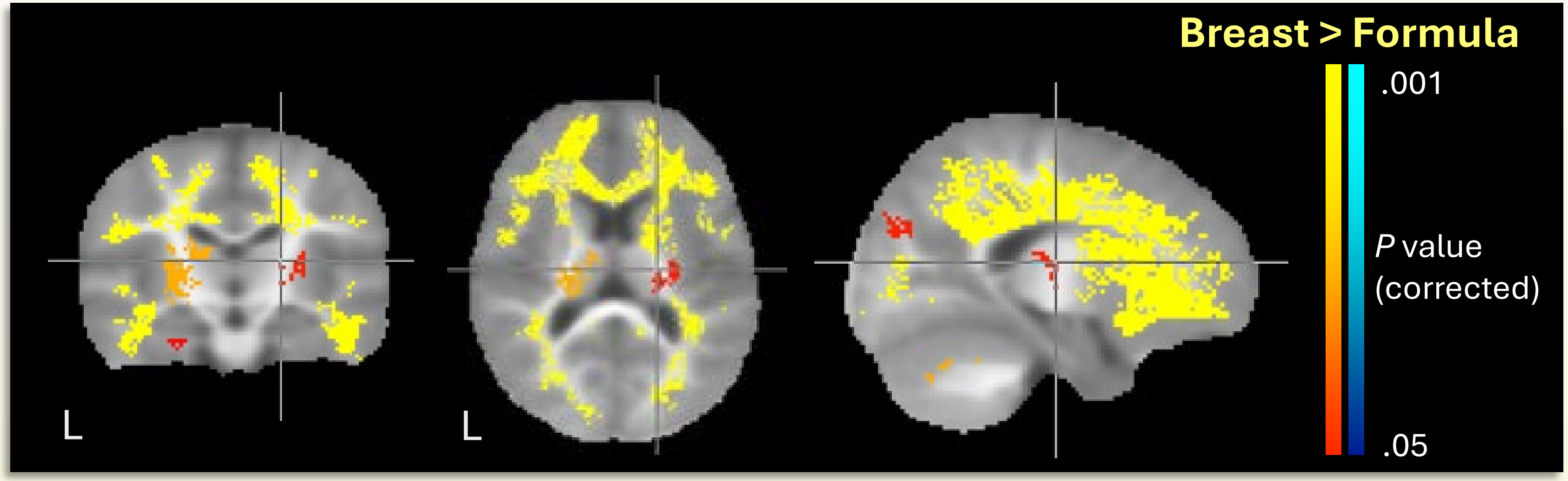


**1.** Kafouri S et al. *Int J Epidemiol*. 2013;42(1):150-159. **2.** Isaacs EB et al. *Pediatr Res*. 2010;67(4):357-362. **3.** Luby JL et al. *J Am Acad Child Adolesc Psychiatry*. 2016;55(5):367-375.

# The Challenges of Pediatric MRI

# Breastfeeding & Neurodevelopment (Cross-Sectional Study)

**Matched cohort study of toddlers (6-60 months of age) who were exclusively breastfed (n = 62) or formula fed (n = 38) for at least 3 months.**

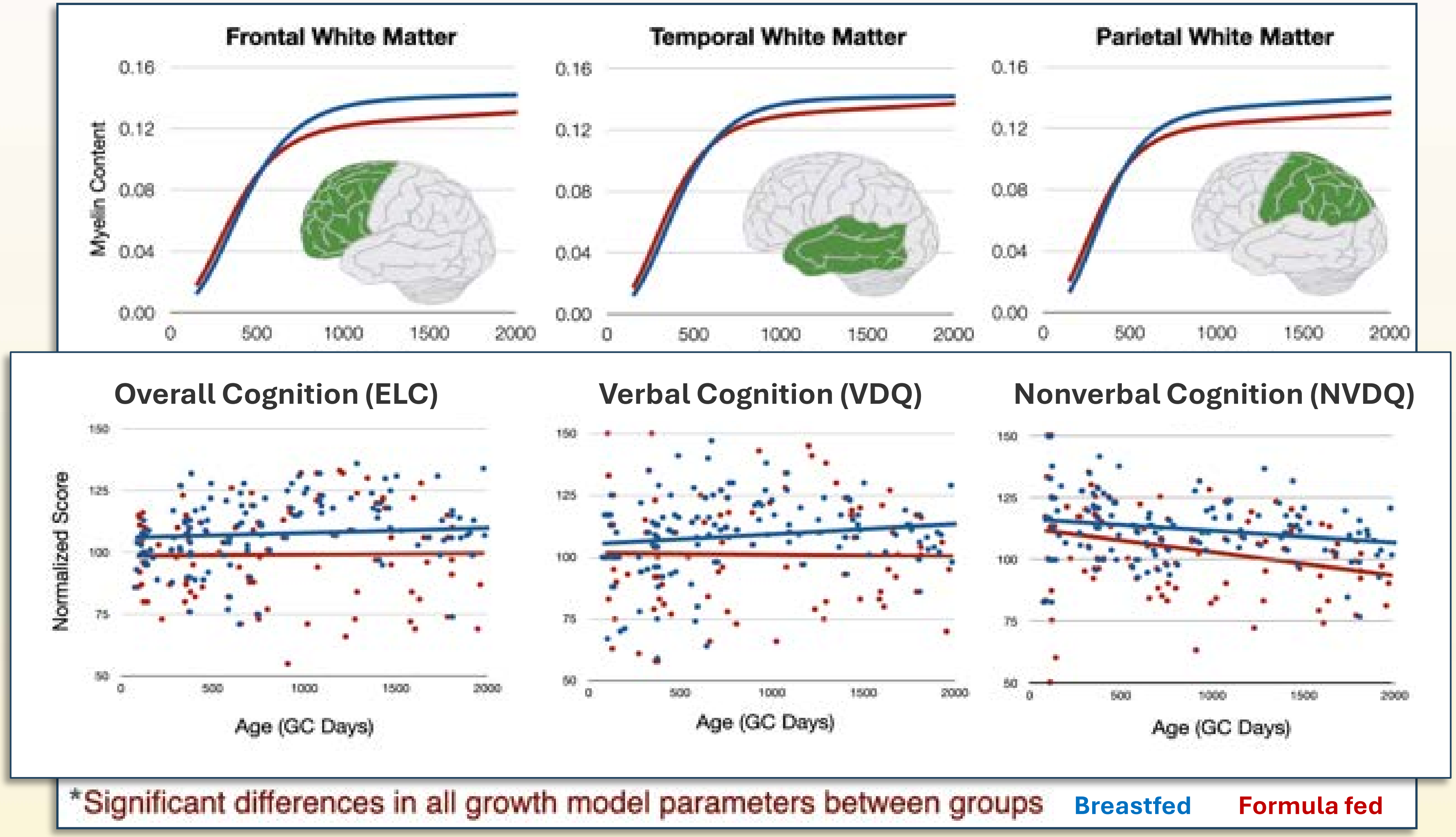



| | Exclusively breastfed | Exclusively formula fed | *P* value |
|---|---|---|---|
| **Fine motor** | 64.8 ± 10.9 | 56 ± 7.7 | <.0001 |
| **Visual reception** | 56.2 ± 8.7 | 51.3 ± 10.8 | .0085 |
| **Receptive language** | 61.9 ± 7.7 | 49.3 ± 12.5 | <.0001 |
| **Expressive language** | 50.5 ± 13 | 43.3 ± 13.3 | .0063 |

Deoni SC et al. *Neuroimage*. 2013;82:77-86.

# Breastfeeding & Neurodevelopment (Longitudinal Study)

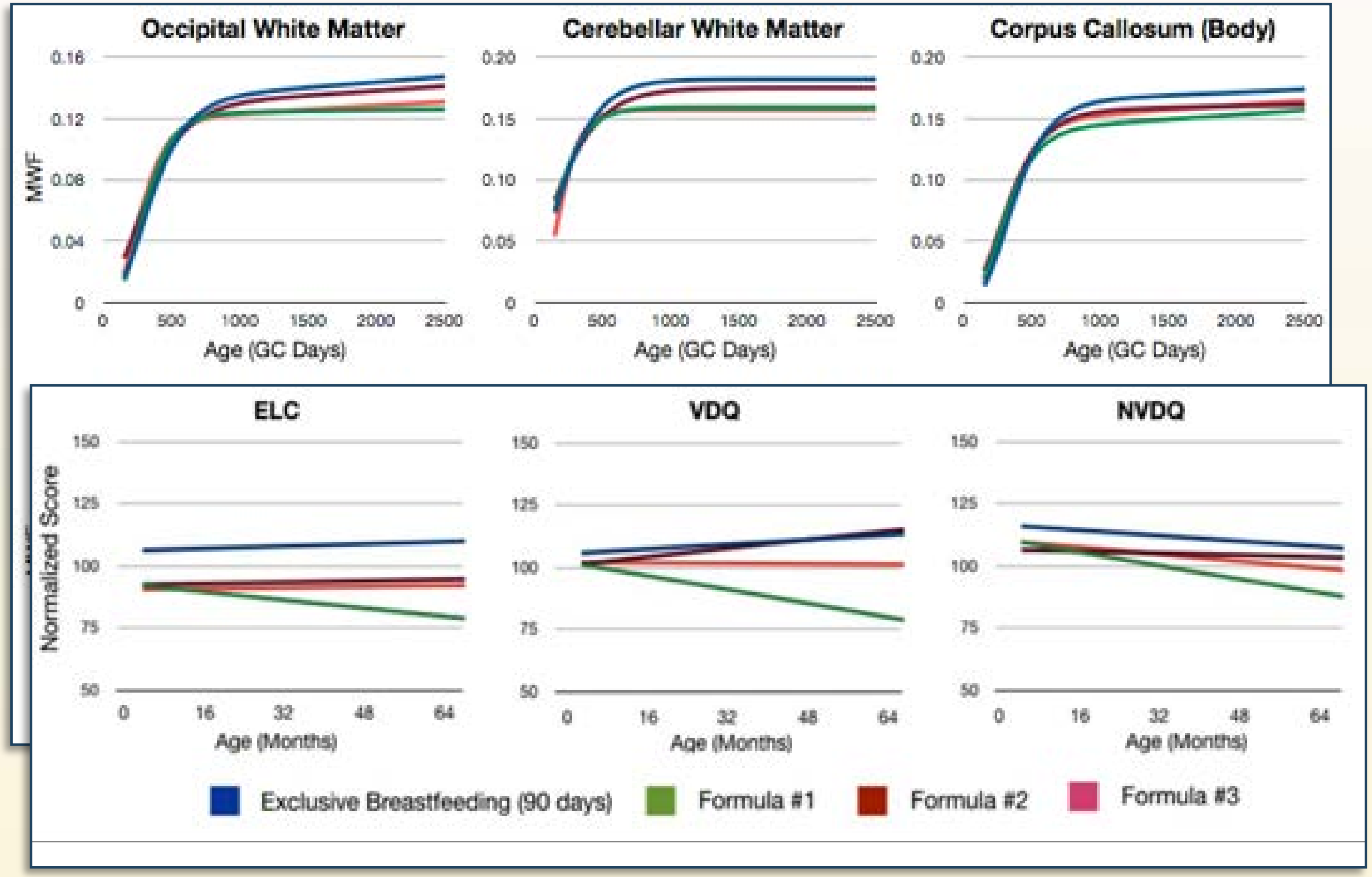
**Matched cohort study of toddlers (2-76 months of age) who were exclusively breastfed (n = 62) or formula fed (n = 88) for at least 3 months.**




Deoni S et al. *Neuroimage*. 2018;178:649-659.

