Human Milk Oligosaccharides and brain development: New Perspectives

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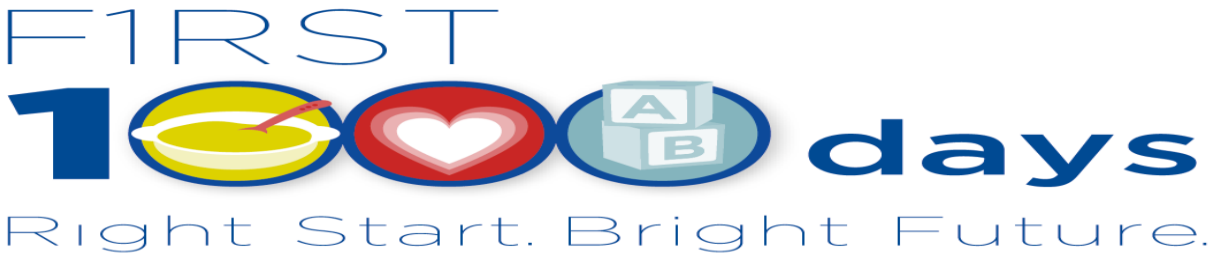
OUTLINE

- Importance of early life nutrition –the first 1000 days of life-till 5th year
- Overview of early brain development
- Human milk- the gold standard: Complexity of its composition and functionality
- Human Milk Oligosaccharides (HMOs) and functions
- Specific HMOs and brain development--HMO 2 fucosyl lactose (2'-FL)
- Key messages

Introduction

- **Adequate nutrition** is necessary for normal brain development.
- Nutrition is especially important during pregnancy and infancy, which are crucial periods for the formation of the brain,
- And lays the foundation for the development of cognitive, motor, and socio-emotional skills throughout childhood and adulthood.
- First 1000days-New NeuroScience



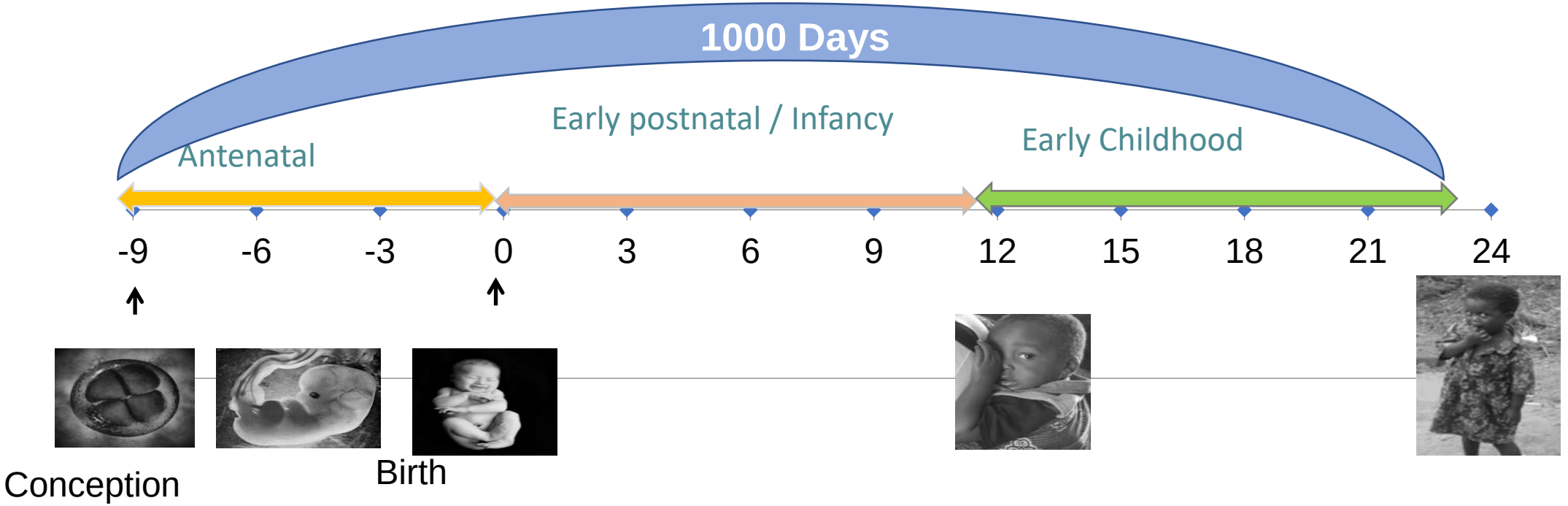
Nutrition from pregnancy-2years of life : a critical window of opportunity





The First 1000 Days "continuum"

