The Role of Nutrition in Brain Development

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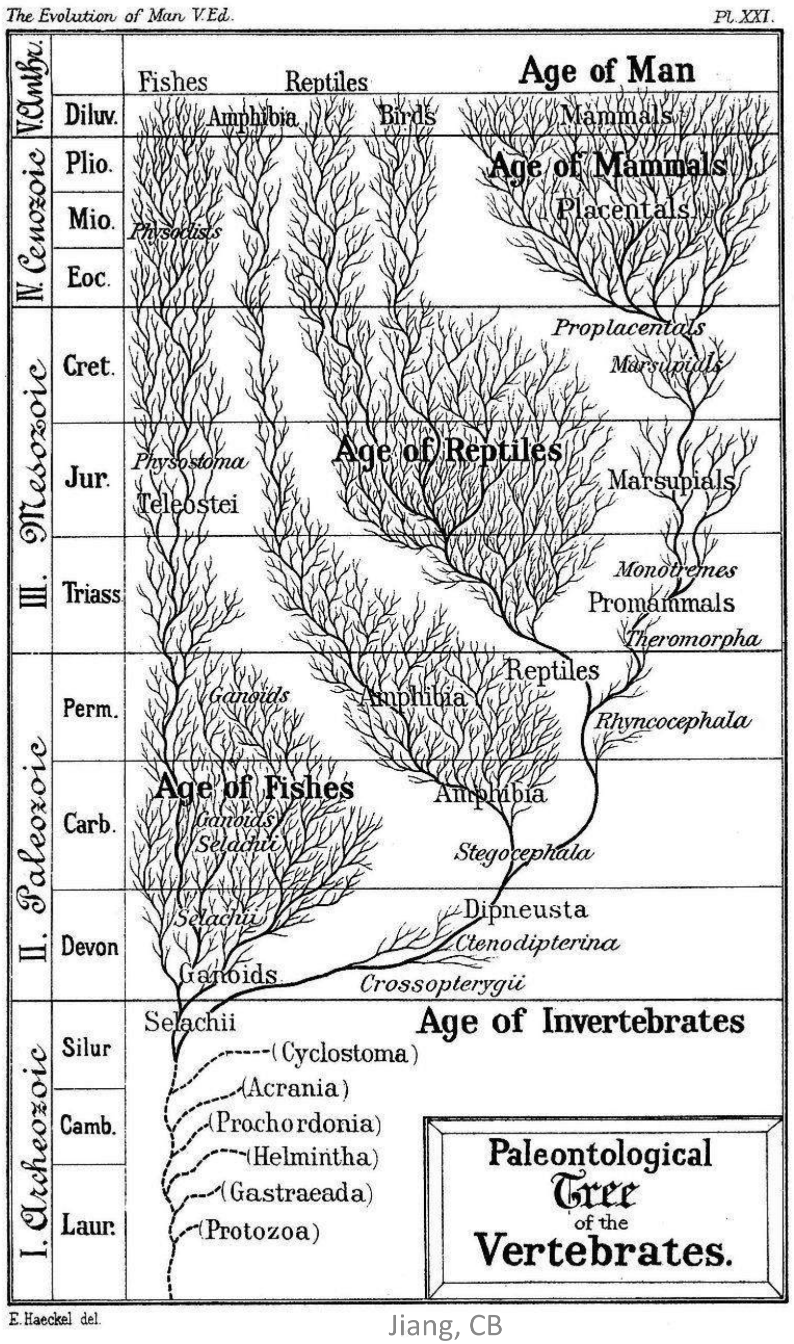

The Evolution of Man V.Ed.
Pl. XXI.
V. Anthr.
IV. Cenozoic
III. Mesozoic
II. Paleozoic
I. Archeozoic
Diluv.
Plio.
Mio.
Eoc.
Cret.
Jur.
Triass.
Perm.
Carb.
Devon
Silur
Camb.
Laur.
Fishes
Reptiles
Age of Man
Amphibia
Birds
Mammals
Age of Mammals
Placentals
Physoclisti
Proplacentals
Marsupials
Age of Reptiles
Physostoma
Teleostei
Marsupials
Monotremes
Promammals
Theromorpha
Reptiles
Ganoids
Amphibia
Rhyncocephala
Age of Fishes
Amphibia
Ganoids
Selachii
Stegocephala
Dipneusta
Selachii
Ctenodipterina
Ganoids
Crossopterygii
Selachii
Age of Invertebrates
(Cyclostoma)
(Acrania)
(Prochordonia)
(Helmintha)
(Gastraeada)
(Protozoa)
Paleontological
Tree
of the
Vertebrates.
E. Haeckel del.