# Influence of Nutrition Intake

| Nutrient | Formula 1 | Formula 2 | Formula 3 | % Difference (Min-Max) |
|---|---|---|---|---|
| ARA (mg/L) | 173 | 238 | 255 | 32 |
| DHA (mg/L) | 62.2 | 117 | 120.6 | 48 |
| Folic Acid (µg/L) | 304 | 232 | 146.2 | 52 |
| Phosphatidylcholine (mg/L) | 85 | 58 | 60 | 29 |
| Sphingomyelin (mg/L) | 28.1 | 62 | 28.1 | 55 |
| Iron (mg/100g) | 10.6 | 8.42 | 11.65 | 28 |
| Choline (mg/100) | 170 | 92.5 | 144 | 46 |

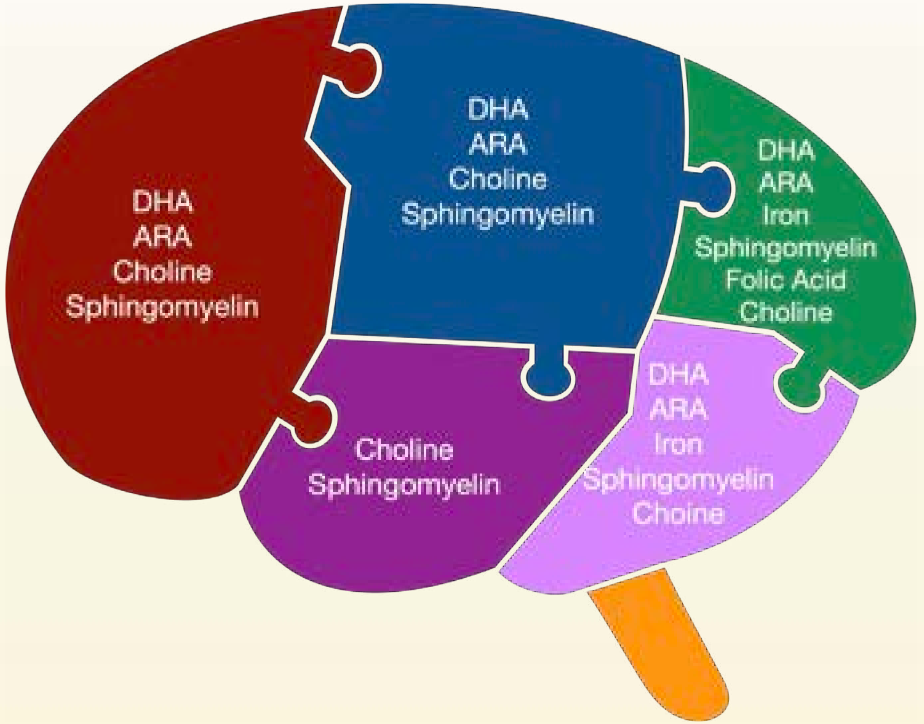



*Significant differences in intercept and slope between **formula #1** and **breastfeeding** and other formulas;
*General difference in intercept of each formula and **breastfeeding** in ELC scores

Deoni S et al. *Neuroimage*. 2018;178:649-659.

# Nutrition Differentially Impacts Regional Growth

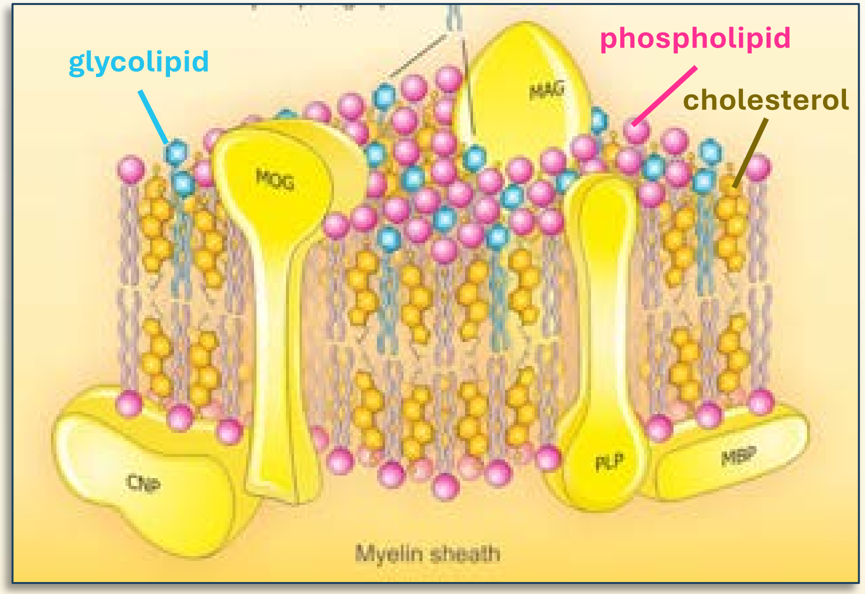
| Region | ARA | DHA | Folic acid | Phosphatidyl-choline | Sphingo-myelin | Iron | Choline |
|---|---|---|---|---|---|---|---|
| Frontal WM | **.002** | **.002** | .030 | **<.0001** | **<.0001** | .150 | **.004** |
| Temporal WM | .040 | .030 | .170 | **.004** | **.002** | .340 | .260 |
| Parietal WM | **<.0001** | **<.0001** | .005 | **<.0001** | **<.0001** | .080 | .080 |
| Occipital WM | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **<.0001** | **.006** |
| Cerebellar WM | **<.0001** | **<.0001** | .013 | **<.0001** | **<.0001** | **<.0001** | .020 |
| Corpus callosum (body) | **.003** | .020 | .450 | **<.0001** | **<.0001** | .280 | .076 |
| Corpus callosum (genu) | .090 | .150 | .630 | **<.0001** | **<.0001** | .270 | .430 |
| Corpus callosum (splenium) | .050 | .020 | .760 | **<.0001** | **<.0001** | .560 | .860 |

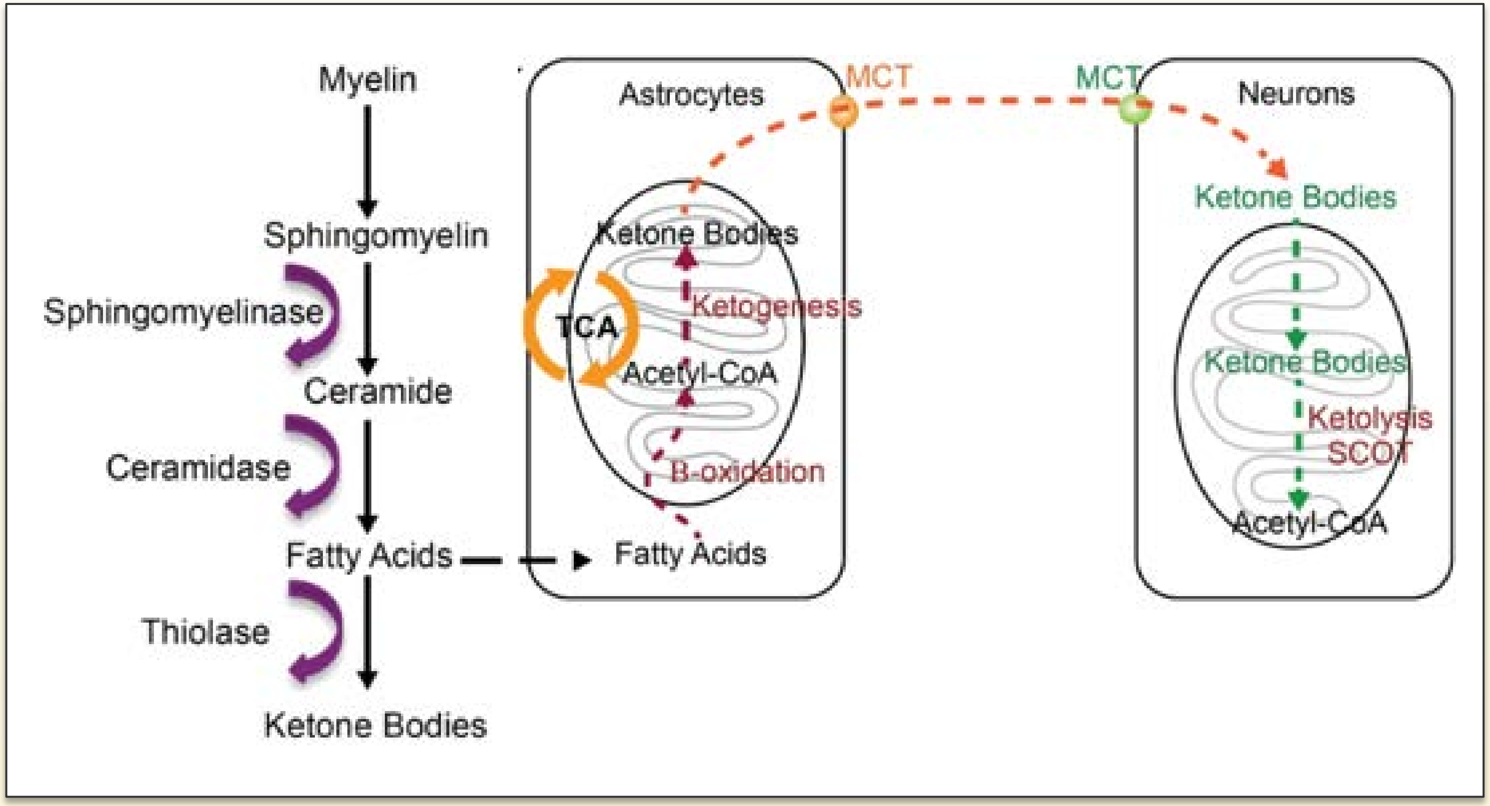



WM, white matter.