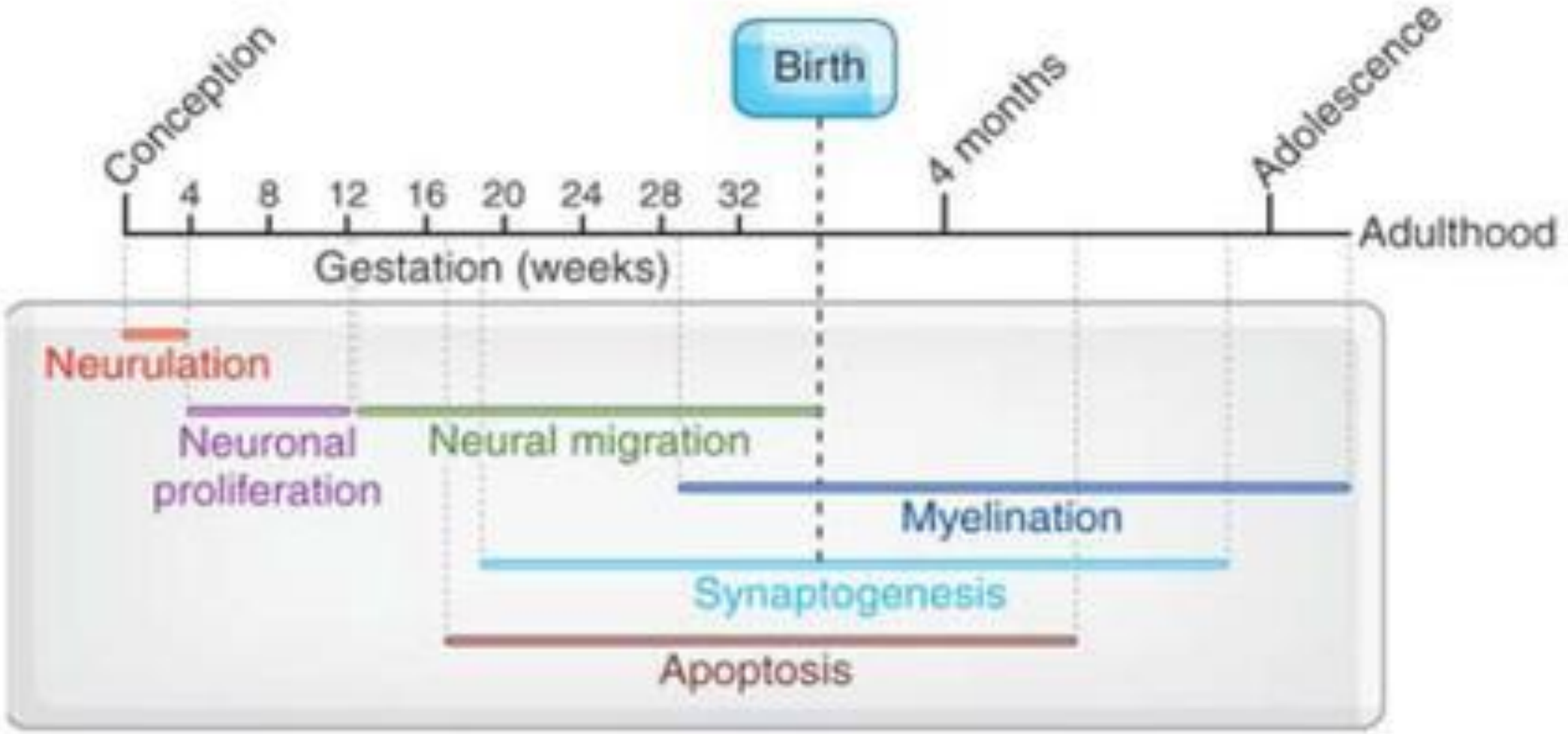
- 270 + 365 + 365 = 1000 ☺

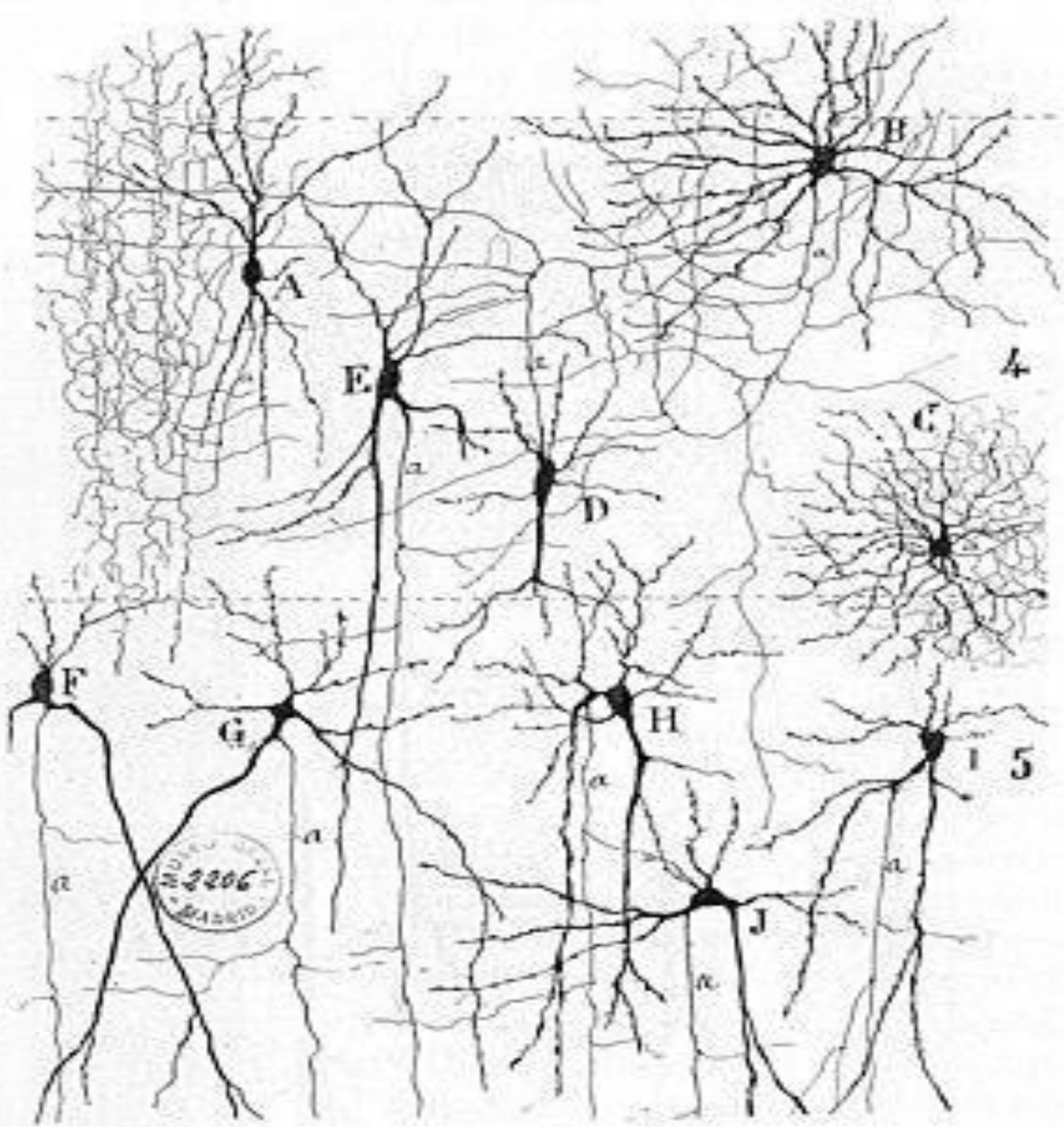


❑Nutrition during this period builds the foundation for a child's ability to grow, learn and thrive.