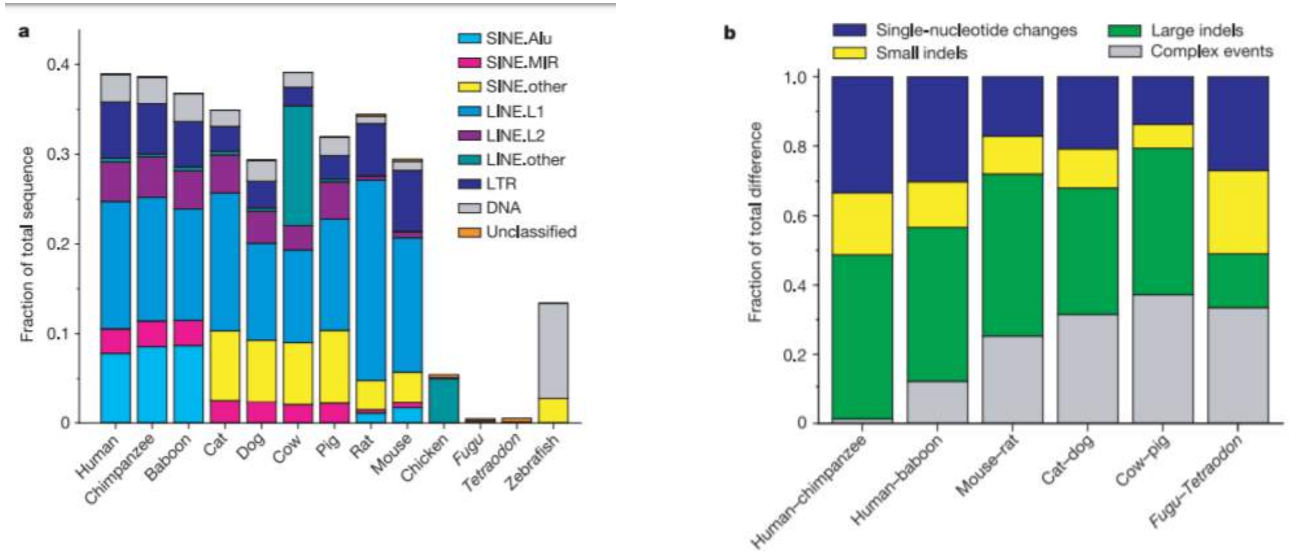
nature
International journal of science

Letter | Published: 14 August 2003

Comparative analyses of multi-species sequences from targeted genomic regions

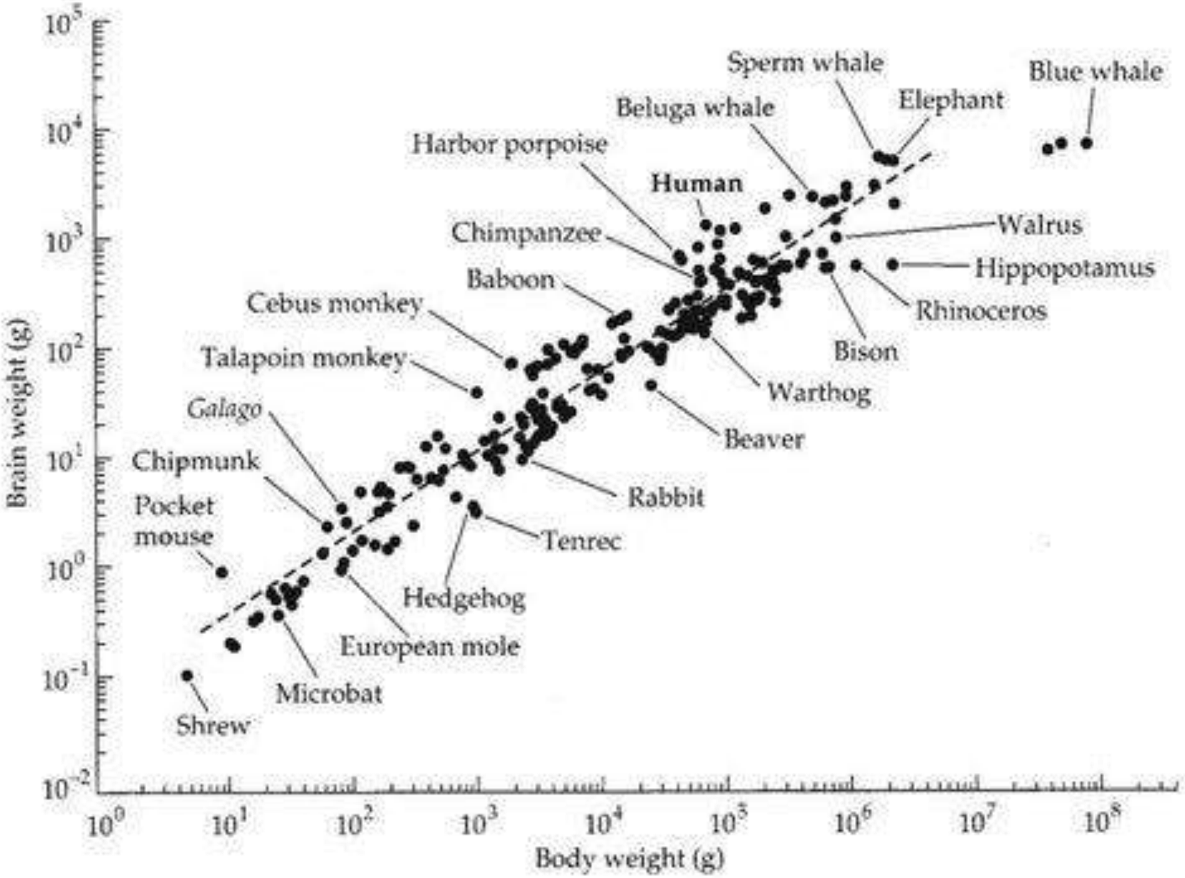
J. W. Thomas, J. W. Touchman, […] E. D. Green

Nature **424**, 788–793 (2003) | Download Citation



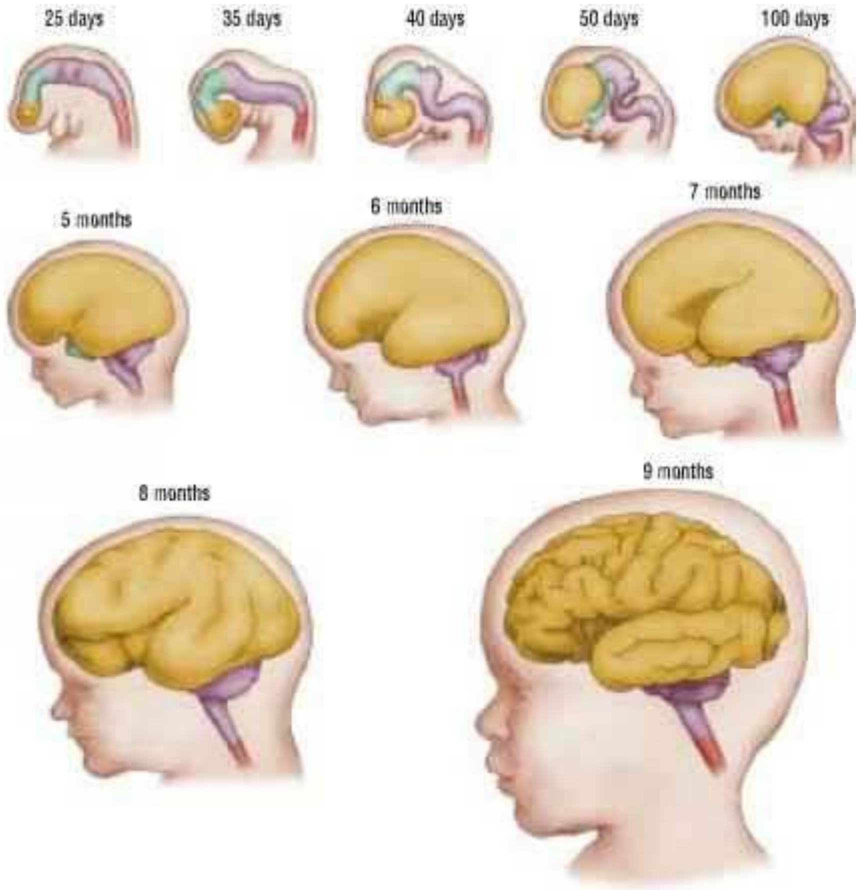
- 基因圖譜顯示:老鼠的20對染色體上共有約25億個鹼基對，與人類23對染色體的29億個鹼基對相當接近。
- 人類與老鼠共享80%的遺傳物質和99%的基因。

腦容量大就聰明???



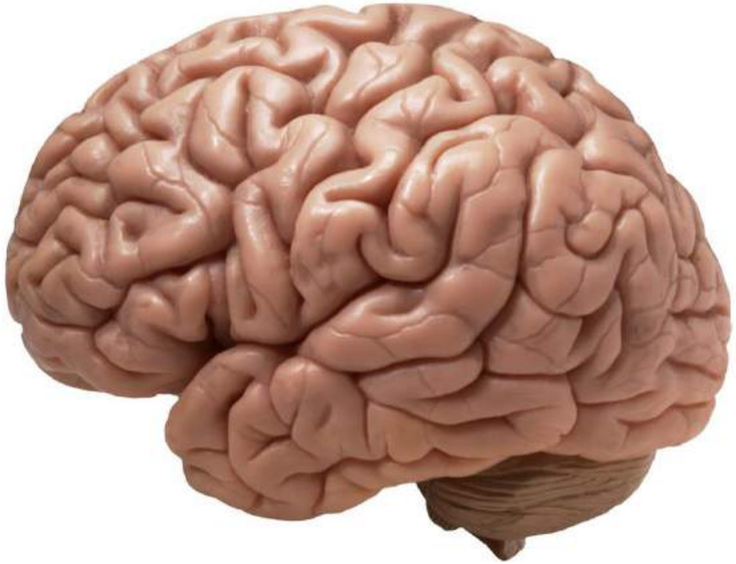
Sperm whale
Blue whale
Elephant
Beluga whale
Harbor porpoise
Human
Chimpanzee
Walrus
Baboon
Hippopotamus
Cebus monkey
Rhinoceros
Talapoin monkey
Bison
Galago
Warthog
Beaver
Chipmunk
Rabbit
Pocket mouse
Tenrec
Hedgehog
European mole
Microbat
Shrew
Brain weight (g)
Body weight (g)

Brain Development is a Complex Process



1. Altshuler, K.M. OCHP paper series on Children's Health and Environment:. 2003;1-48;
2. Semrud-Clikeman M. Research in Brain Function and Learning.