# Nutrition Differentially Impacts Regional Growth

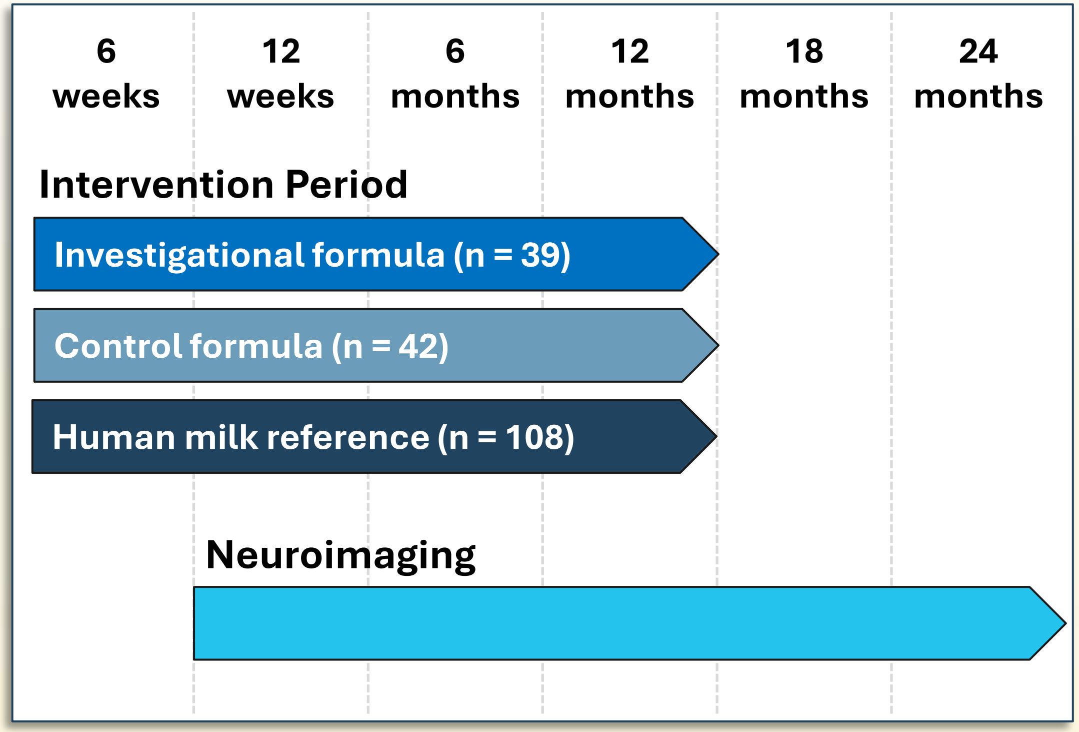
Myelin Sheath



# Testing the Role of Sphingomyelin and Other Nutrients in Neurodevelopment

## Design of a Nutritional RCT Investigating Sphingomyelin Intake and Myelination

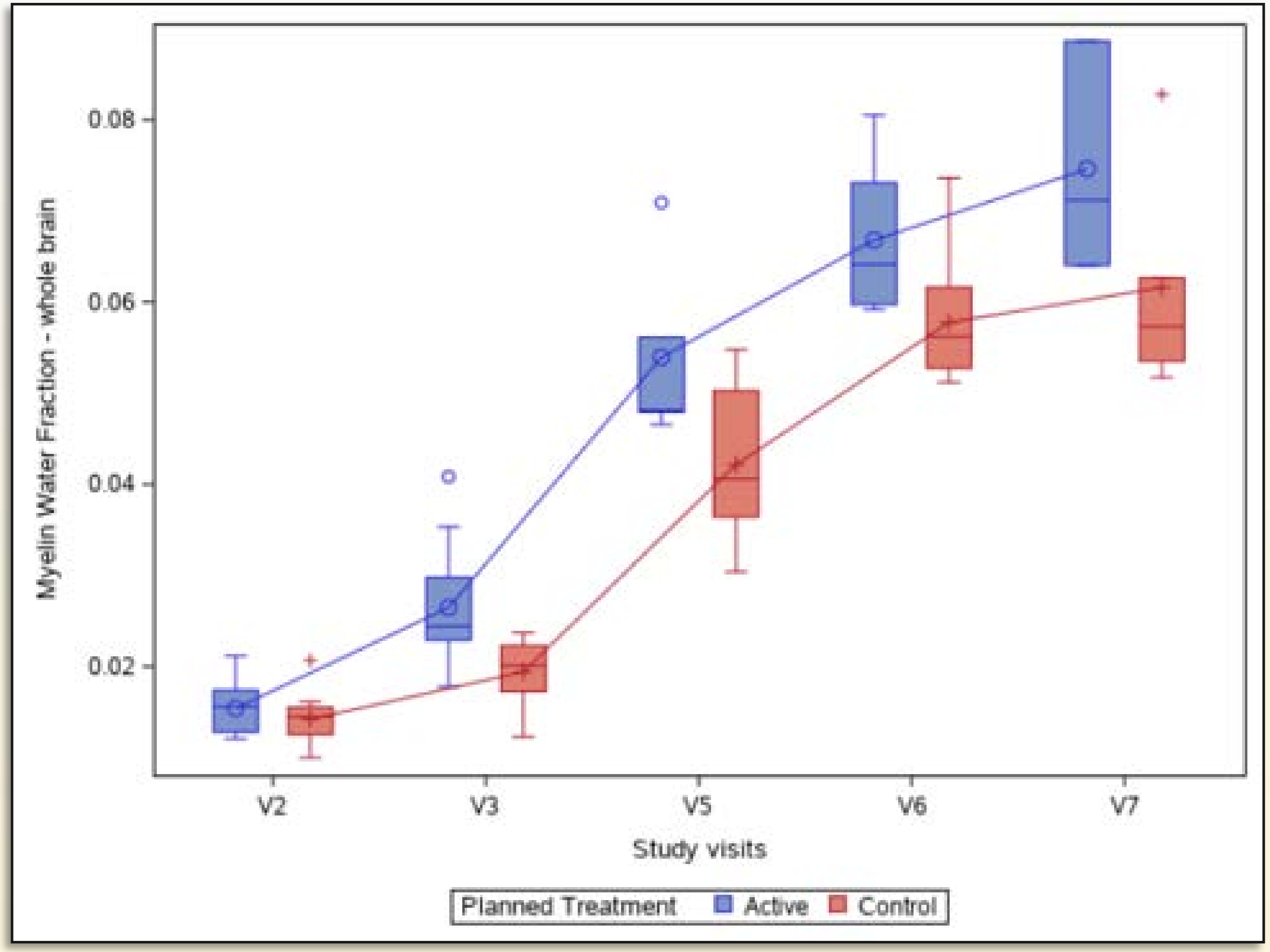



| Nutrients | Investigational Formula | Control Formula | Human Milk Reference[a] |
|---|---|---|---|
| Energy, kcal/200 mL | 132 | 132 | |
| Myelin blend | | | |
| Sphingomyelin (mg/L) | 105 | 22 | 86.7 |
| DHA (mg/L) | 132 | 71 | 89.8 |
| ARA (mg/L) | 132 | 71 | 172.0 |
| Iron (mg/L) | 8.6 | 4.0 | 0.3 |
| Folate (µg/L) | 219 | 85 | 24.5 |

a. 3- and 6-month average

Schneider N et al. *Nutrients*. 2023;15(20):4439.

# Longitudinal Patterns of Myelination



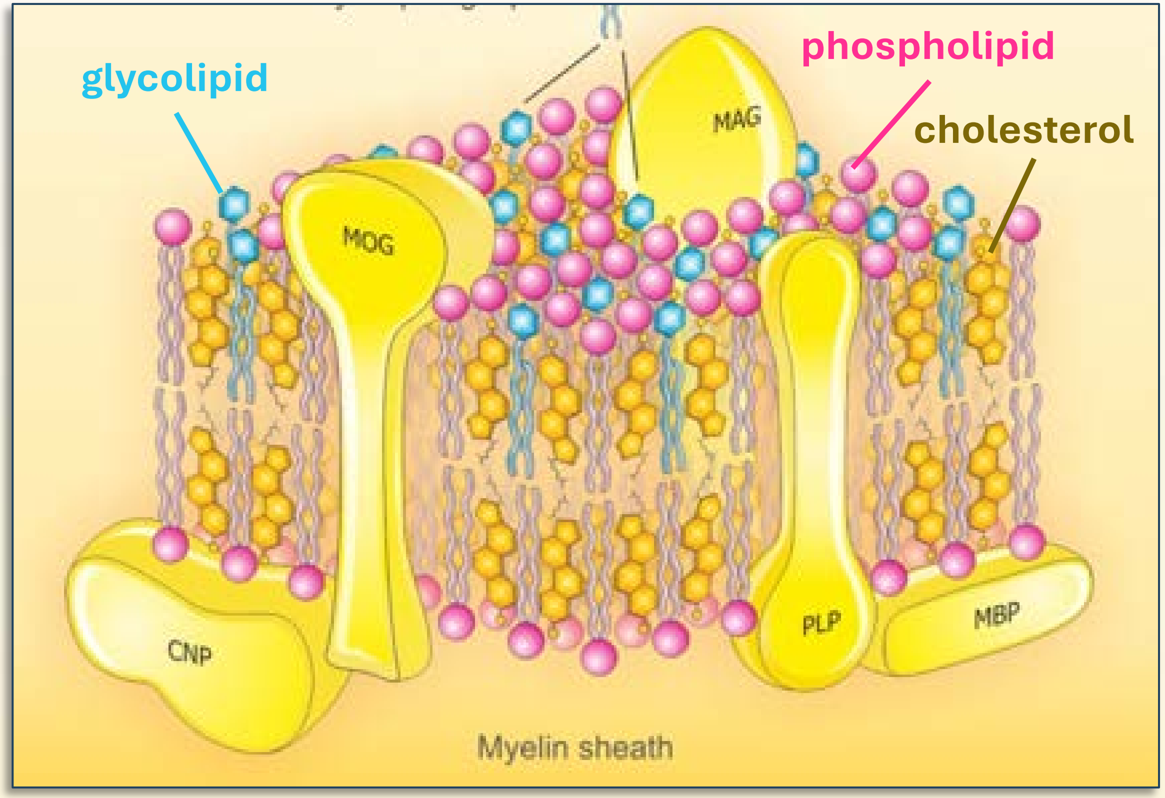

**Compared with infants fed the control formula, those fed the interventional formula had:**

- Significantly increased brain myelin content at 3, 6, 12, and 24 months of age
- Significantly increased rate of myelination throughout the first year of life

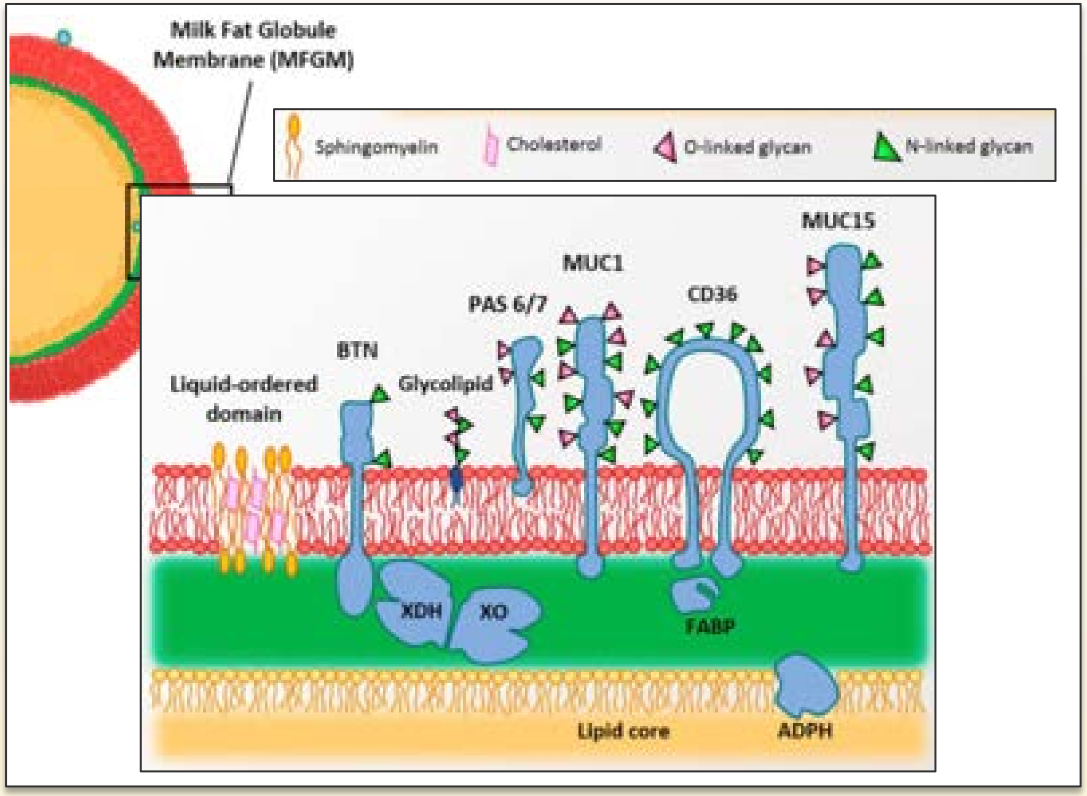
Schneider N et al. *Nutrients*. 2023;15(20):4439.