Acknowledgement: Linda Aldair

Stages of brain development

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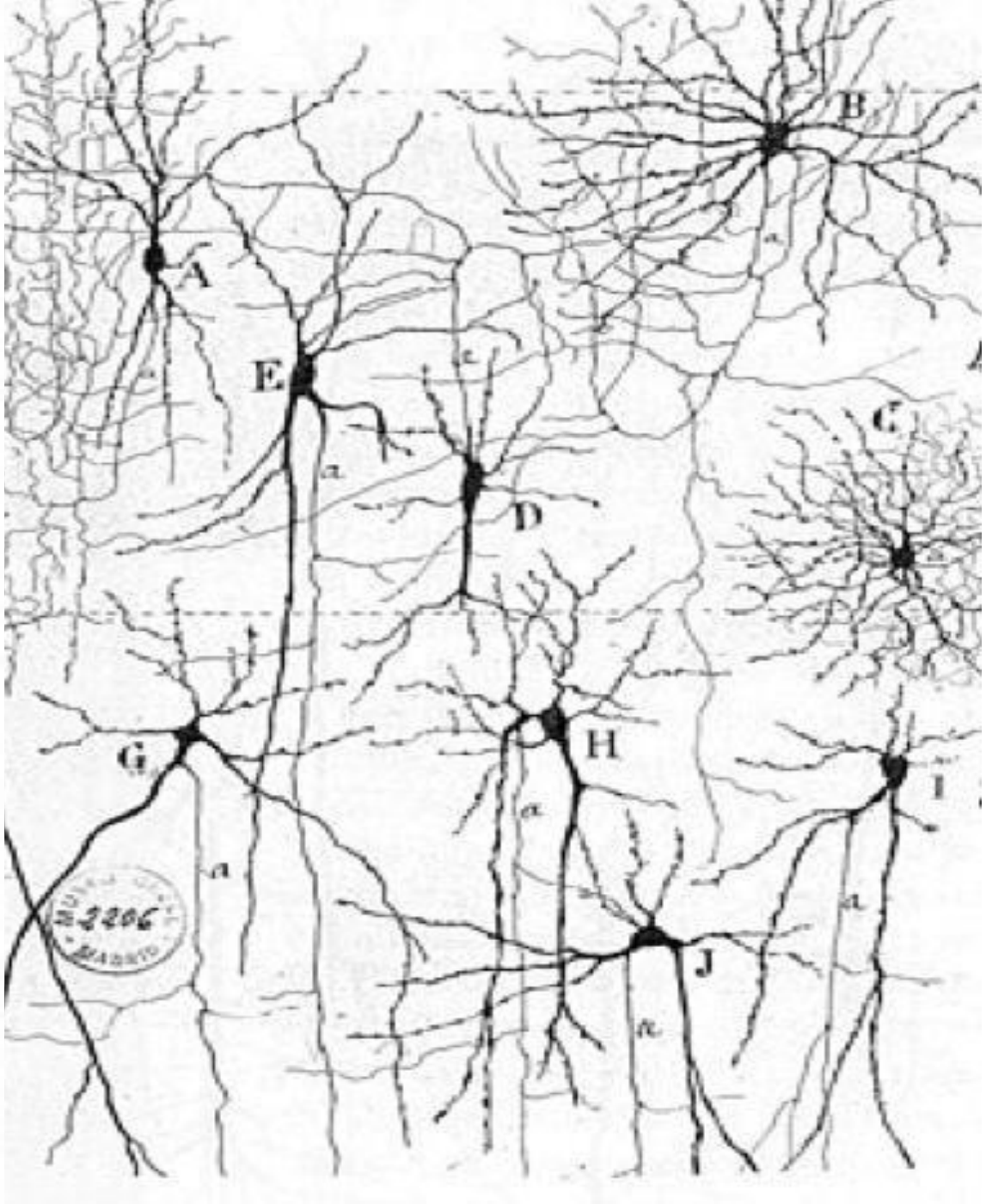
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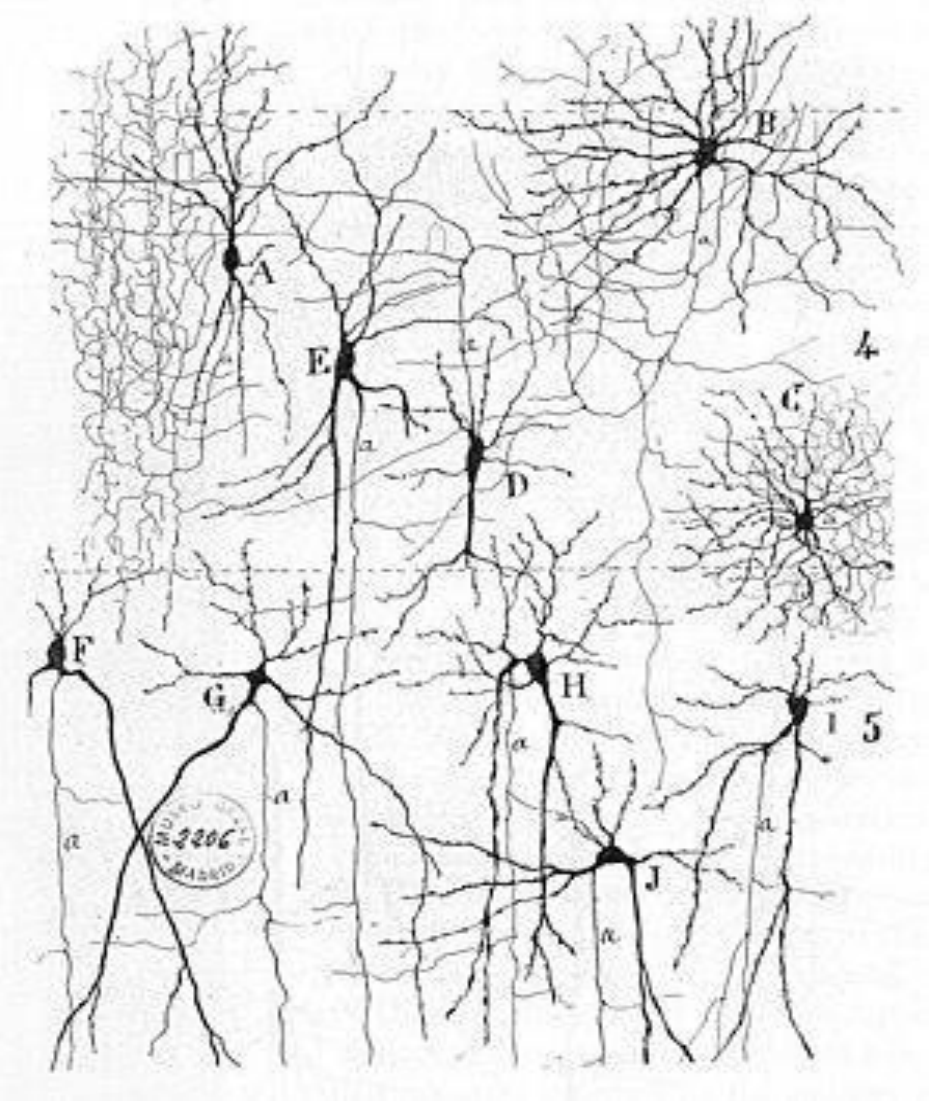
Synaptogenesis

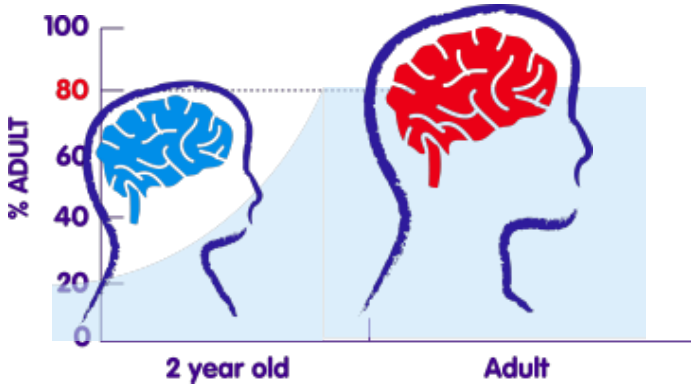
- To arrive at the more than 100 billion neurons that are the normal complement of a newborn baby at birth, the brain must grow at the rate of about 250,000 nerve cells per minute, on average, through out the course of pregnancy.
- A toddler's brain forms more than 1 million connections/synapses every second.
- Furthermore, the neural connections per neuron will increase from about 2,500 per neuron from birth to about 15,000 per neuron by age 2-3 years.
- **Brain size** increases by **4-fold** during the preschool period, reaching approximately 90% of adult volume by age 5-6



BRAIN

By 2 years the brain weighs between 1.04kg and 1.2kg and will have reached around 80% of its adult size of 1.2 to 1.5 kg

80% of brain size achieved around 2 years



Between 1 and 3 years of age, half of overall resting energy is consumed by the brain, compared with just 20% of adults.

Nutrition and stimulating interaction play a vital role in brain and cognitive development during the first years of life.

Change the First Five Years and You Change Everything"

Key factors influencing brain development

General

- Gene expression (nature)
- Environmental factors (nurture)
- → Molecular cues guide development and are dependent upon the experiences of the developing child

Environmental factors

- Socioeconomic status
- Social interactions and Urbanization
- Pollution
- Stress
- **Nutrition**

Kolb B, Gibb R. J Can Acad Adolesc Psychiatry. 2011;20: 265-76; 2. Hanson JL, et al. Plos One 2013;8:e80954; 3. WDR team 2018, using data from Nelson and others (2017). Available here: http://bit.do/WDR2018-Fig_S2-

Breastfeeding: ancient art through the ages and a modern miracle

- Human milk remains the gold standard in infant nutrition
- Breastmilk is present at birth, and is adequate in quantity and composition for the newborn
- It contains all the baby needs for optimal nutrition, growth and development
- Breastfeeding is the natural and best way of feeding an infant, and positively influences their development and health
- Breast milk provides the ideal balance of nutrients for the infant and contains countless bioactive ingredients such as immunoglobulins, hormones, oligosaccharides and others