The Brain

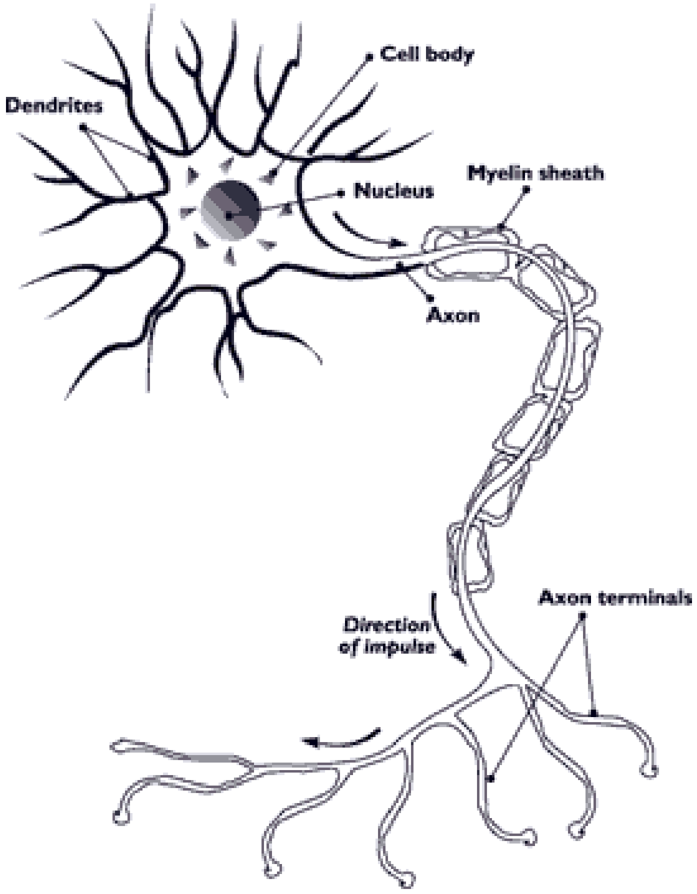


Weighs 1300-1400 grams at maturity, 350-400 grams at birth

Composed of 86 billion neurons[1], plus an equal number of glial cells[2]

[1]Herculano-Houzel, 2011, *Ann NY Acad Sci, 1225*:191-199
[2]Azevedo et al., 2009, *J Comp Neurol, 513*: 532-541

The Neuron



- 1 mm to > 1 m length
- Transmits binary electrochemical pulses from 0.61m/sec to 119m/sec
- Each neuron has (on average) 7000 synapses, yielding 10^{11} total connections within the brain[1]

[1]Drachman, *Neurology,* 2005, 64:2004-2005

The **1,000 days** between **a woman's pregnancy and her child's 2nd birthday** offer a unique window of opportunity to shape healthier and more prosperous futures. The **right nutrition** during this 1,000 day window can have a **profound impact on a child's ability to grow, learn, and rise out of poverty**. It can also shape a **society's long-term health, stability and prosperity**

http://www.thousanddays.org/

嬰兒8大原始反射

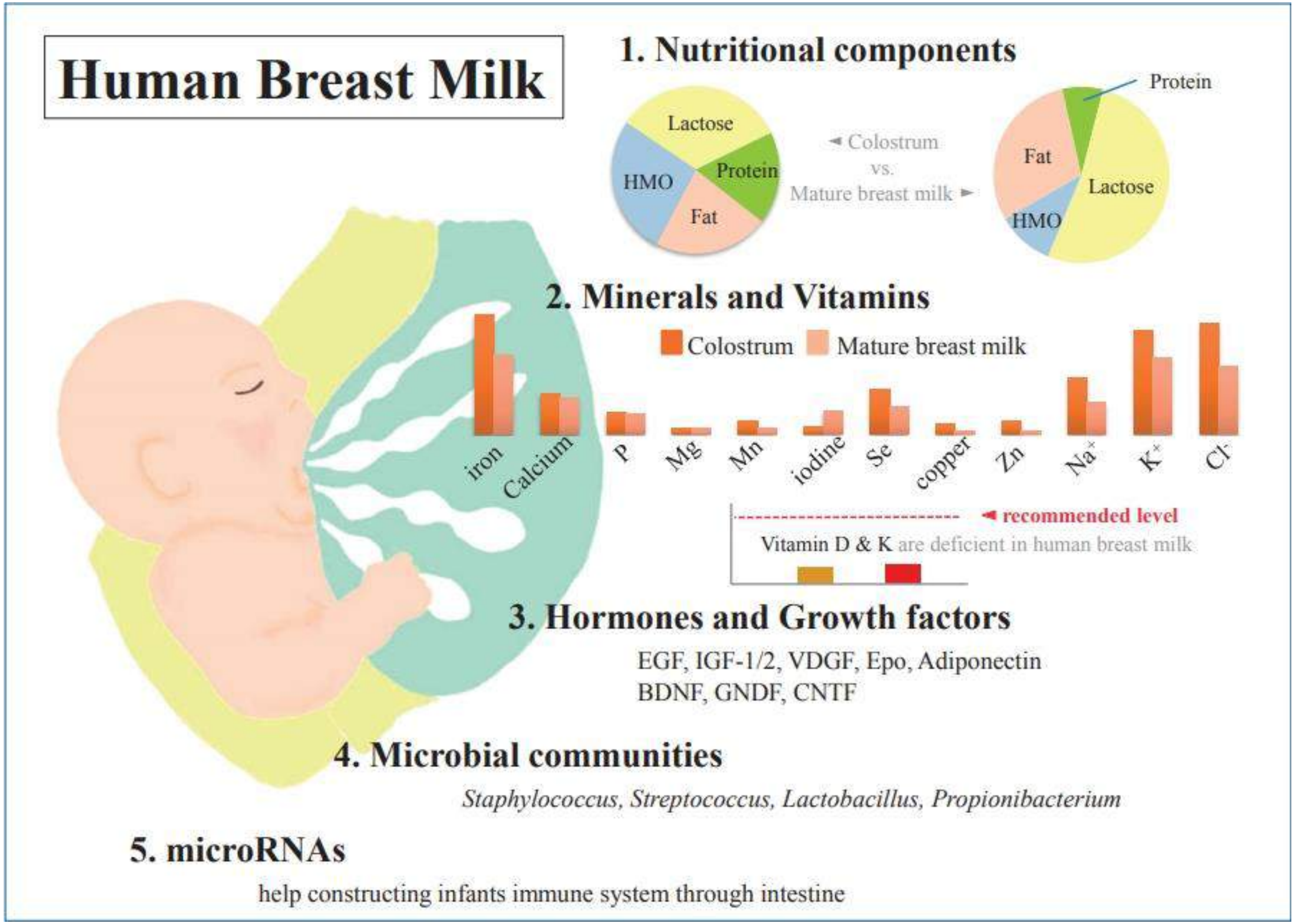
- **尋乳反射（Rooting Reflex）**
- **吸吮反射（Sucking Reflex）**
- **吞嚥反射（Swallowing reflex）**
- 抓取反射（Palmar/Plantar Grasp Reflex）
- 驚嚇反射（Moro Reflex）
- 牽引反射（Traction reflex）
- 踏步反射（Stepping/walking Reflex）
- 頸張力不對稱反射（Tonic Neck Reflex）