# MFGM As a Source of Myelin Nutrients

## Myelin Sheath




## MFGM



# MFGM As a Source of Myelin Nutrients

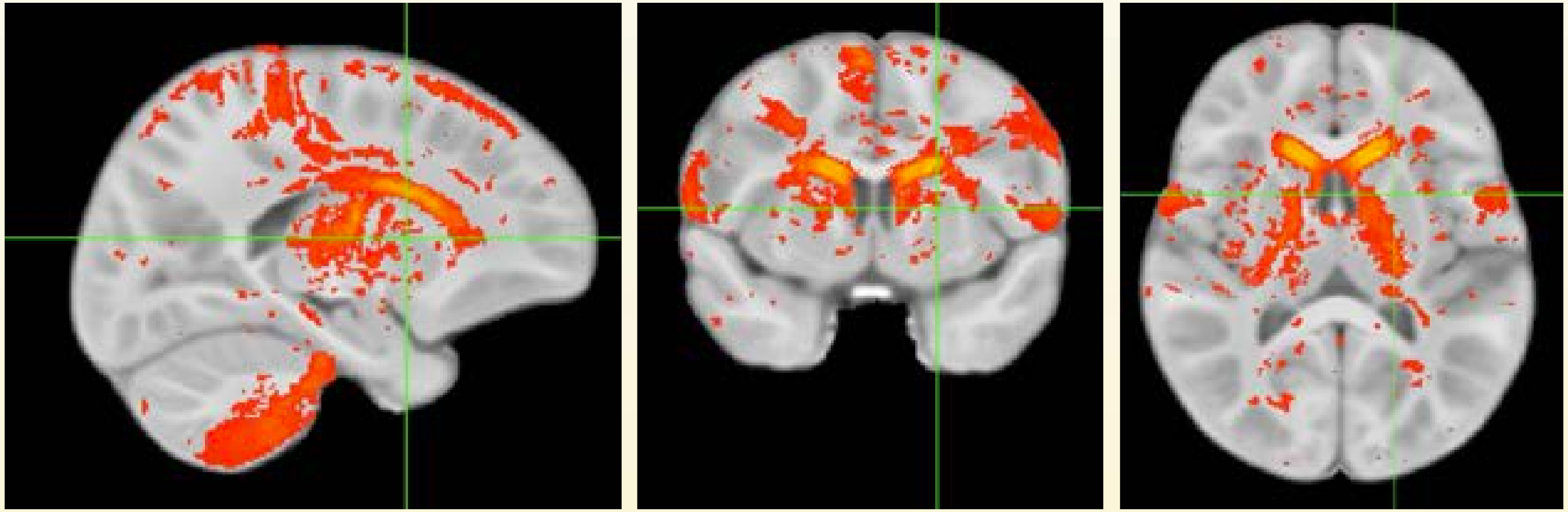
BAMBAM Study of Health Neurodevelopment

2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

**Infants who received formula without added bovine MFGM (n = 28)**

**Infants who received formula with added bovine MFGM (n = 43)**

Healthy term infants who received ≥90% formula for the first 3 months of life without a family history of learning or psychiatric disorders (excluding maternal MDD during pregnancy)



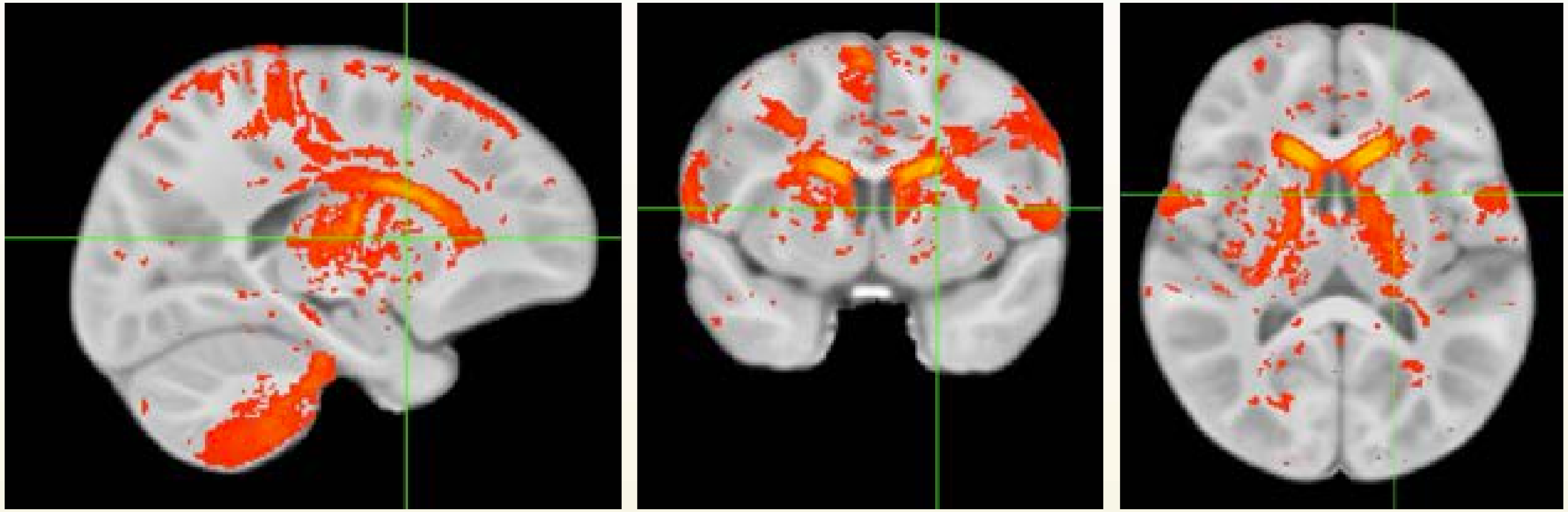
**Infants who received the formula with added MFGM had:**

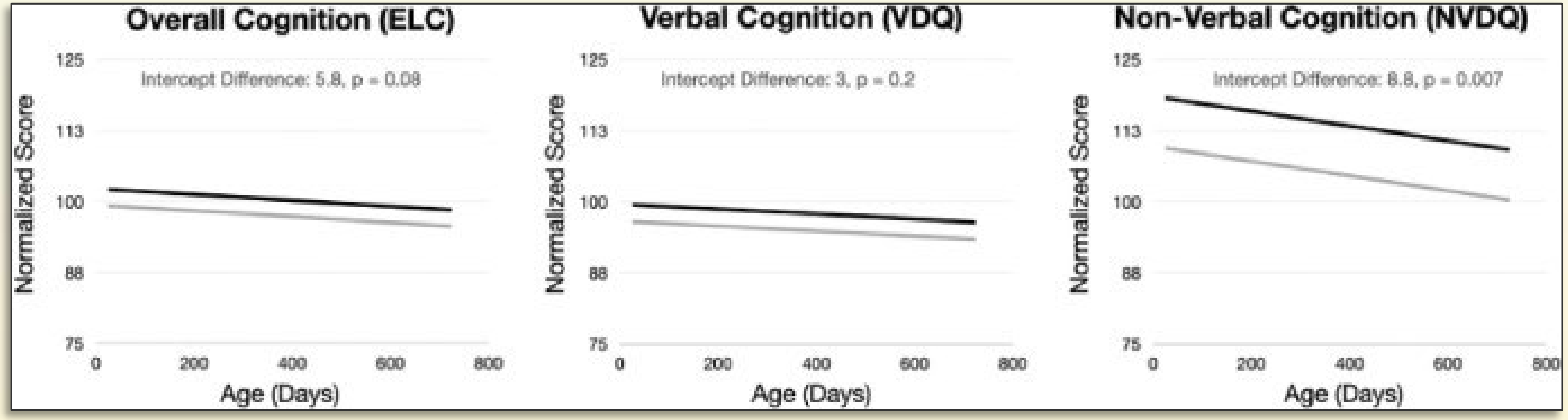
- Significantly increased brain myelin content over the first 2 years of life throughout motor related regions.



Deoni SC et al. Preprint. 2024. doi:10.21203/rs.3.rs-4999582/v1

# MFGM As a Source of Myelin Nutrients






**Infants who received the formula with added MFGM had:**

- Significantly increased brain myelin content over the first 2 years of life throughout motor related regions.
- Significantly increased motor skill development.



Deoni SC et al. Preprint. 2024. doi:10.21203/rs.3.rs-4999582/v1

# Key Takeaways

- Nutrients, including folic acid, iron, cholesterol, LC-PUFAs, and sphingomyelin are important for white matter development and brain connectivity
- These nutrients are amply provided in human milk and partially explain observed cognitive differences between breastfed and formula-fed infants
- Formulas with supplemental DHA and sphingomyelin appear to promote improved myelination and brain maturation
- Observational and RCT findings suggest we can improve infant neurodevelopment through improved nutrition, even in a generally healthy child population
- Nutrition is only one of many factors that influence a child's development: love, read, and play with your child!

# Advanced Baby Imaging Lab

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ECHO
Environmental influences on Child Health Outcomes
A program supported by the NIH