Nutrition and brain development

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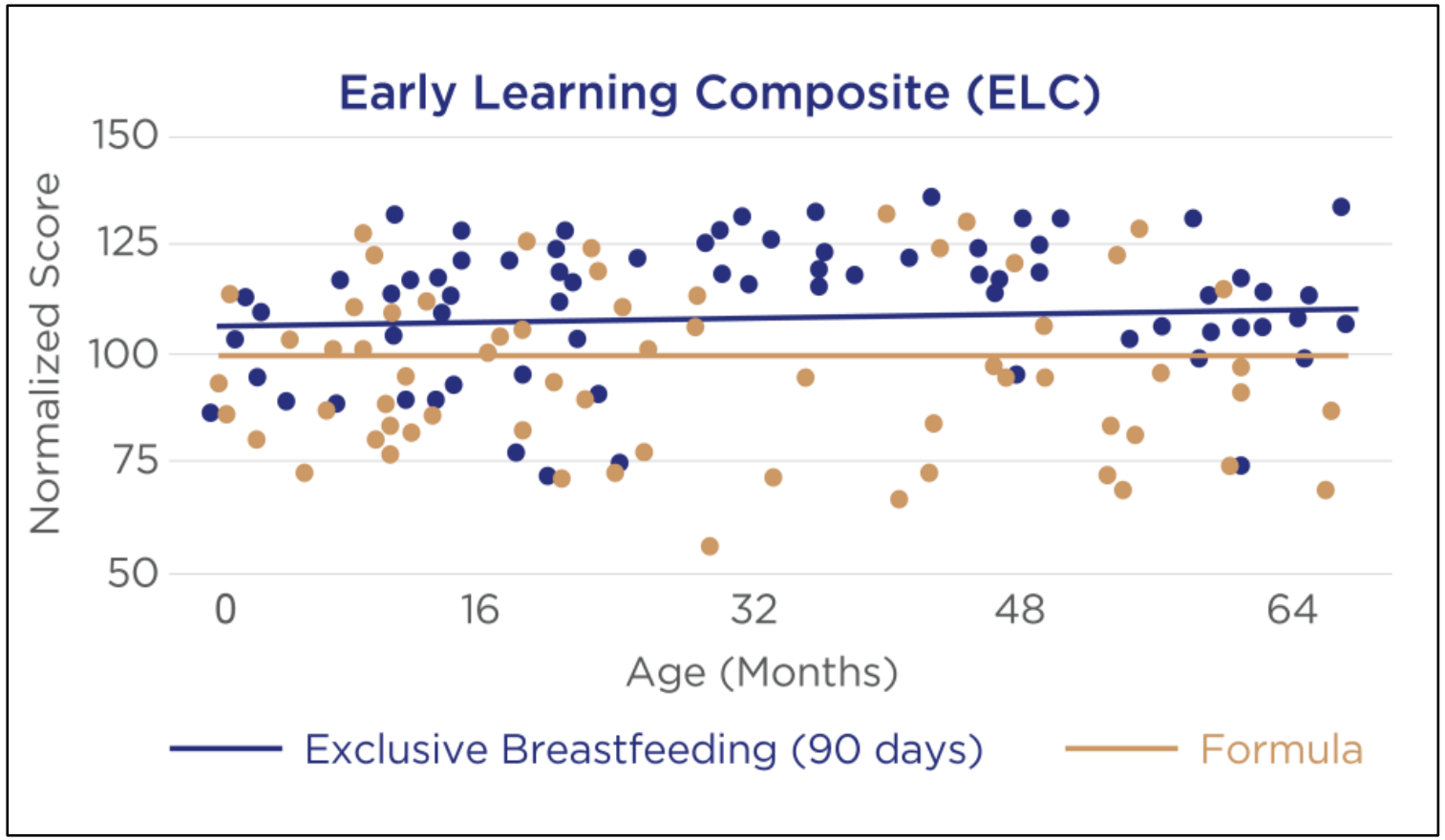
Neuroimage. 2018 September ; 178: 649–659. doi:10.1016/j.neuroimage.2017.12.056.

Early nutrition influences developmental myelination and cognition in infants and young children

Sean Deoni[a,*], **Douglas Dean III**[b], **Sarah Joelson**[a], **Jonathan O'Regan**[c], and **Nora Schneider**[d]

[a]Advanced Baby Imaging Lab, Memorial Hospital of Rhode Island, Pawtucket, RI, United States [b]University of Wisconsin-Madison, Waisman Centre, Madison, WI, United States [c]Nestle Development Centre, Askeaton Co, Limerick, Ireland [d]Nestle Research Centre, Nestec Ltd, Neurodevelopment & Cognition, Lausanne, Switzerland

Deoni et al. (2017): Early nutrition influences developmental myelination and cognition in infants and young children



J Pediatr. 2016 October ; 177: 133–139.e1. doi:10.1016/j.jpeds.2016.06.045.

Breast milk feeding, brain development, and neurocognitive outcomes: a 7-year longitudinal study in infants born <30 weeks' gestation

Mandy B. Belfort, MD, MPH[1], **Peter J. Anderson, PhD**[2,3], **Victoria A. Nowak, MBBS**[4], **Katherine J. Lee, PhD**[2,3], **Charlotte Molesworth, MBiostat**[2,3], **Deanne K. Thompson, PhD**[2,3,6], **Lex W. Doyle, MD**[2,3,6], and **Terrie E. Inder, MBChB, MD**[1]

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Objectives

- To determine the associations of breast milk intake after birth with neurological outcomes at term equivalent and 7 years of age in very preterm infants

Study design

- 180 infants born <30 weeks' gestation or <1250 grams birth weight
- calculated the number of days on which infants received >50% of enteral intake as breast milk from 0–28 days of life.
- Outcomes included brain volumes measured by magnetic resonance imaging at term equivalent and 7 years of age, and cognitive (IQ, reading, mathematics, attention, working memory, language, visual perception) and motor testing at years.

Results

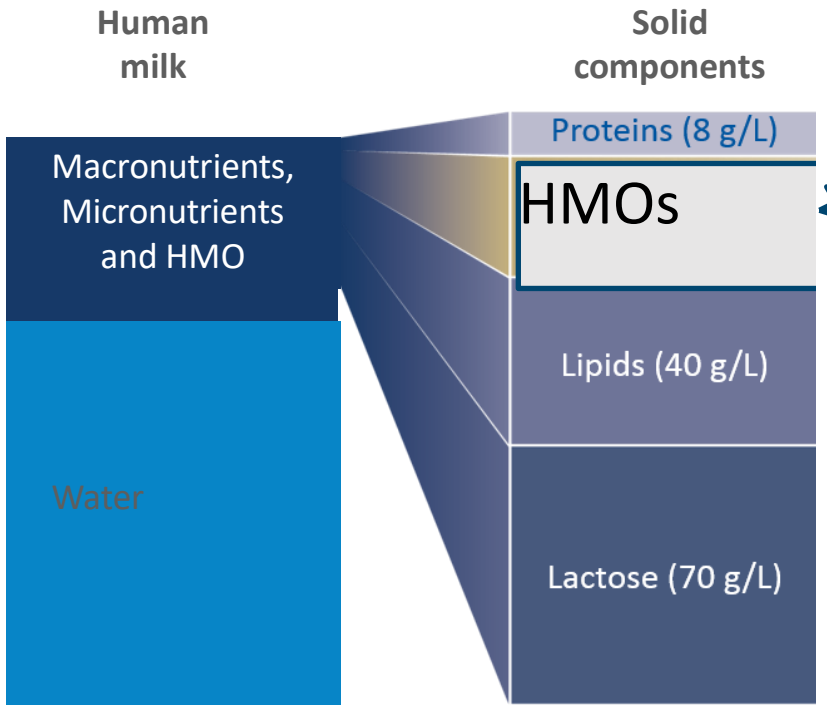
- Predominant breast milk feeding in the first 28 days of life was associated with larger deep nuclear gray matter volume at term equivalent age and better IQ, academic achievement, working memory, and motor function at 7 years of age in very preterm infants.