WHO/NMH/NHD/09.01
WHO/FCH/CAH/09.01

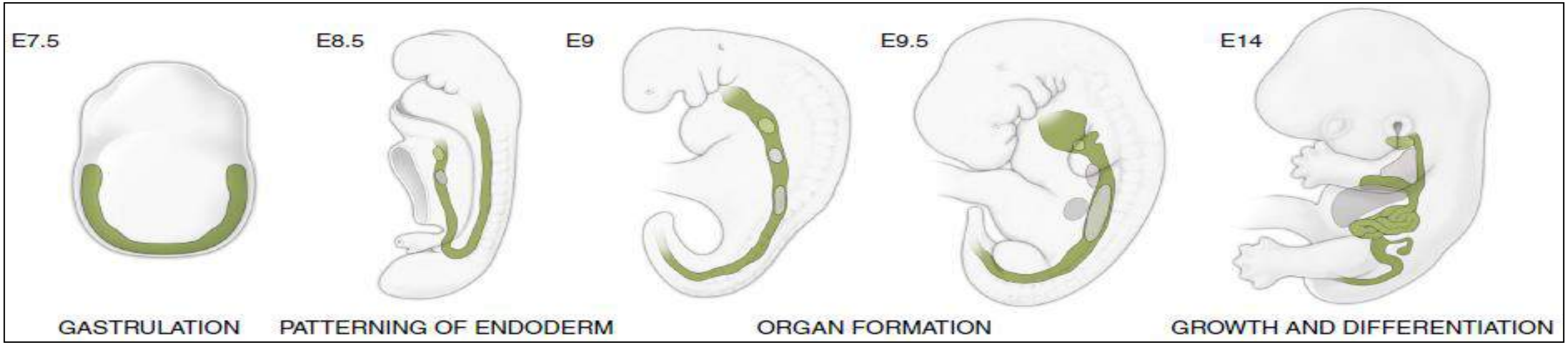
World Health Organization

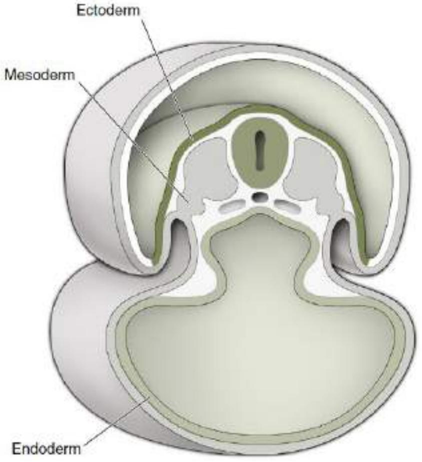
unicef

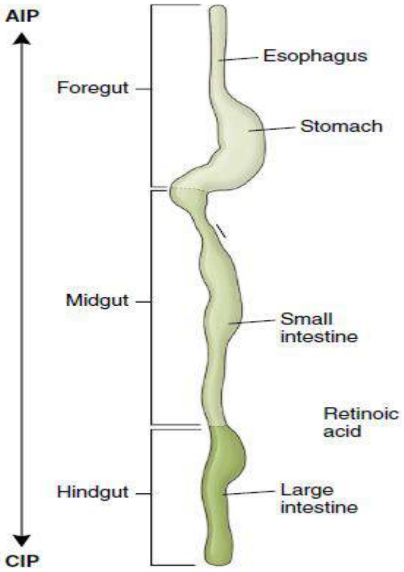
WHO and **UNICEF** recommend that babies are fed nothing but **breast milk** for their **first 6 months**, after which they should continue breastfeeding – as well as eating other safe and nutritionally adequate foods – until 2 years of age or beyond.

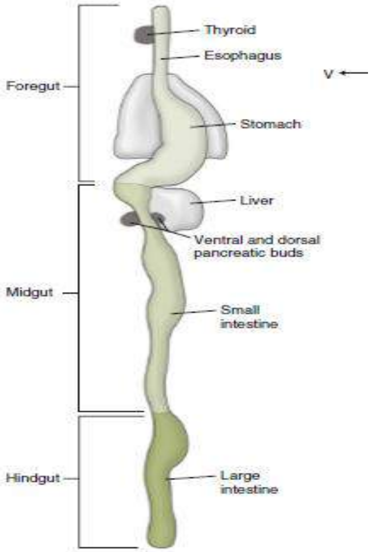

Human Breast Milk
1. Nutritional components
Lactose
HMO
Protein
Fat
◄ Colostrum
vs.
Mature breast milk ►
Protein
Fat
Lactose
HMO
2. Minerals and Vitamins
Colostrum
Mature breast milk
iron
Calcium
P
Mg
Mn
iodine
Se
copper
Zn
Na+
K+
Cl-
◄ recommended level
Vitamin D & K are deficient in human breast milk
3. Hormones and Growth factors
EGF, IGF-1/2, VDGF, Epo, Adiponectin
BDNF, GNDF, CNTF
4. Microbial communities
Staphylococcus, Streptococcus, Lactobacillus, Propionibacterium
5. microRNAs
help constructing infants immune system through intestine

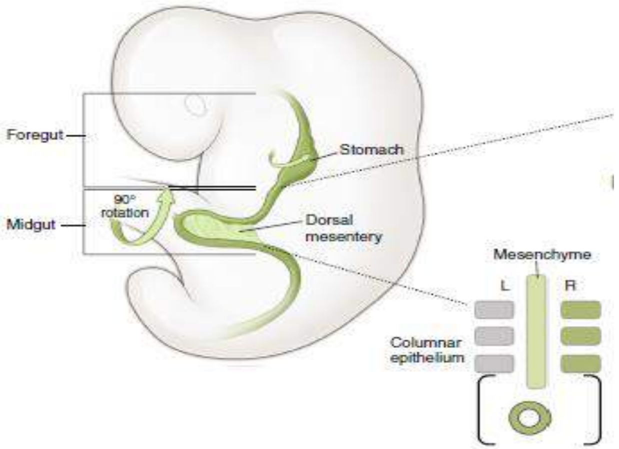
Formation of Digestive System from a Primitive Gut Tube