BILL & MELINDA GATES foundation

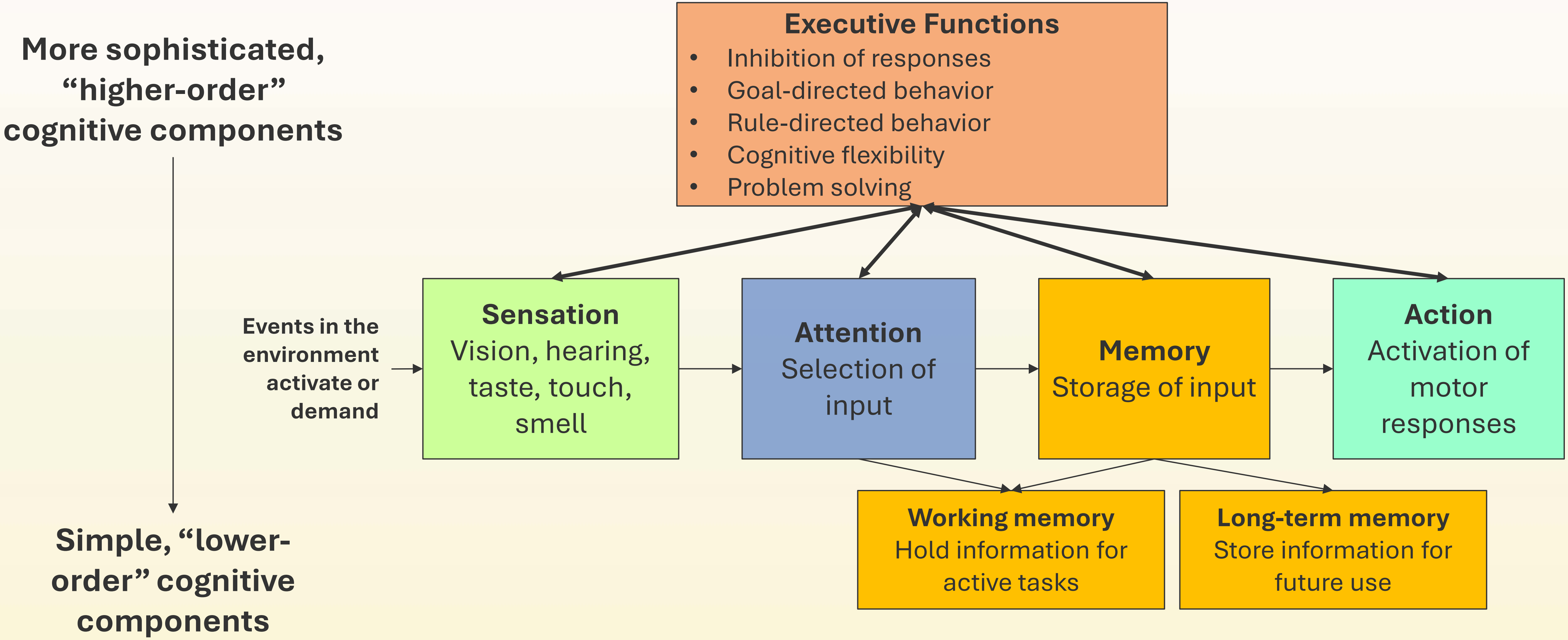
Nestle Research

# Supplemental MFGM & Neurodevelopmental Outcomes

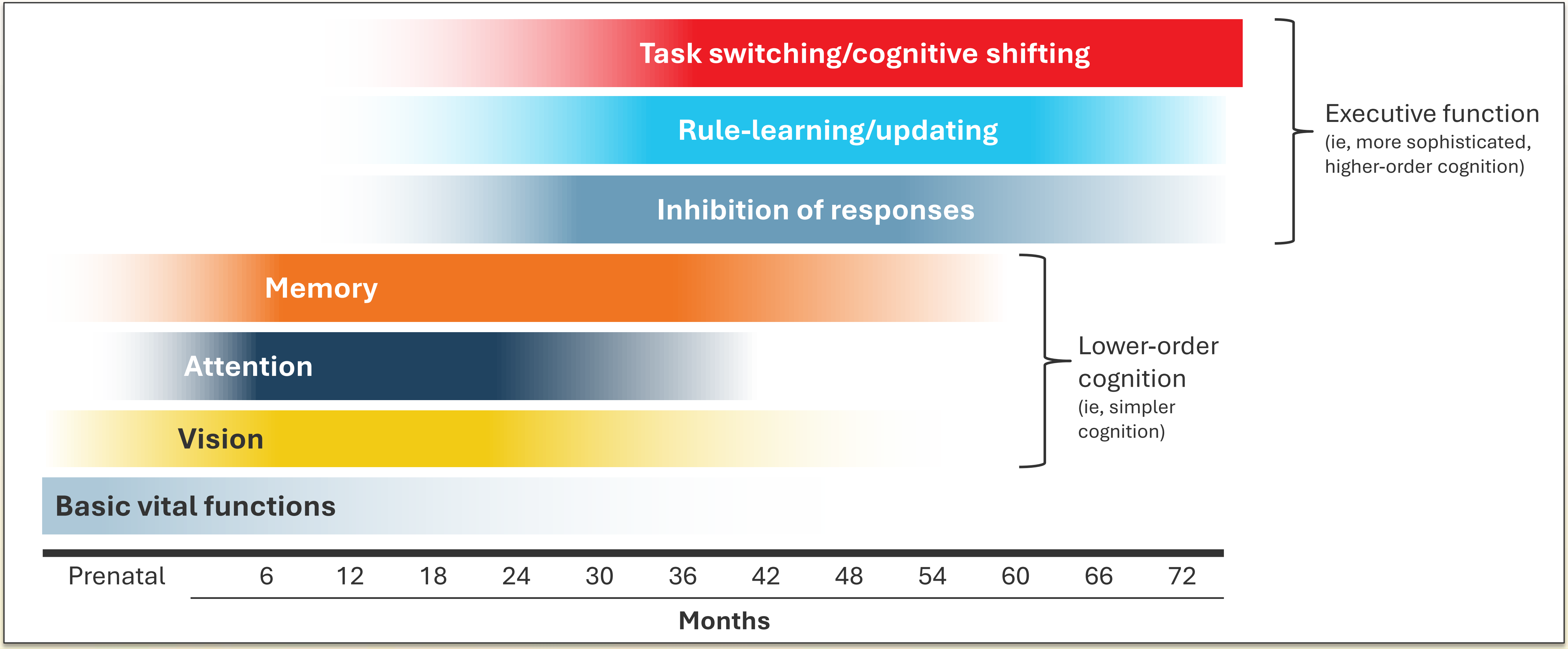
## Assessing Cognitive Outcomes

John Colombo, PhD

# Specific Cognitive Functions



# Developmental Course of Cognitive Functions



# Clinical Trial Outcomes to Measure Brain Development

**When designing a clinical trial, identifying outcomes to effectively evaluate the treatment is critical.**

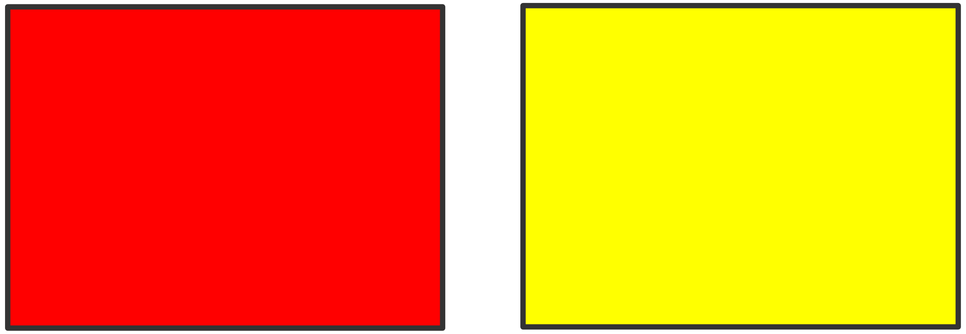
***Options for measuring neurodevelopment include:***

- Screening assessments
- Parent report measures (questionnaires)
- Standardized global developmental measures
- Tests of specific cognitive skills

# Measuring Executive Function: Modified Stroop Task[1,2]

- **Test:** asks children to respond to a stimulus based on a nonintuitive rule
- **Cognitive process measured:** inhibitory control, rule-learning and strategy, and working memory
- **Age group:** ≥30 months

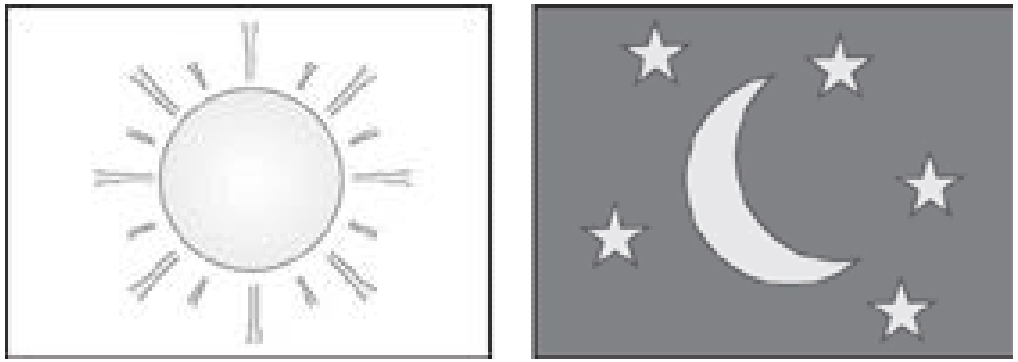
**Color Task Variant**



"Yellow"
(or "Banana")

"Red"
(or "Apple")

**Day/Night Task Variant**



"Night"

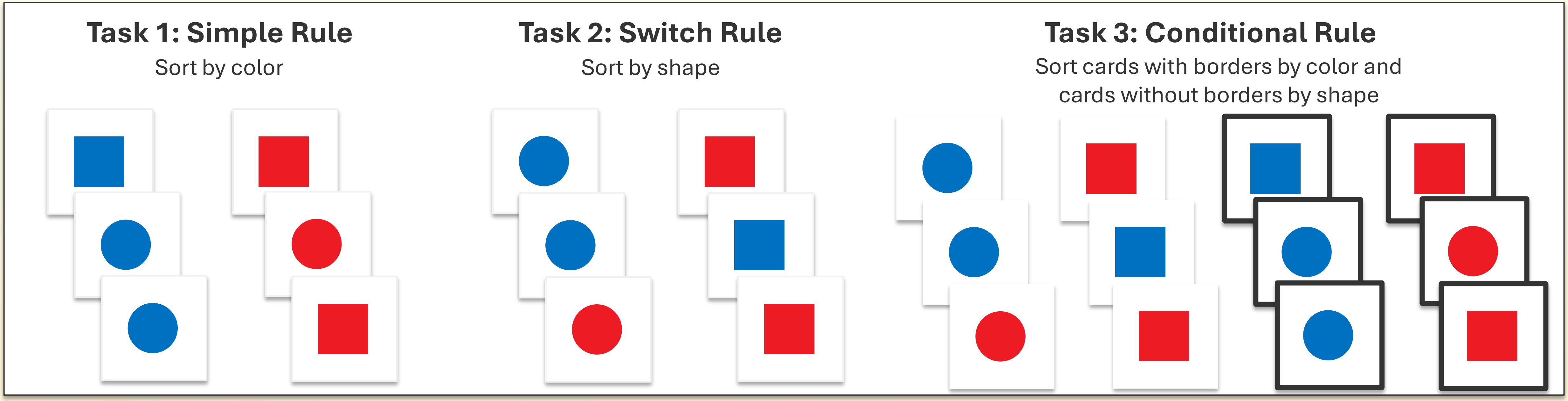
"Day"



**1.** Colombo J et al. *Am J Clin Nutr*. 2019;109(5):1380-1392. **2.** Colombo J et al. *J Pediatr*. 2023;261:113483.

# Measuring Executive Function: Dimensional Change Card Sort (DCCS) Task[1-3]

- **Test:** asks children to sort cards into boxes based on a specific characteristic (eg, color) and then asks them to *switch* and sort cards based on a different characteristic (eg, shape) and then again based on a conditional rule
- **Cognitive process measured:** rule-learning and cognitive flexibility
- **Age group:** ≥30 months

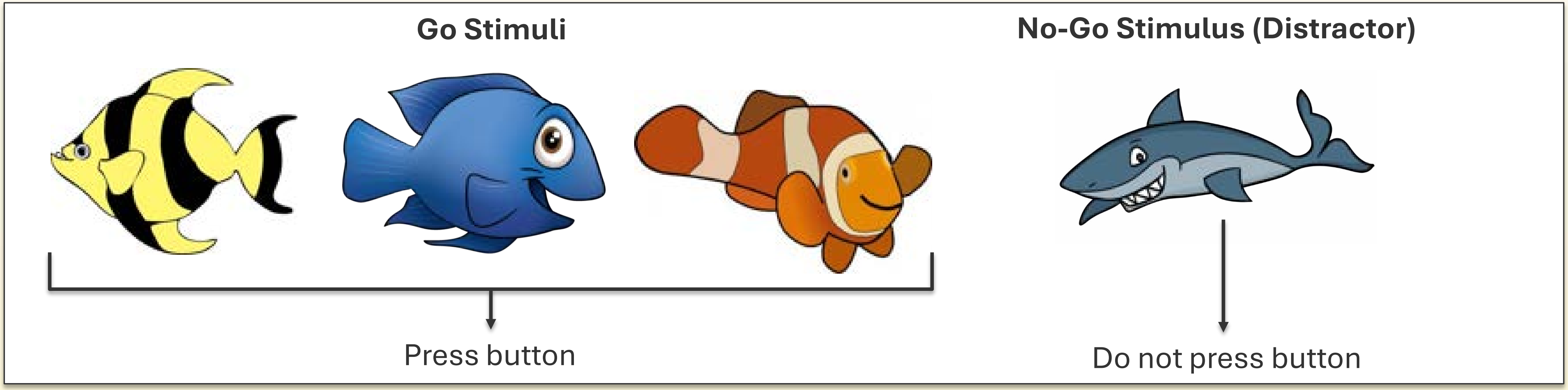





**1.** Colombo J et al. *Am J Clin Nutr*. 2019;109(5):1380-1392. **2.** Colombo J et al. *J Pediatr*. 2023;261:113483. **3.** Zelazo PD. *Nat Protoc*. 2006;1(1):297-301.

# Measuring Executive Function: Go/No-Go Task

- **Test:** asks children to perform a quick motor response when specific stimuli are displayed (ie, “go” stimuli) and withhold this response for other stimuli (ie, “no-go” stimuli or distractors); often used in conjunction with event-related brain potential (ERP) recording[1]
- **Measures:** inhibitory control[1]
- **Age group:** usually ≥60 months, but has been used in younger children with some success[2]