HUMAN MILK OLIGOSACCHARIDES (HMOs)

HMOs IN BREAST MILK

- Human milk is the perfect food for infants; Contains countless bioactive ingredients such as immunoglobulins, hormones, oligosaccharides and other components
- One important component is human milk oligosaccharides (HMOs), which are multifunctional glycans, naturally present in human milk. They are particularly interesting because of their quantity and structural diversity .
- Studies have shown that the amount of HMO in breast milk can be different between women and also during different stages of lactation . The highest concentration of HMO occurs in colostrum and amounts to 20–25 g/L, and then falls in mature milk to 5–15 g/L .
- The milk of mothers who have given birth to premature babies has higher HMO concentrations than the milk of mothers who gave birth at term
- Dominant HMO in 80% of mothers is 2’- fucosyl-lactose (2FL)

HMOs are the third largest solid component of breast milk

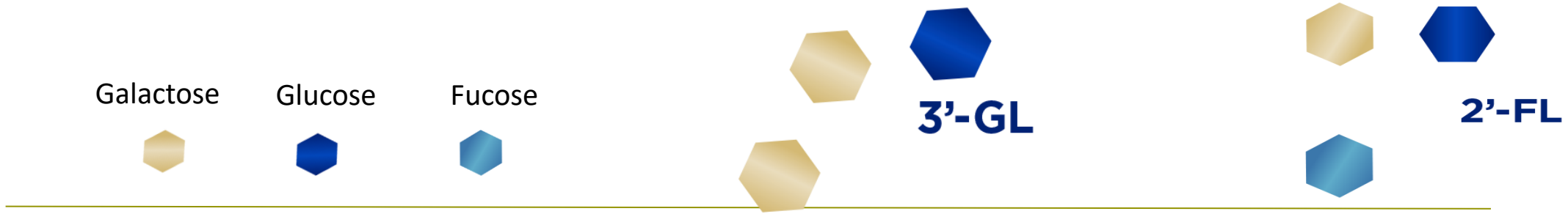


HMO levels range between: 20 - 25 g/L for colostrum and 5 and 15 g/L for mature milk[1,2]

The HMO fraction is larger than that of proteins and can therefore be considered a key component of human breast milk.[1,2]

SEVERAL DIFFERENT OLIGOSACCHARIDES IDENTIFIED

- HMOs are made of five basic monosaccharides: glucose (Glc), galactose (Gal), N-ethylglucosamine (GlcNAc), fucose (Fuc) and sialic acid (SA).
- Over **200** different structures have been identified, both short chain and long chain and it is estimated that there are over **1000**
- Only 1 to 2% of HMOs can be absorbed in the intestine, 98-99% remain intact up to the colon, **thus influencing the composition and activity of the infant's gut microbiota**.
- For example, 3'-Galactosyllactose (**3'-GL**) and 2'-Fucosyllactose (**2'FL**) are breastmilk oligosaccharides

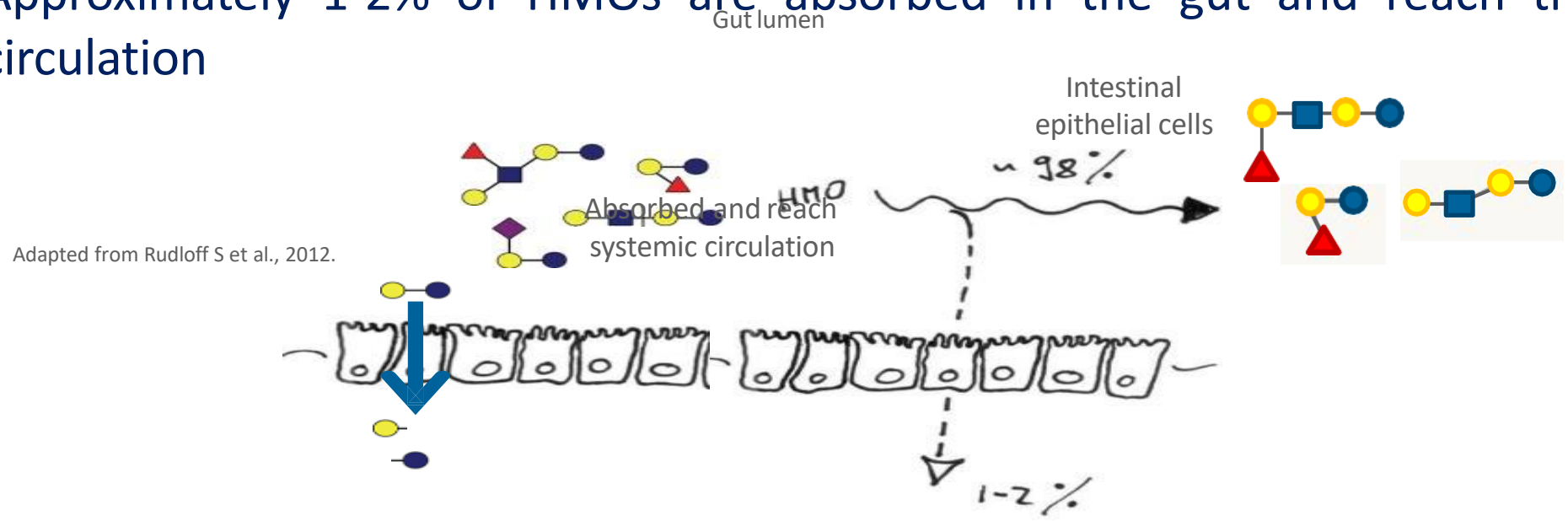


1. Urashima, Tadasu, et al. *Trends in Glycoscience and Glycotechnology* 30.172 (2018): SE51-SE65. **2.** Oozeer, Raish, et al. *The American journal of clinical nutrition* 98.2 (2013): 561S-571S **3**. Jantscher-Krenn, E., and L. Bode. *Minerva Pediatr* 64.1 (2012): 83-99. 4. Newburg, et al. *The Journal of nutrition* 146.2 (2015): 358-367. 5. Yu, Zhuo-Teng, N. Nanda Nanthakumar, and David S. Newburg The Journal of nutrition 146.10 (2016): 1980-1990. 6. Rudloff, Silvia, and Clemens Kunz. "Milk oligosaccharides and metabolism in infants." Advances in nutrition 3.3 (2012): 398S-405S.