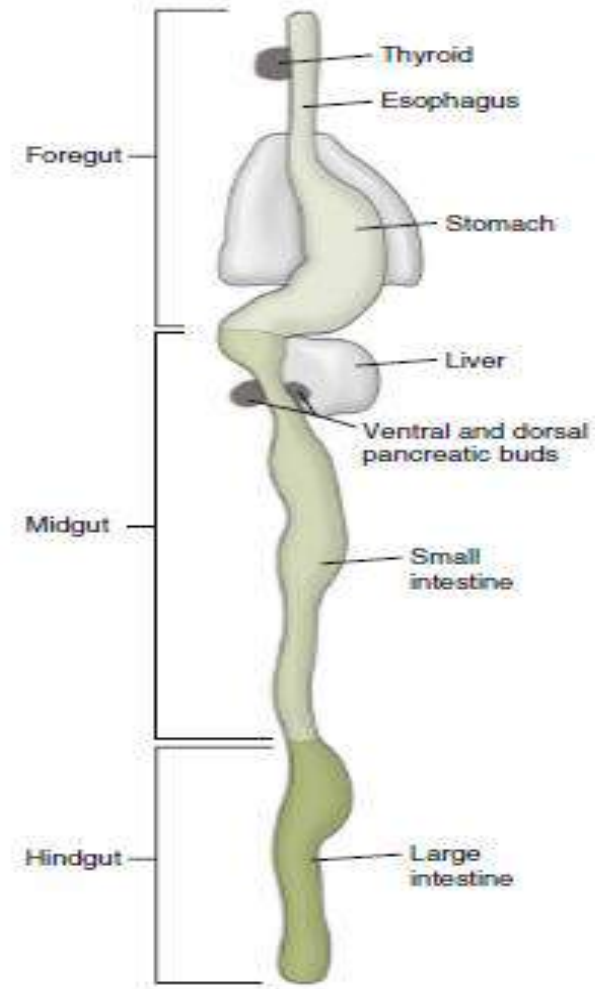


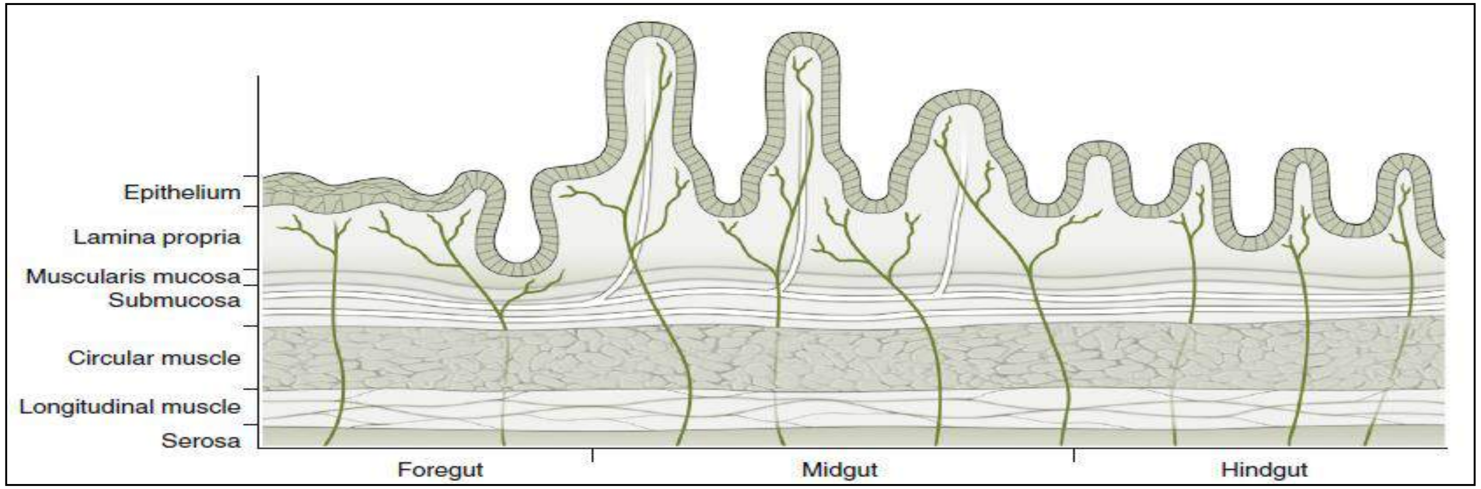


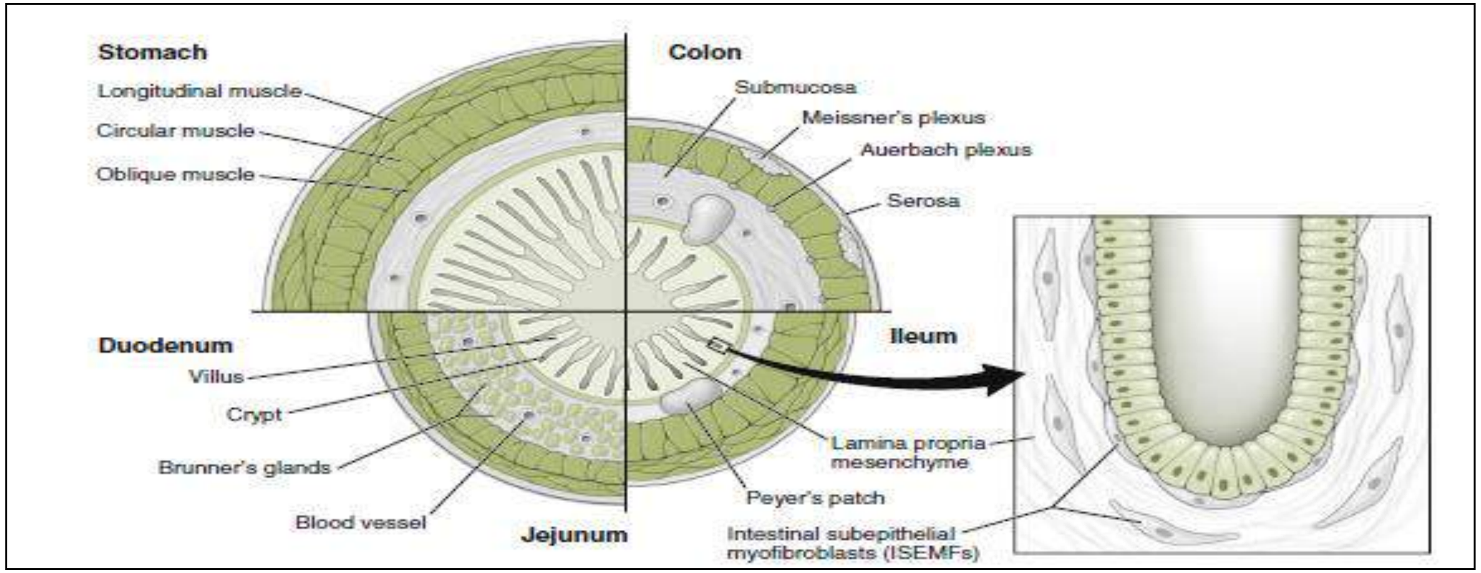




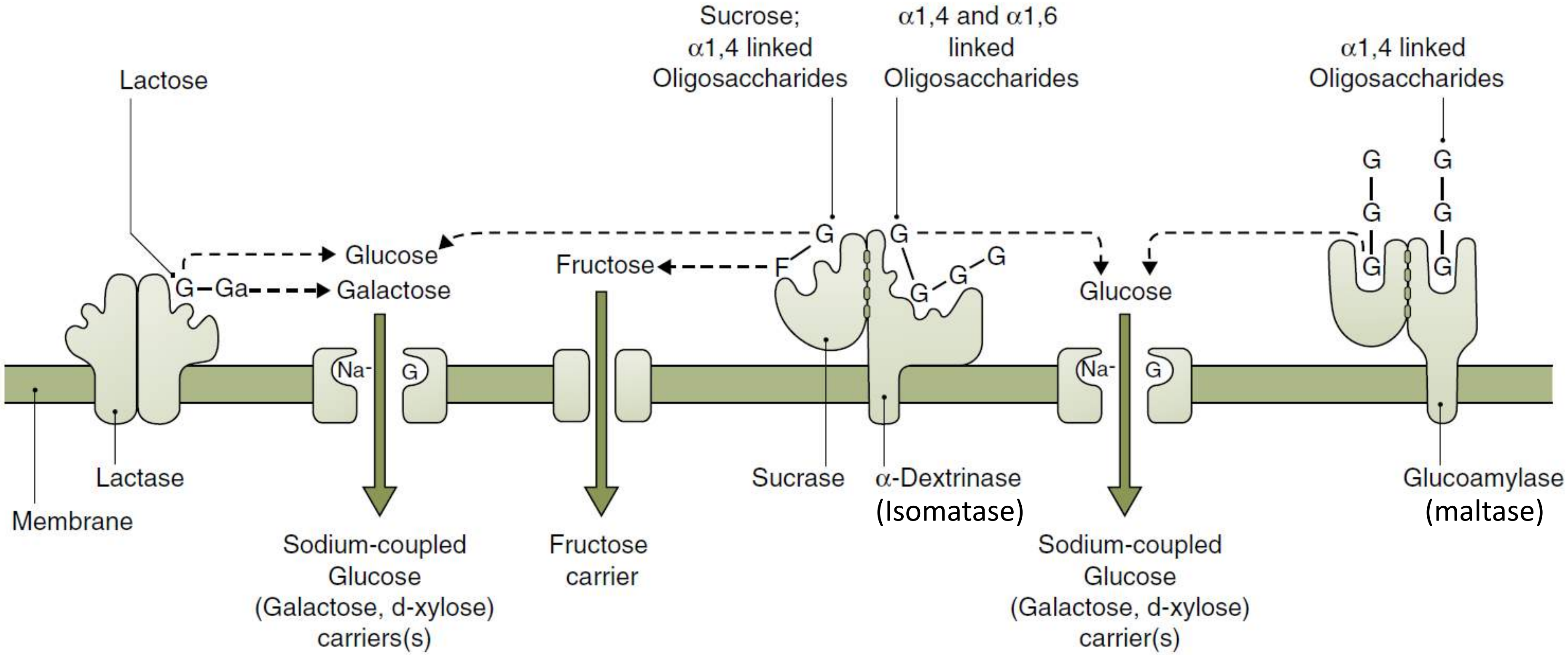