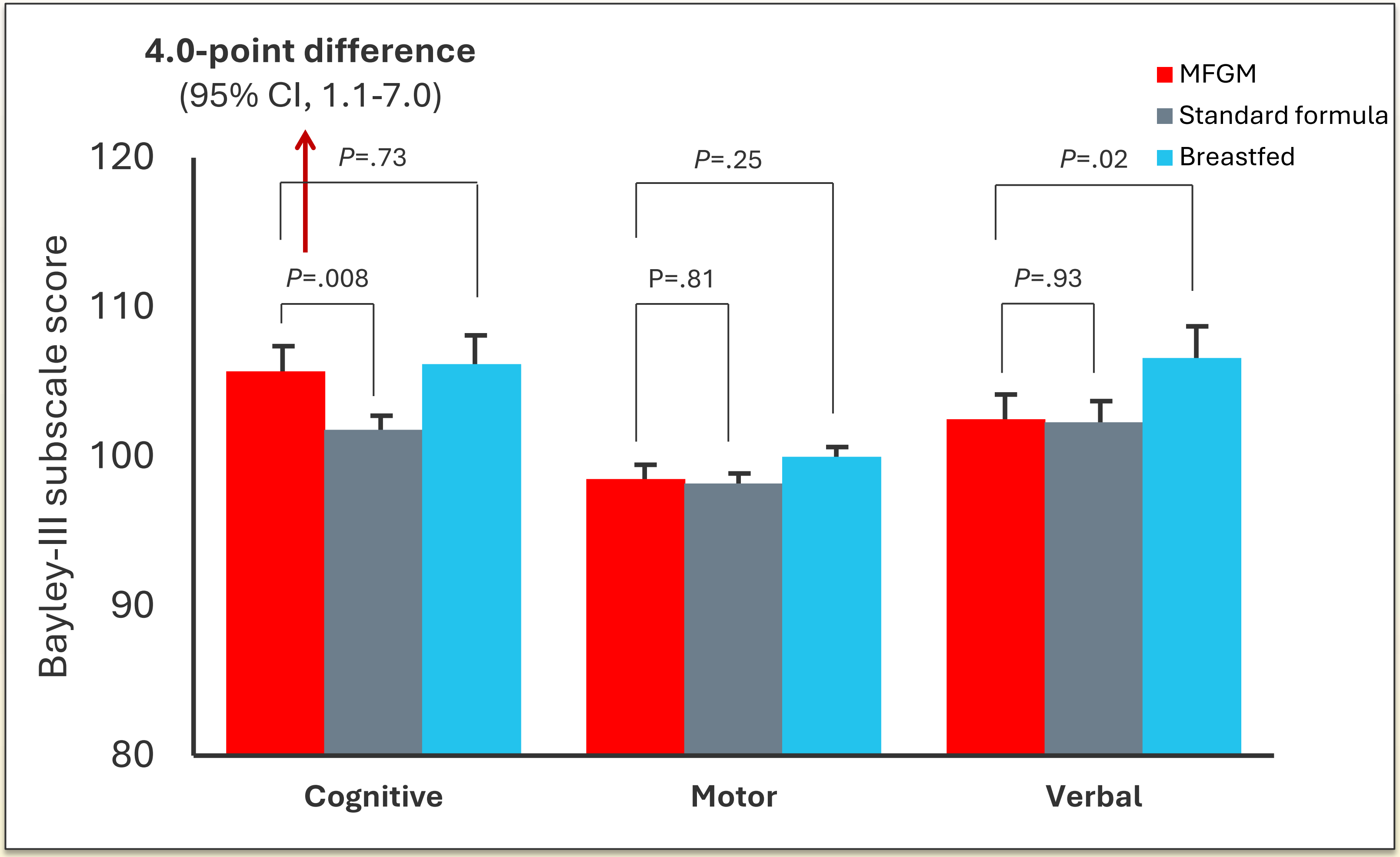



**1.** Meule A. *Front Psychol*. 2017;8:701. **2.** Holmboe K et al. *PLoS One*. 2021;16(12):e0260695.

# Supplemental MFGM & Neurodevelopmental Outcomes

## Effects of MFGM Supplementation

# Swedish MFGM Study: Neurodevelopment at 12 Months




- Randomized, controlled study
- 160 healthy formula-fed infants were randomized to receive:
  - Standard formula until 6 months of age (n = 68)
  - Standard formula supplemented with MFGM (4% wt:wt) until 6 months of age (n = 73)
- A breastfed reference group was also recruited from the same hospital (n = 72)



Timby N et al. Am J Clin Nutr. 2014;99:860-868.

# Studying the Benefits of MFGM Supplementation in Infant Formula: the Lighthouse MFGM Clinical Trial

- **Study design**
  - Prospective double-blind randomized controlled trial (RCT)
  - Enrolled **451 infants** who were randomized to 12 months of feeding with:
    - » Standard cow's milk-based formula (control)
    - » Standard cow's milk-based formula with added bovine MFGM (5 g/L) and lactoferrin (0.6 g/L) (MFGM+LF) (intervention)
- **Primary outcome:** difference in Bayley Scales of Infant Development, 3rd edition (Bayley-III) cognitive composite scores at 12 months
- **Secondary outcomes:** tolerability/safety, growth/anthropometrics, and other measures of development



Li F et al. *J Pediatr*. 2019;215:24-31.e8.

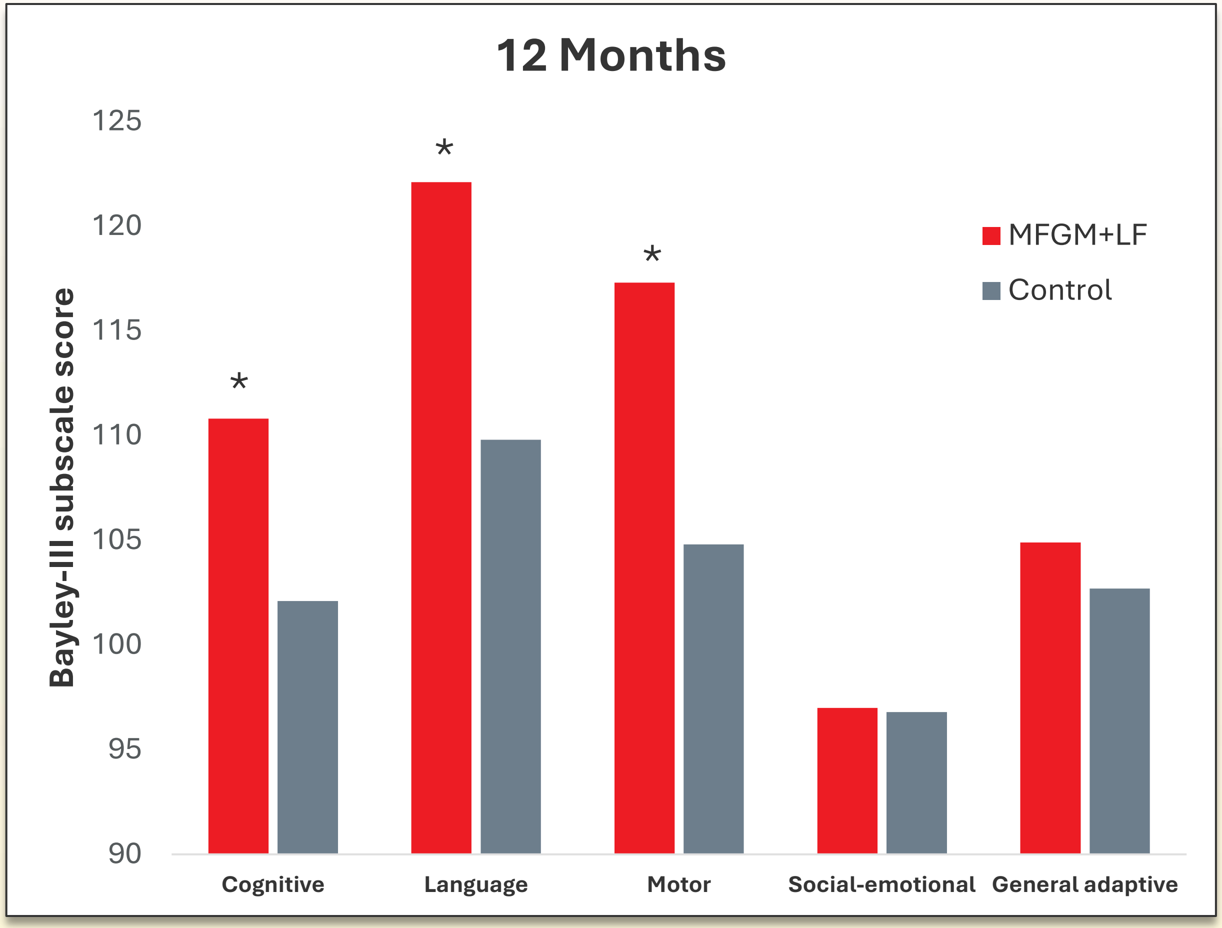
# The Lighthouse MFGM Clinical Trial: Ages and Stages Questionnaire Outcomes

**ASQ Domain Scores (Repeated Measures Analysis), Mean ± SE**

| Domains | Day 120 | | Day 180 | | Day 275 | | *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 | .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 | .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 | .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 | .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 | <.001 |

Li F et al. *J Pediatr*. 2019;215:24-31.e8.

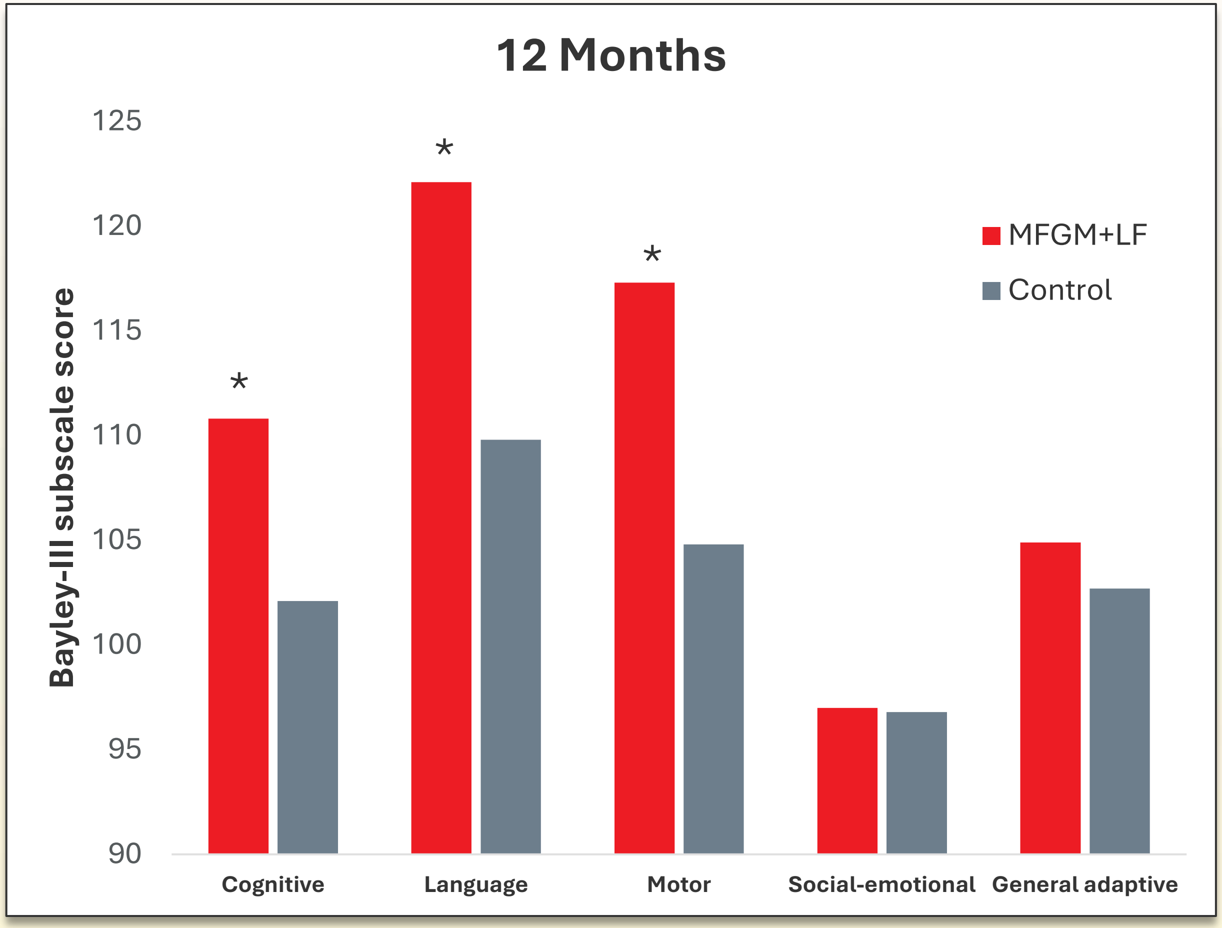
# The Lighthouse MFGM Clinical Trial: Bayley-III Outcomes at 12 Months