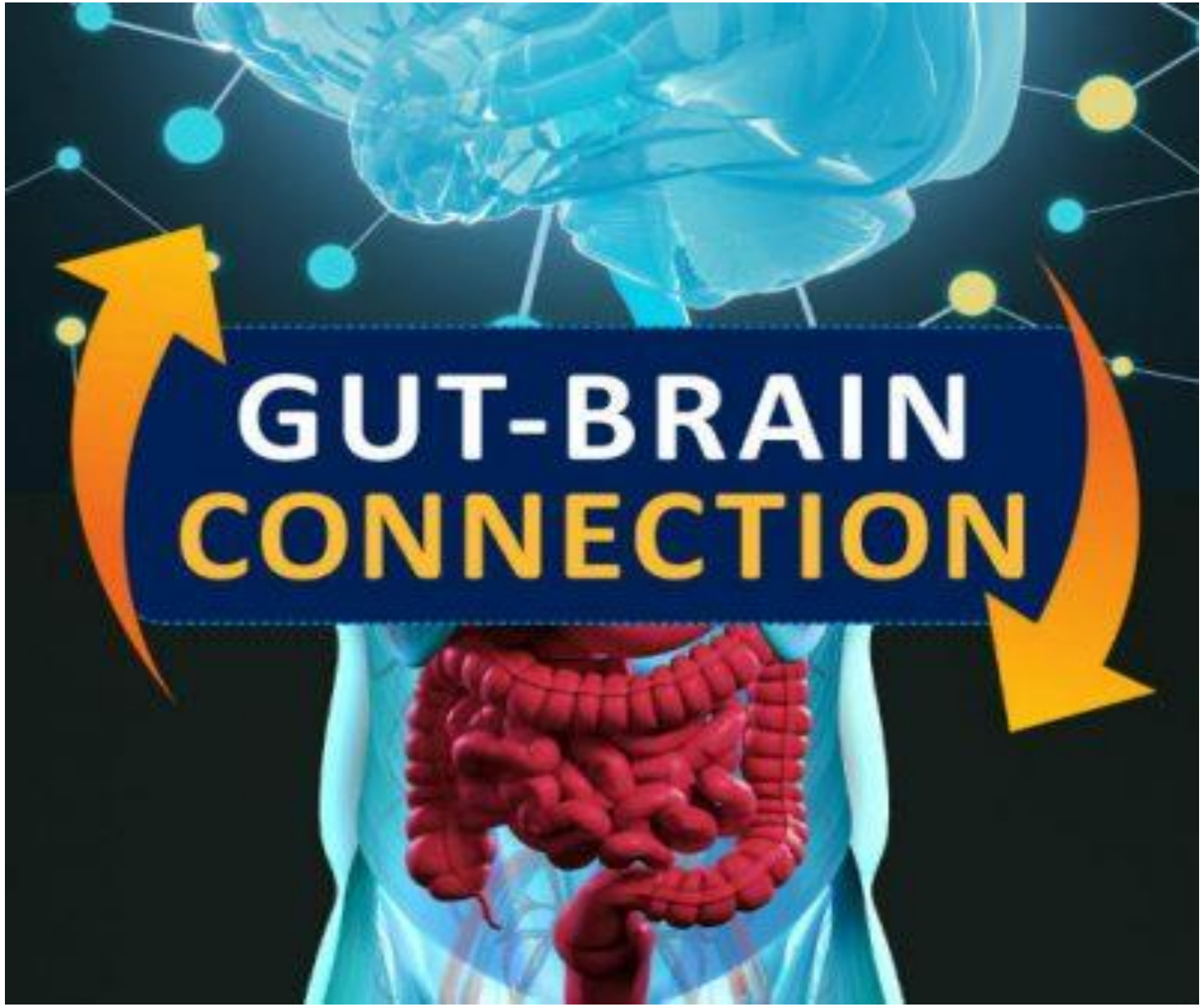
METABOLISM OF HMOS

- An infant's gut cannot digest HMOs because of lack of production of the necessary enzymes and reach the lower gut unchanged.
- They are prebiotics ie substances that the body cannot digest but act as food for the beneficial bacteria **(probiotic**) in the gut and encourage their growth especially Bifidobacteria—(fertilizer effect)

- Approximately 1-2% of HMOs are absorbed in the gut and reach the systemic circulation



Adapted from Rudloff S et al., 2012.

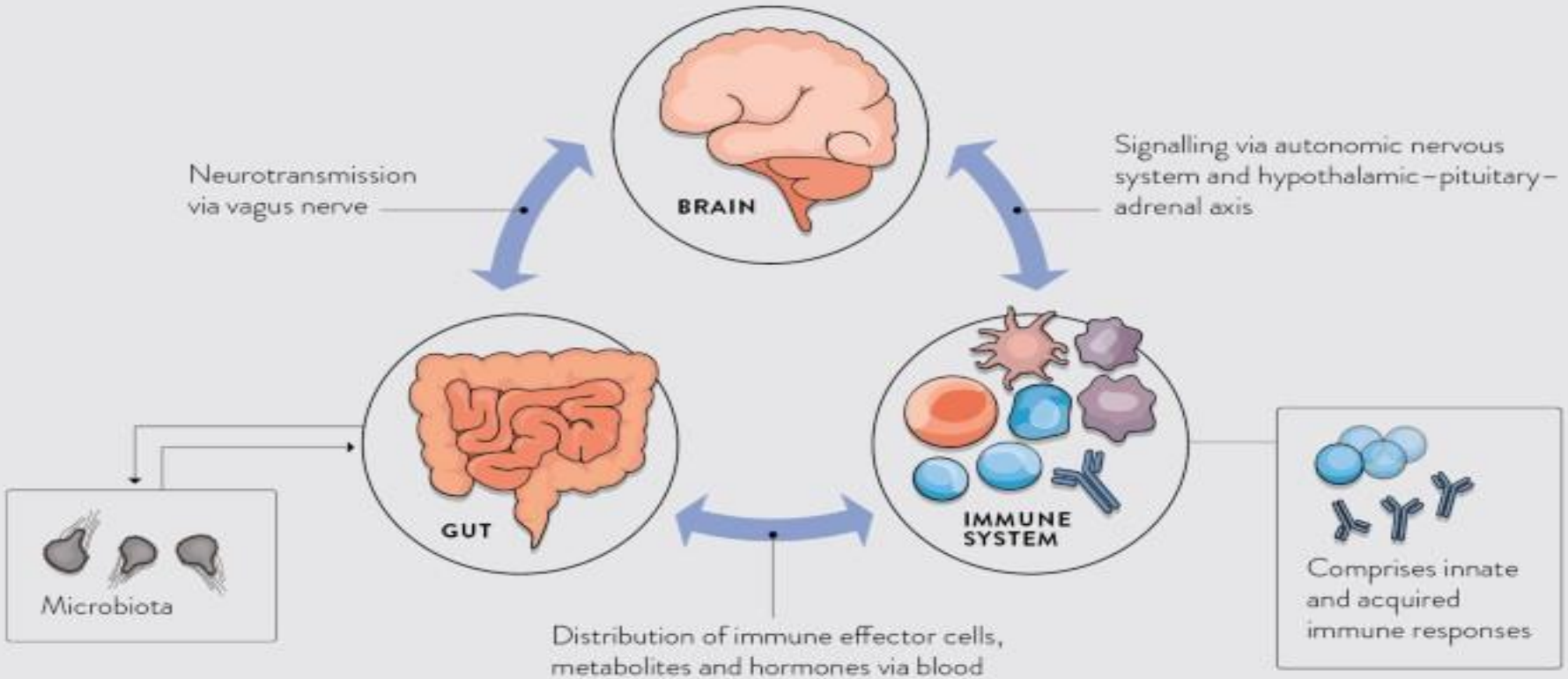

GUT-BRAIN
CONNECTION

HUMAN MILK OLIGOSACCHARIDES

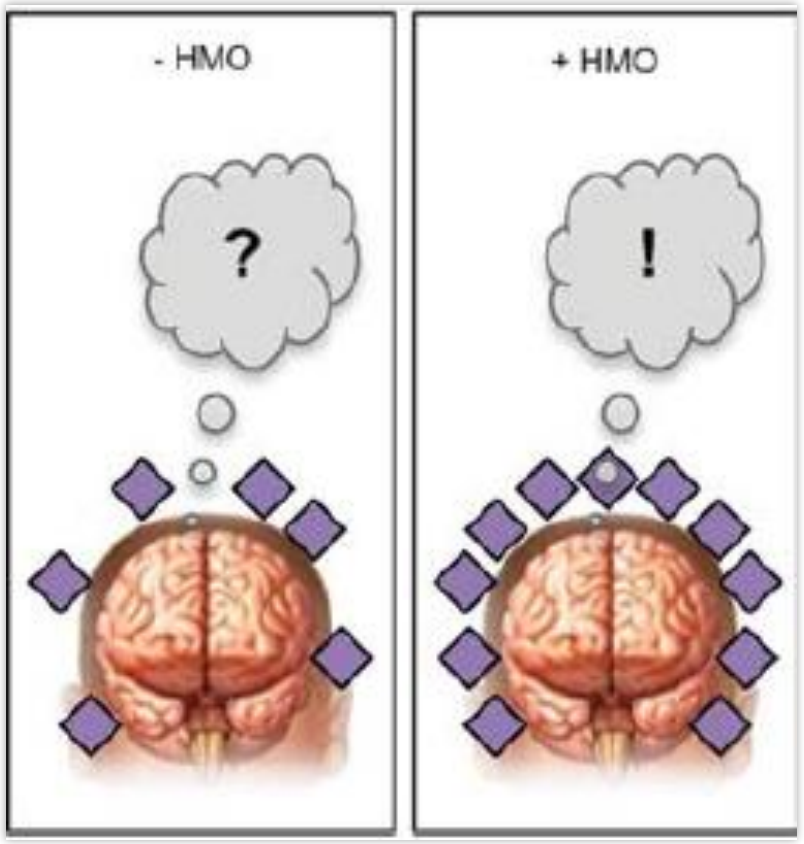
SUPPORTING HEALTHY DEVELOPMENT

GUT–BRAIN–IMMUNE AXIS

The gut contains millions of neurons and comprises more than 70% of the body's immune system.