Regional differentiation



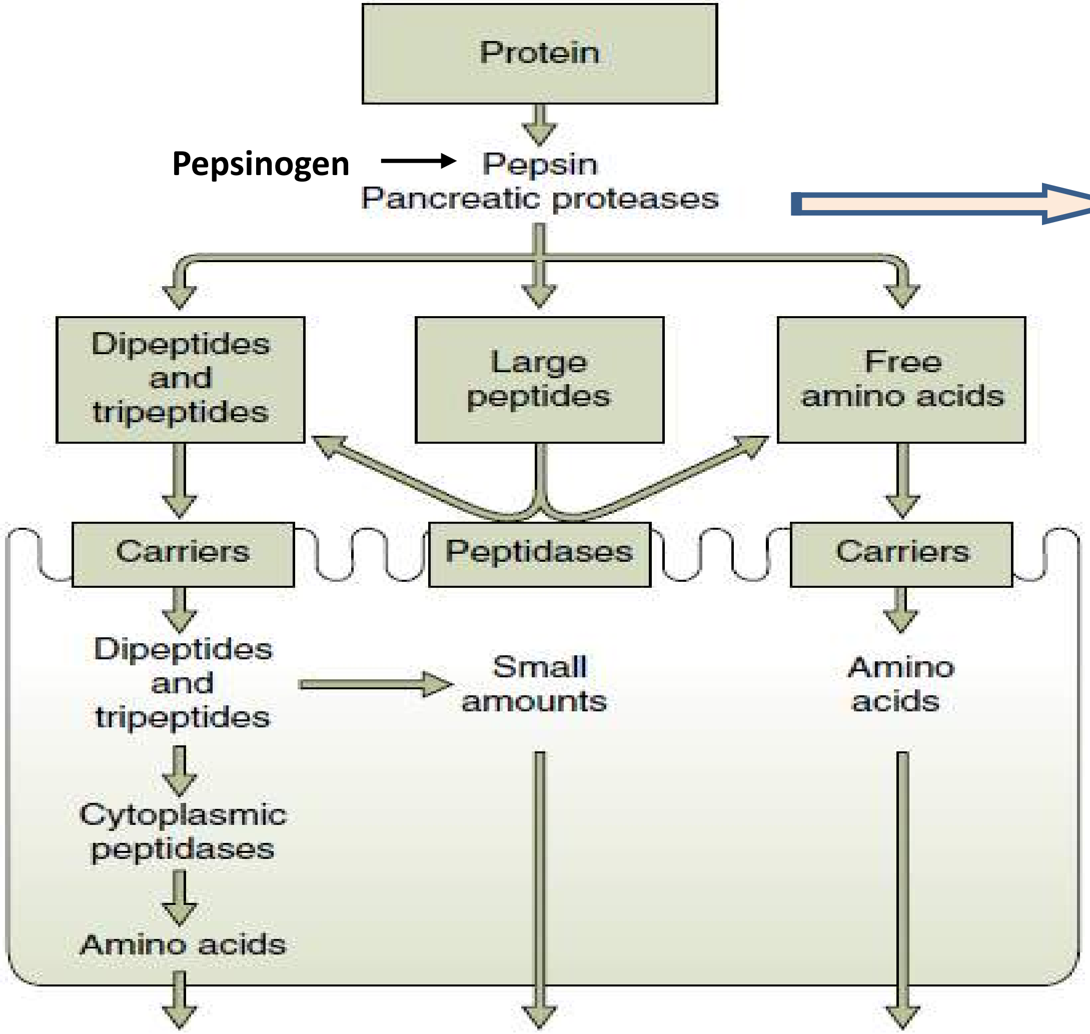




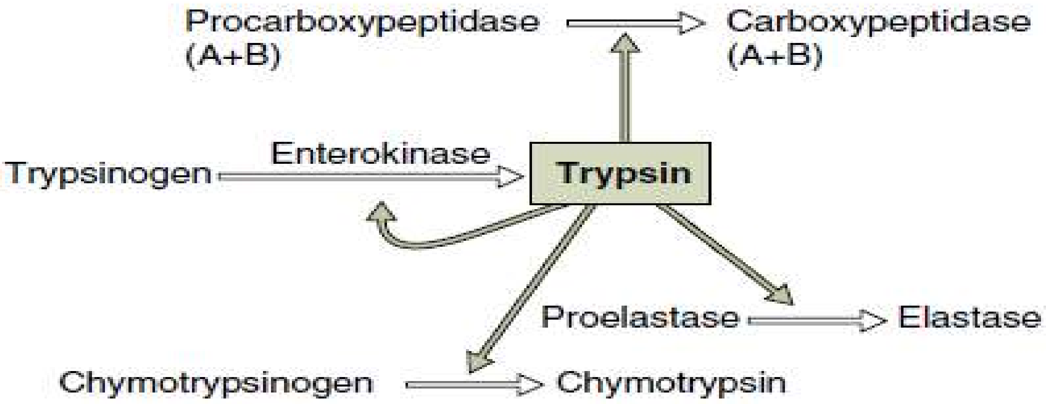
Brush border digestion and absorption of carbohydrate