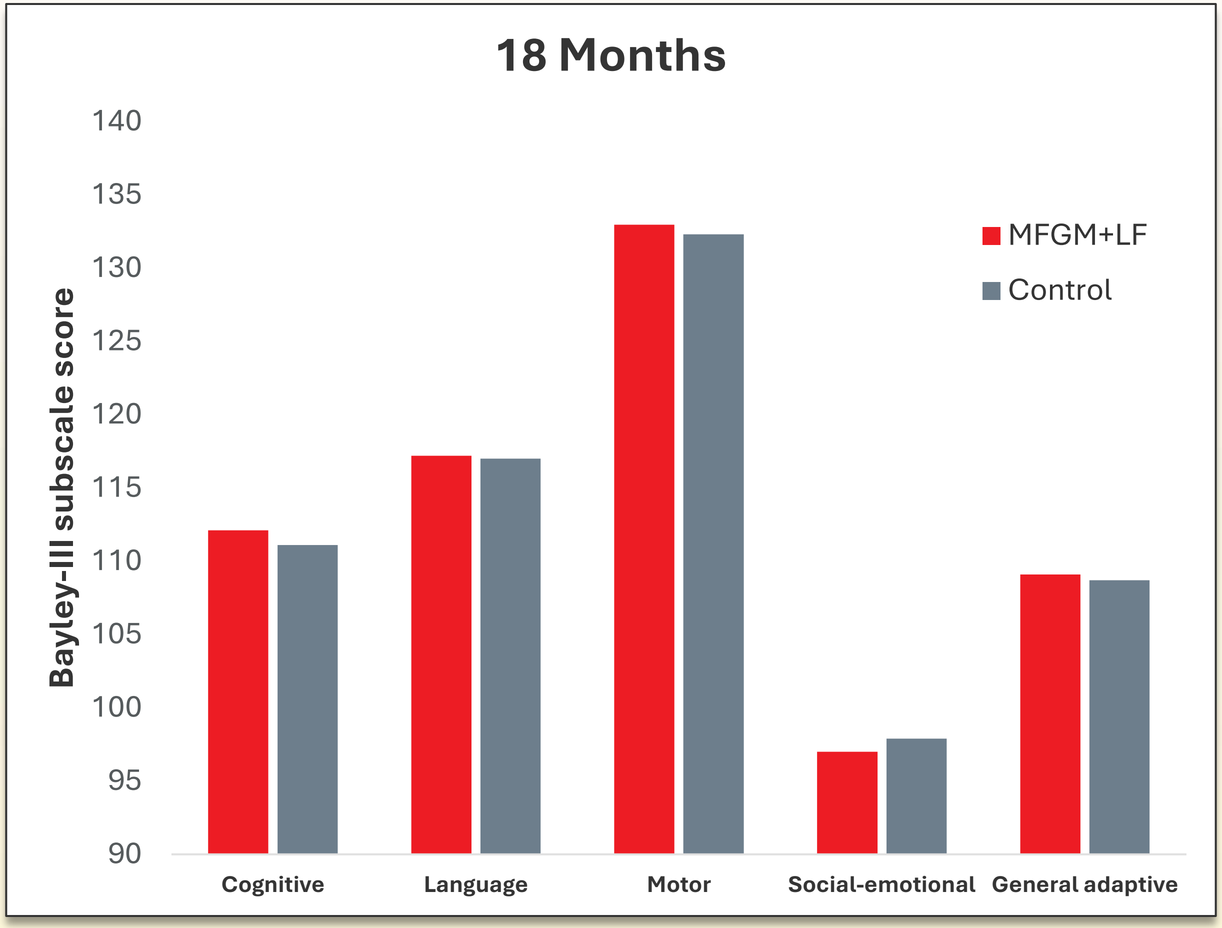



**P* <.001

Li F et al. *J Pediatr*. 2019;215:24-31.e8.

# The Lighthouse MFGM Clinical Trial: Bayley-III Outcomes at 18 Months




*$P$ <.001

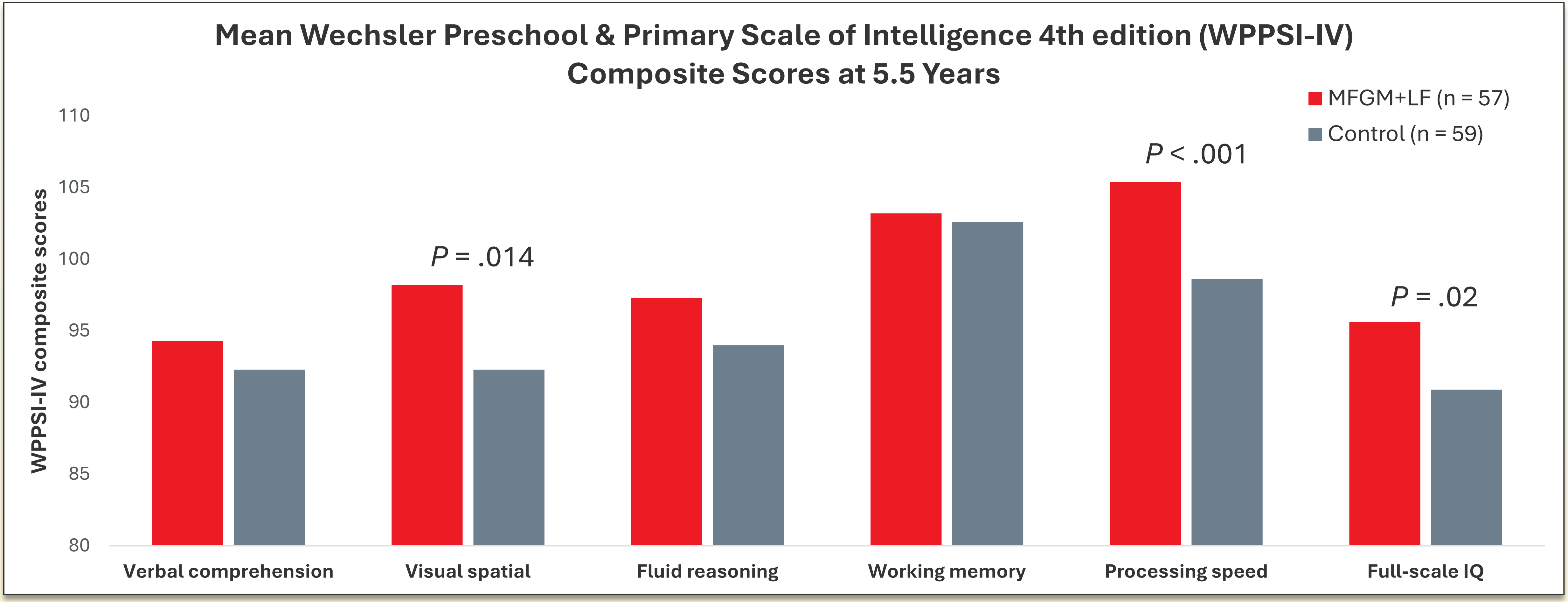
Li F et al. *J Pediatr*. 2019;215:24-31.e8.

# The Lighthouse MFGM Clinical Trial: Long-Term Follow-Up

- **Follow-up study design**
  - Enrolled trial participants who completed 12 months of the assigned study feeding who were 5.5 years (±2 months) at the time of follow-up testing
  - **116** of **292 participants** meeting eligibility criteria were enrolled
    - » No differences in demographic characteristics between those who did or did not participate in the follow-up study
- **Primary outcome measures**
  - WPPSI-IV Full-Scale IQ (a measure of overall intellectual ability)
  - 5 primary WPPSI-IV indices (measures of the domain-specific abilities of verbal comprehension, visual spatial, fluid reasoning, working memory, and processing speed)

Colombo J et al. *J Pediatr*. 2023;261:113483.

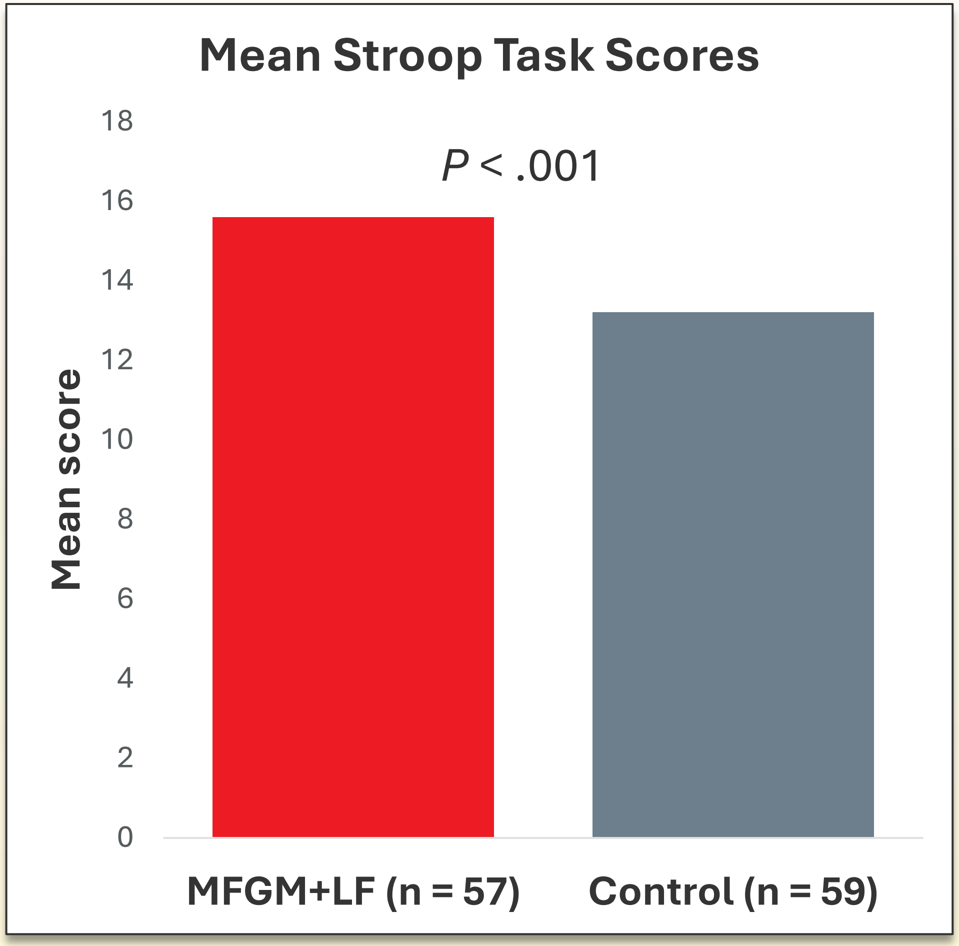
# The Lighthouse MFGM Clinical Trial Long-Term Follow-Up: Outcomes at 5.5 Years

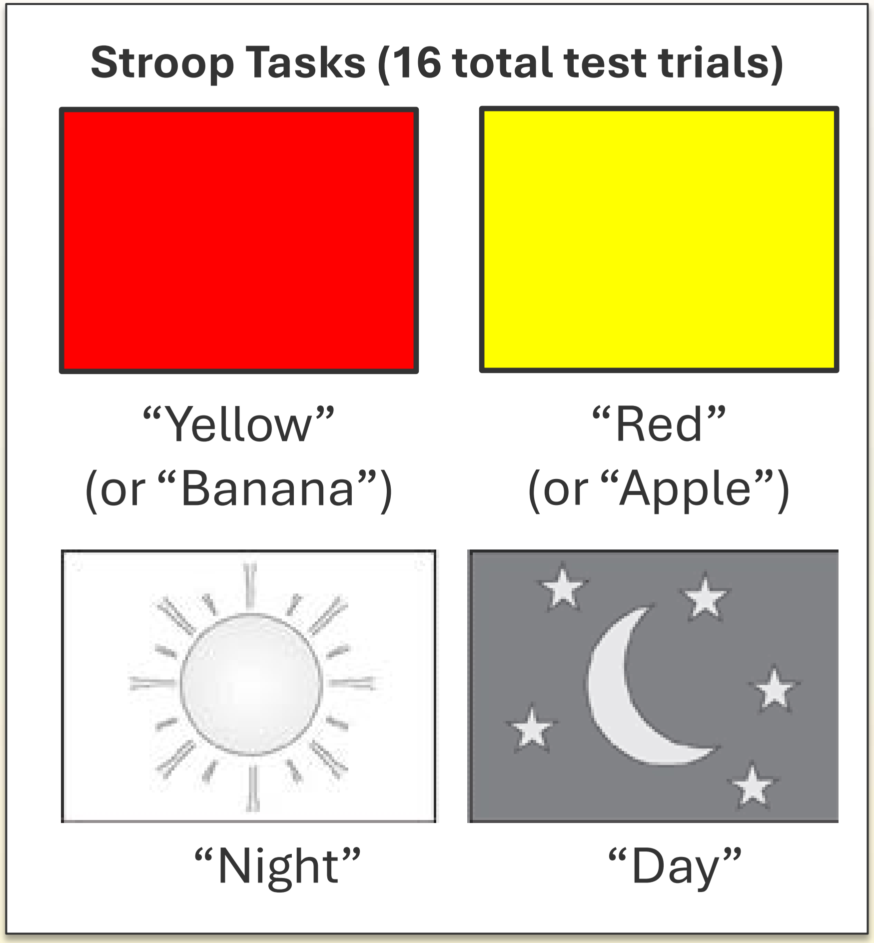





Colombo J et al. *J Pediatr*. 2023;261:113483.