FUNCTIONS OF HMOs



HMOs* provide fucose and sialic acid as a potentially essential nutrient for brain and cognitive development
Adapted from Bode L. 2012[2]

Nutrients for the brain[1,2] ***(source of fucose and sialic acid)***

- **Brain development**
- **Cognitive development**

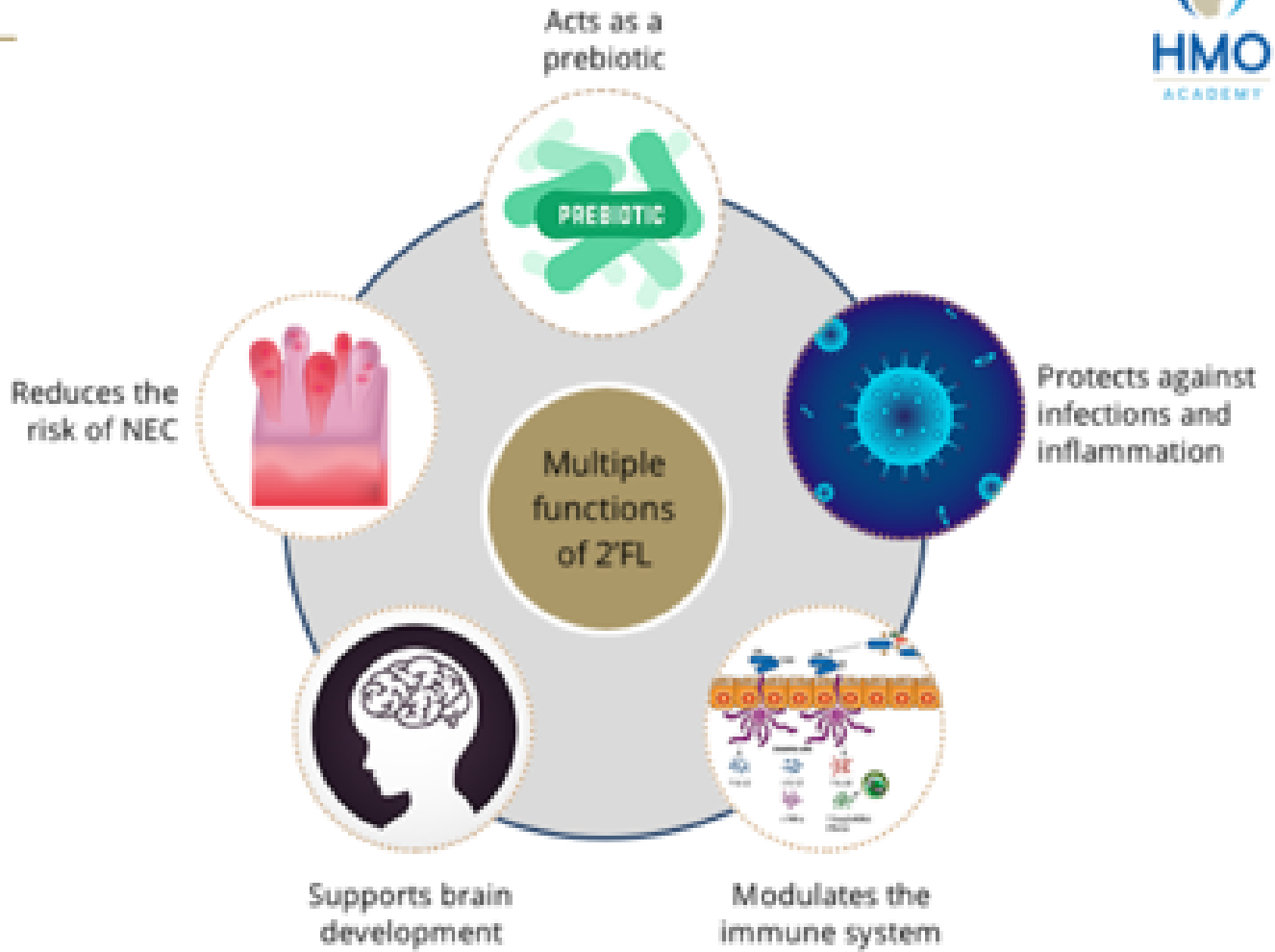
*HMO: Human milk oligosaccharides

1. Jantscher-Krenn, E., and L. Bode. "Human milk oligosaccharides and their potential benefits for the breast-fed neonate." Minerva Pediatr 64.1 (2012): 83-99.
2. Bode, Lars. "Human milk oligosaccharides: every baby needs a sugar mama." *Glycobiology* 22.9 (2012): 1147-1162.

Role of specific HMOs to support brain development—2’Fucosyl lactose (2’-FL)

Background

- 2'FL is the most abundant and most studied HMO
- Higher levels of 2'FL in breast milk were associated with lower rates of *Campylobacter* diarrhoea
- Preclinical studies suggest that 2'FL has multiple functions
- Synthesised 2'FL is structurally identical to that of human milk and is currently added in some infant formulae
- The use of 2'FL in infant formulae has been approved as safe by the European Union and the US-FDA



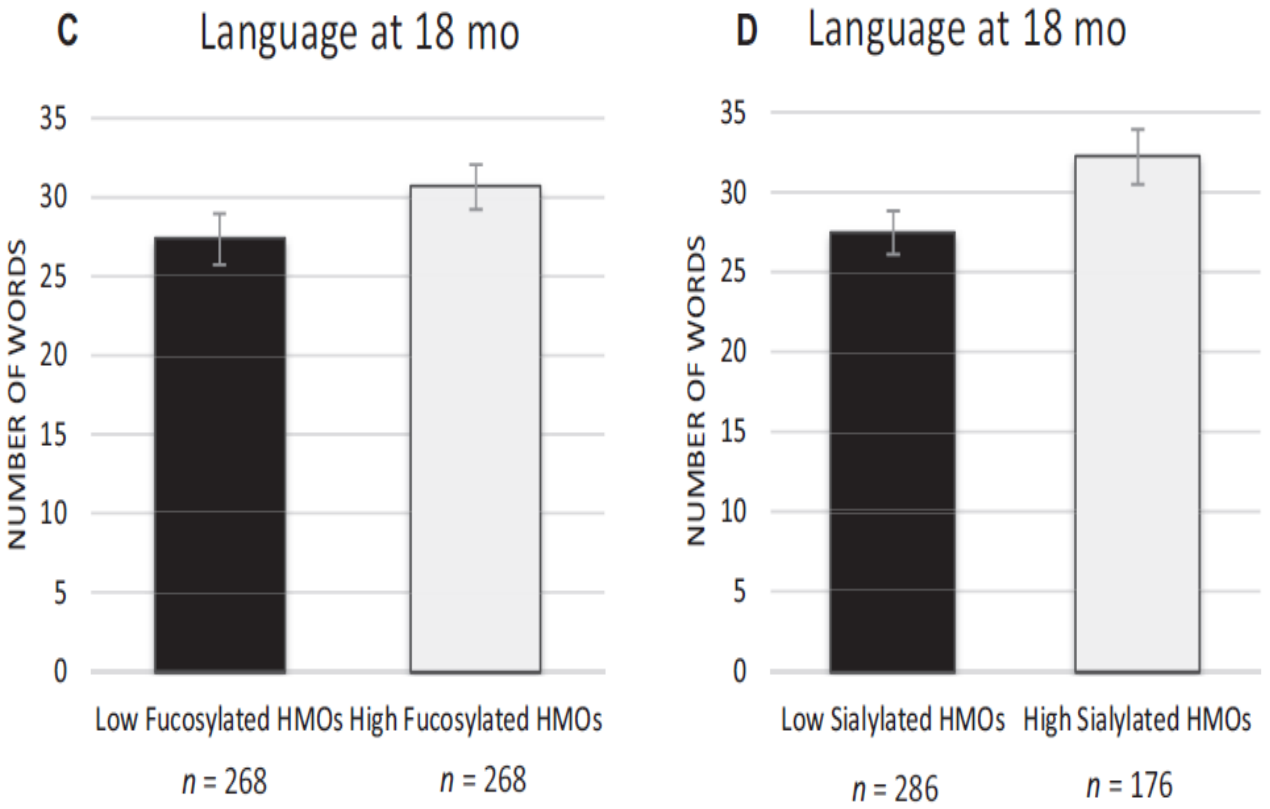
2'FL, 2'-fucosyllactose; FDA, Food and Drug Administration; GRAS, Generally Recognized as Safe; HMO, human milk oligosaccharide; NEC, necrotising enterocolitis.