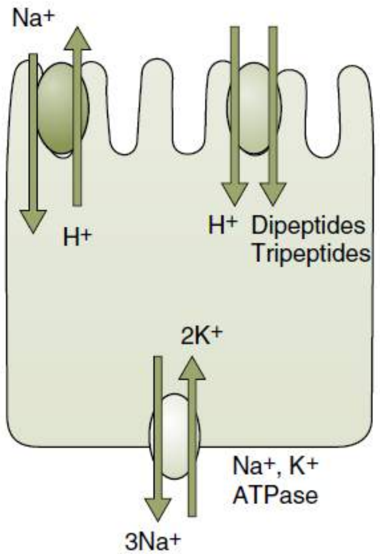


Digestion and absorption of PROTEIN



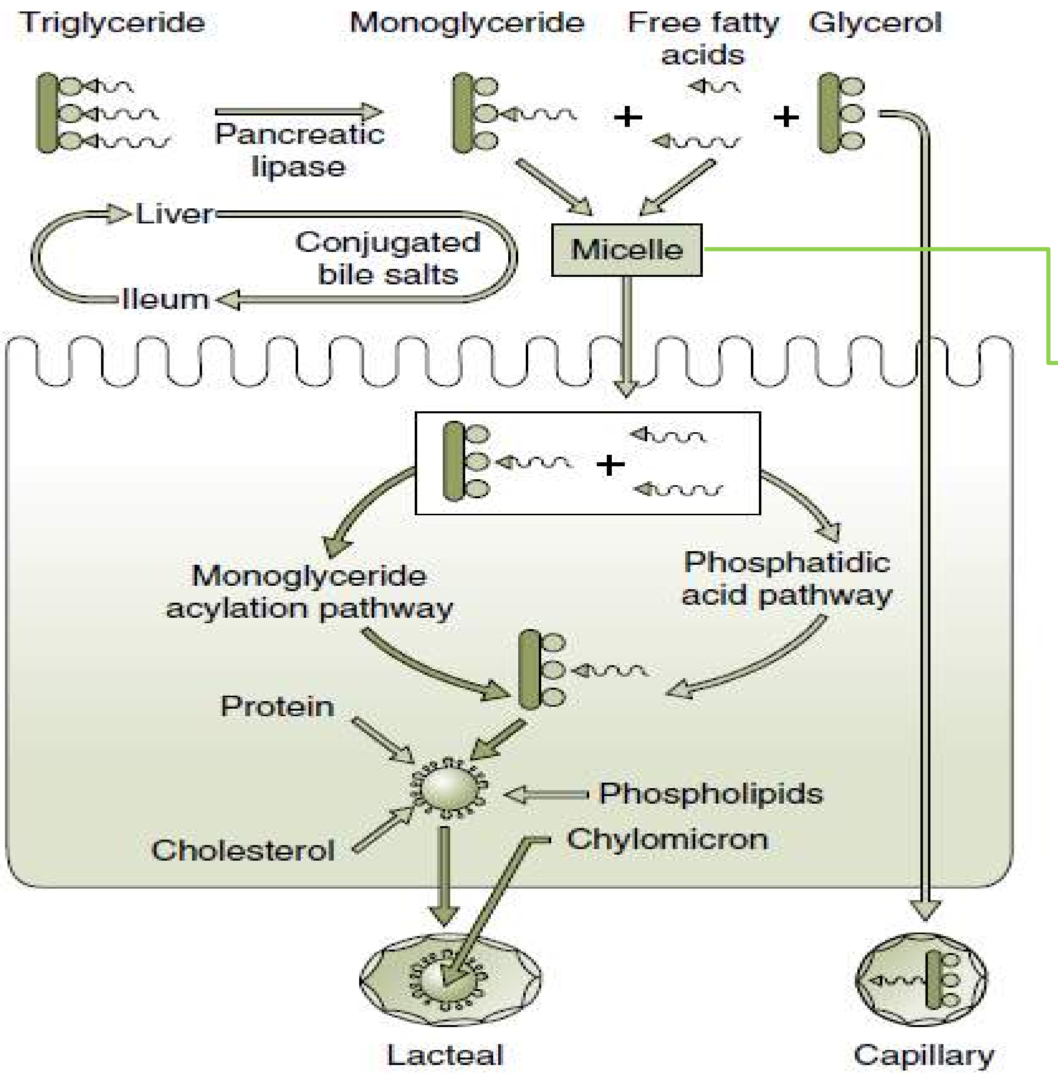
Pancreatic enzyme activation

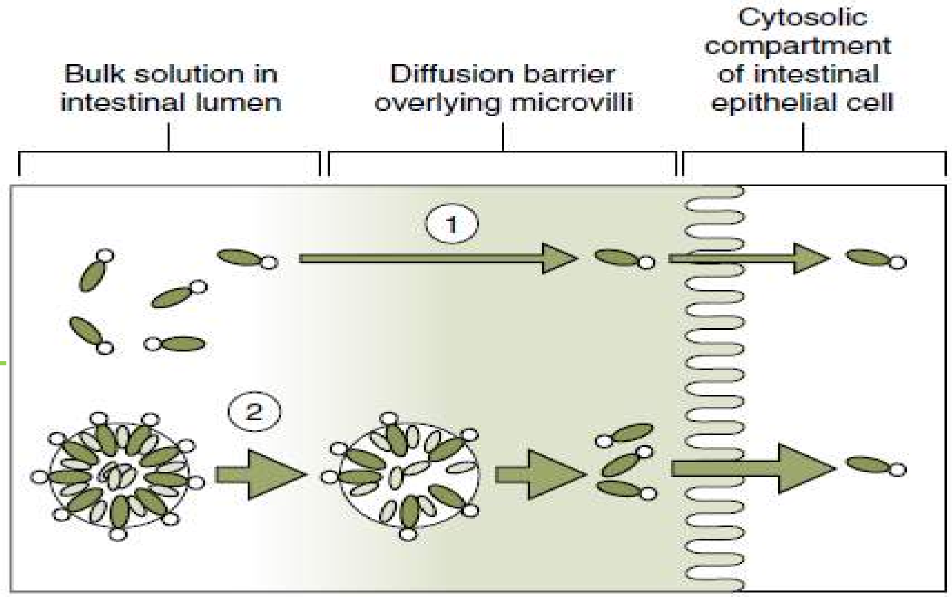




Polypeptide-Proton Cotransport

Digestion and absorption of TG