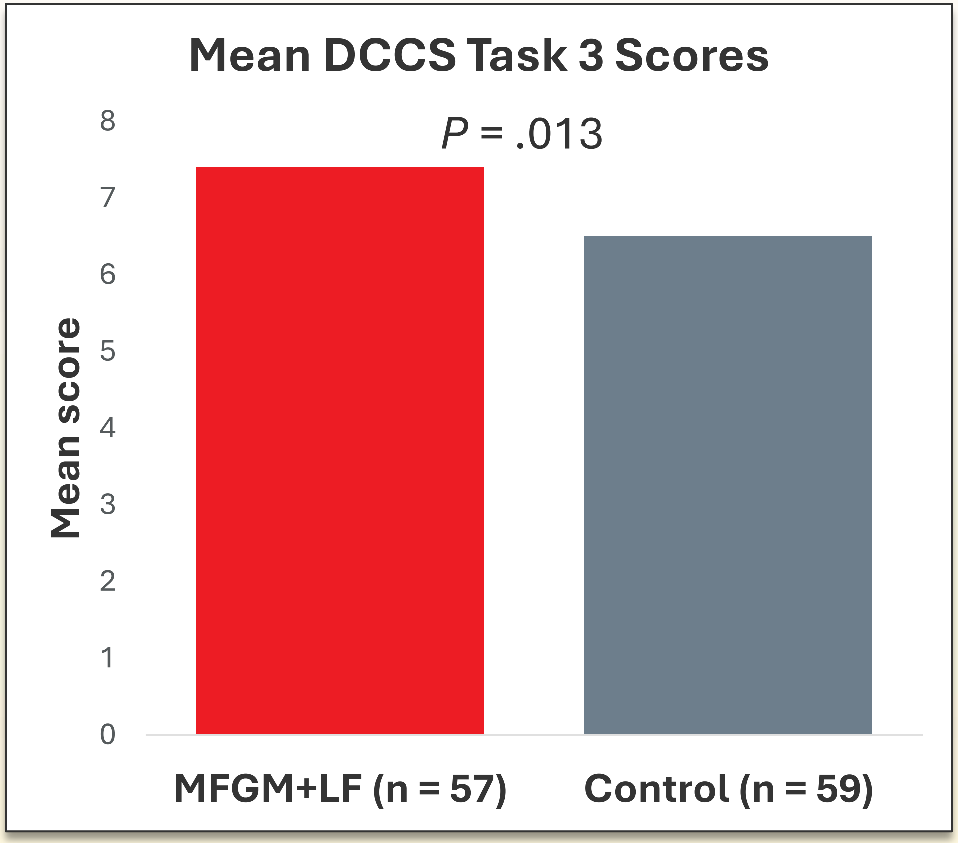
# The Lighthouse MFGM Clinical Trial Long-Term Follow-Up: Stroop Task at 5.5 Years

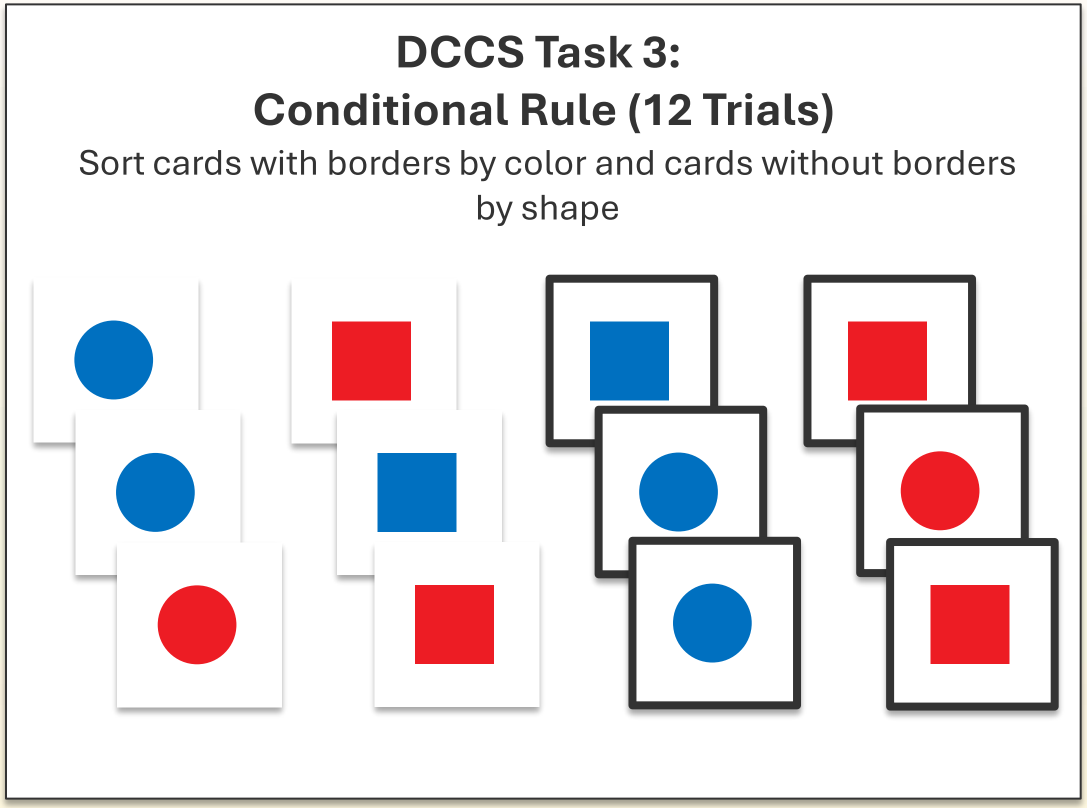



Colombo J et al. *J Pediatr*. 2023;261:113483.

# The Lighthouse MFGM Clinical Trial Long-Term Follow-Up: DCCS Task at 5.5 Years




**Note:** There were no between-group differences in the DCCS task 1 (simple rule) or task 2 (switch rule) scores.



Colombo J et al. *J Pediatr.* 2023;261:113483.

# Studying the Benefits of MFGM Supplementation in Infant Formula: the COGNIS Clinical Trial

- **Study design**
  - Prospective double-blind randomized controlled trial (RCT)
  - Enrolled **170 infants** who were randomized to 18 months of feeding with:
    - » Standard cow's milk-based formula (control)
    - » Standard cow's milk-based formula with added functional compounds, including MFGM, synbiotics, and LC-PUFAs (intervention)
- **Primary outcome:** difference in neurocognitive development measured by Bayley-III scores and other assessments at 4 and 6 years
- **Secondary outcomes:** tolerability/safety, growth/anthropometrics, infections, and other measures of development

Nieto-Ruiz A et al. *Nutrients*. 2020;12(2):535.

# COGNIS Clinical Trial: Neurocognitive Outcomes at 6 Years of Age

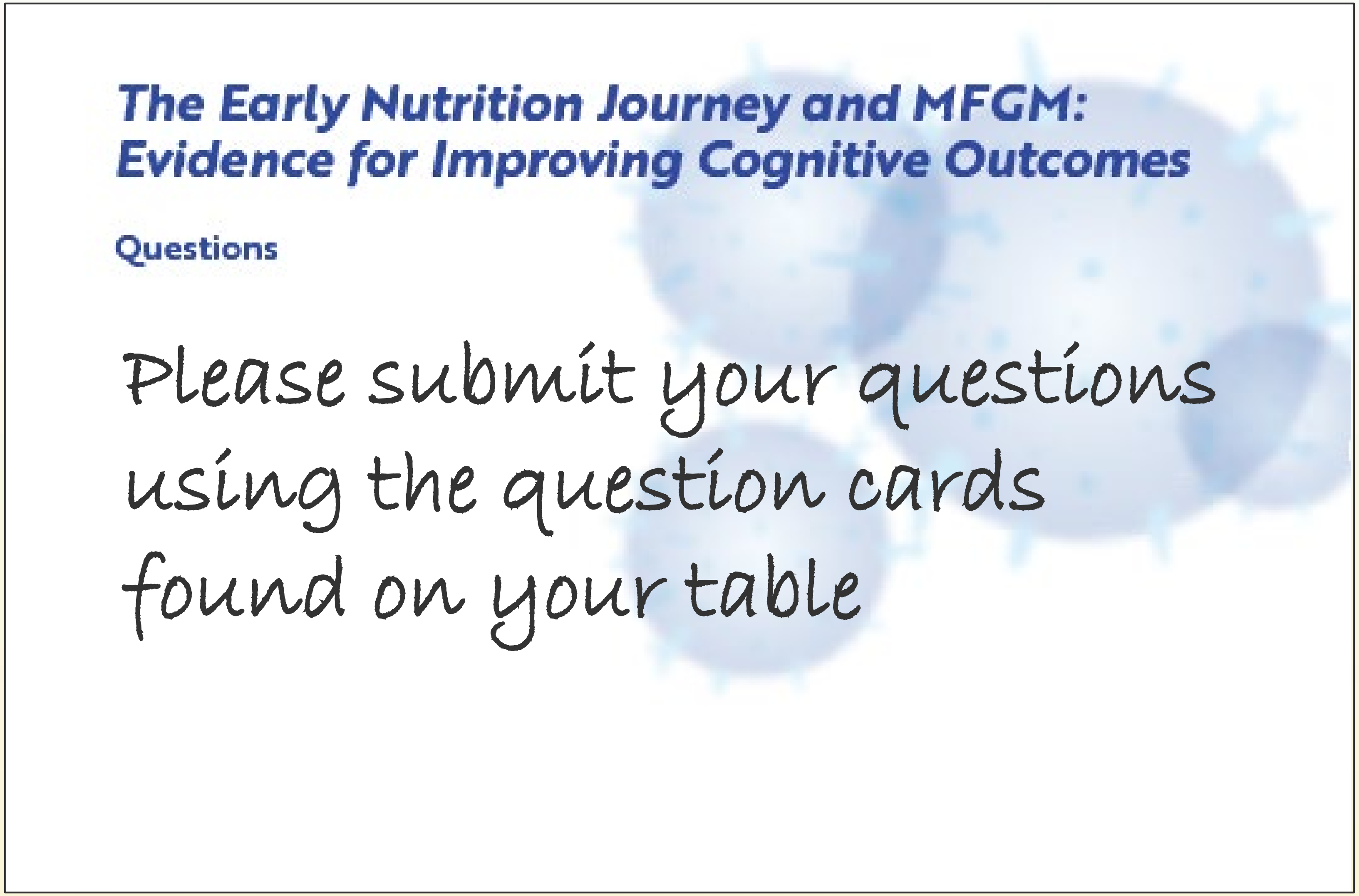
| K-BIT domain | Standard formula (n = 37) | Intervention formula (n = 39) | Breastfed reference (n = 32) | Adjusted *P* value (standard vs interventional formula) |
|---|---|---|---|---|
| **Vocabulary** | 107.91 ± 13.44 | 113.16 ± 13.31 | 103.73 ± 14.26 | .022 |
| **Matrices** | 111.51 ± 12.07 | 113.21 ± 12.00 | 111.78 ± 11.07 | .113 |
| **IQ** | 109.64 ± 11.67 | 113.46 ± 11.50 | 105.54 ± 12.40 | .031 |

Nieto-Ruiz A et al. *Front Nutr.* 2022;9:820224.

# Key Takeaways

- In randomized trials, MFGM supplementation in infant formula has been associated with improved short- and long-term cognitive outcomes, including:
  - Language
  - IQ
  - Executive function
- The effects of early nutrition persist well beyond the period of feeding and into early childhood
  - These nutrients may play a role in the programming of brain structure and function in infancy and early childhood

# Questions?


The Early Nutrition Journey and MFGM:
Evidence for Improving Cognitive Outcomes
Questions
Please submit your questions using the question cards found on your table

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# Thank you for joining us.