Sialyllated and fucosylated HMOs are both associated with language development

Associations of human milk oligosaccharides and bioactive proteins with infant growth and development among Malawian mother-infant dyads

Josh M Jorgensen,[1] Rebecca Young,[1] Per Ashorn,[2,3] Ulla Ashorn,[2] David Chaima,[4] Jasmine CC Davis,[5] Elisha Goonatilleke,[5] Chiza Kumwenda,[4,6] Carlito B Lebrilla,[5,7] Kenneth Maleta,[4] Elizabeth L Prado,[1] John Sadalaki,[4] Sarah M Totten,[5] Lauren D Wu,[5] Angela M Zivkovic,[1,8] and Kathryn G Dewey[1]

- Malawian mother-infant pairs (N = 869)
- Breast milk HMO content at 6 months of age
- A checklist based on the MacArthur– Bates Communicative Development Inventory used for language evaluation



RESEARCH ARTICLE

Human milk oligosaccharide 2′-fucosyllactose links feedings at 1 month to cognitive development at 24 months in infants of normal and overweight mothers

Paige K. Berger[1], Jasmine F. Plows[1], Roshonda B. Jones[1], Tanya L. Alderete[2], Chloe Yonemitsu[3], Marie Poulsen[4], Ji Hoon Ryoo[1], Bradley S. Peterson[1], Lars Bode[3], Michael I. Goran[1]*

Objective

To determine the impact of 2'FL from breast milk feeding on infant cognitive development at 24 months of age relative to maternal obesity and breast milk feeding frequency.

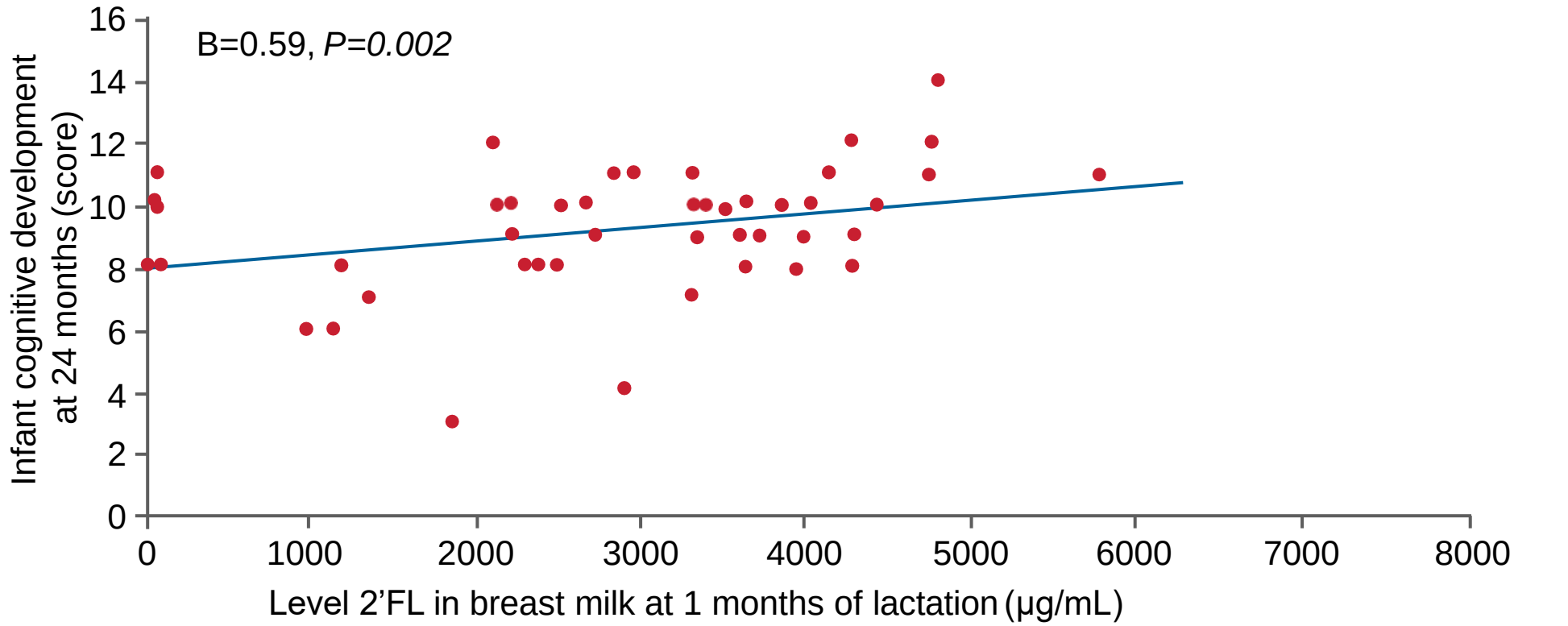
Methods and materials

- Hispanic mother-infant pairs (N = 50) were recruited across the spectrum of pre-pregnancy BMI
- Breast milk was collected at 1 and 6 months, and feedings/day were reported
- Nineteen HMOs were analyzed using high-performance liquid chromatography, with initial interest in 2'FL
- Infant cognitive development score was assessed with the Bayley-III Scale at 24 months.

Results

- Maternal pre-pregnancy BMI was not related to feedings/day or HMOs, but predicted
- poorer infant cognitive development (P = 0.03).
- Feedings/day (β = 0.34) and 2'FL at 1 month predicted better infant cognitive development (both P. 0.01).
- The association of feedings/day with infant cognitive development was no longer significant after further adjustment for 2'FL (estimated mediation effect = 0.13, P= 0.04).
- There were no associations of feedings/day and 2'FL at 6 months with infant cognitive development.

2'FL in breast milk at 1 month is associated with better infant cognitive development at 24 months of age



Adapted from Berger, et al. 2020.

SL, sialyllactose.

KEY MESSAGES

- Nutrition is crucial for brain development especially in the first 1000days of birth up till the first 5 years
- Effective development of the brain requires *optimal nutrition* from conception. At birth newborn brain has 100 billion neurons.
- Human milk is the gold standard nutrition for infants, supporting the development of a healthy immune system and brain development.
- Human milk oligosaccharides are the 3rd largest component of breast milk and are significant for the development of the gut-brain-immune axis.
- HMOs –have prebiotic, anti-inflammatory, anti –adhesive, immune-modulation and serve as nutrients for the brain for brain development, neuronal transmission and synaptogenesis.
- 2FL HMO is the most abundant HMO in human milk seen in 80% of mothers. New concepts have shown that in addition to promoting growth of bifidobacteria, it improves brain development, language and infant cognitive development.

It is easier to **build strong children** than to **repair broken men**.

Frederick Douglass