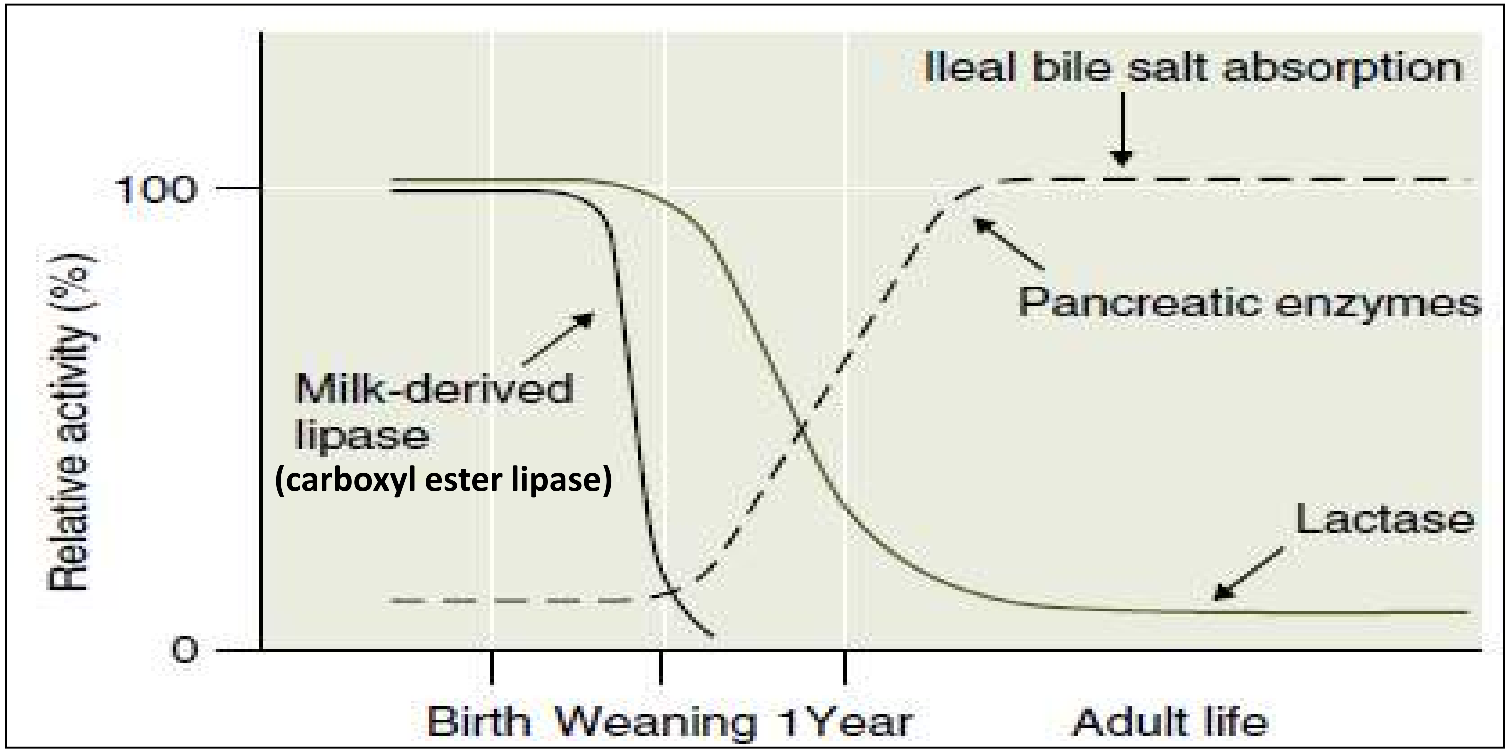




J Clin Invest. 1976;58[1]:97–108.

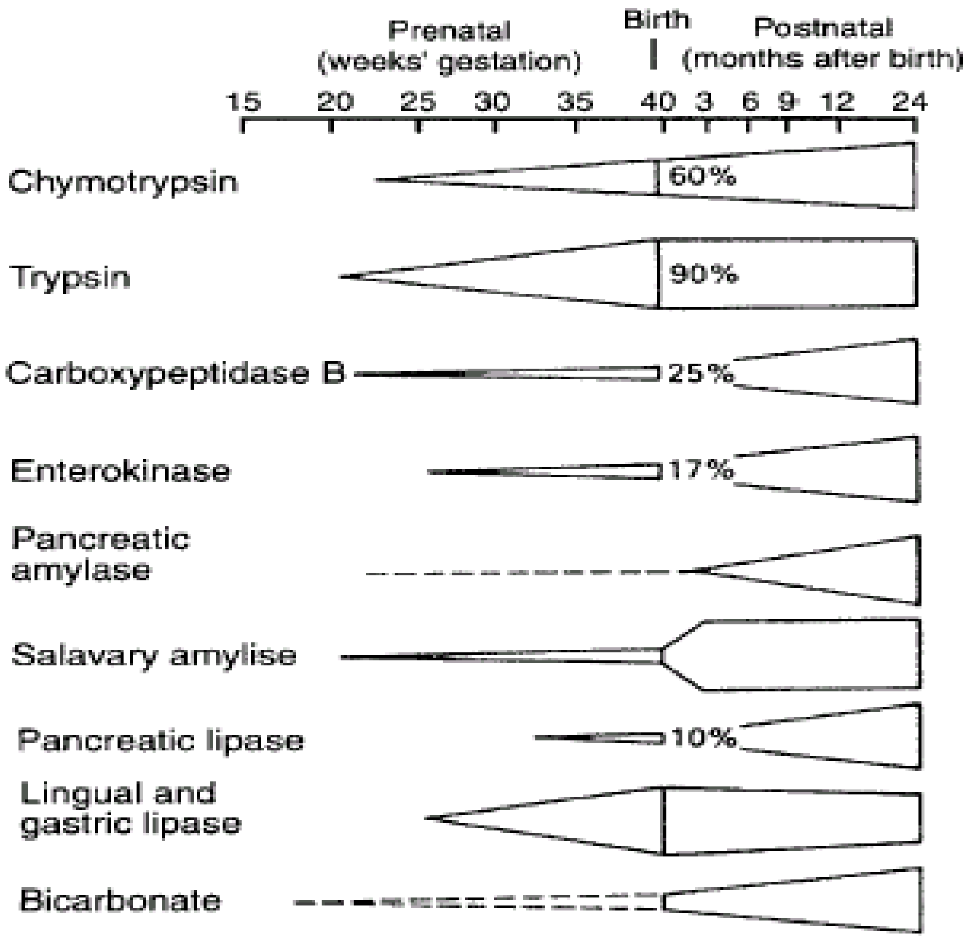
Adapted from Johnson L. Gastrointestinal Physiology, Essential Medical Physiology. Philadelphia: Lippincott-Raven; 1997.

Major changes in digestive function in neonates



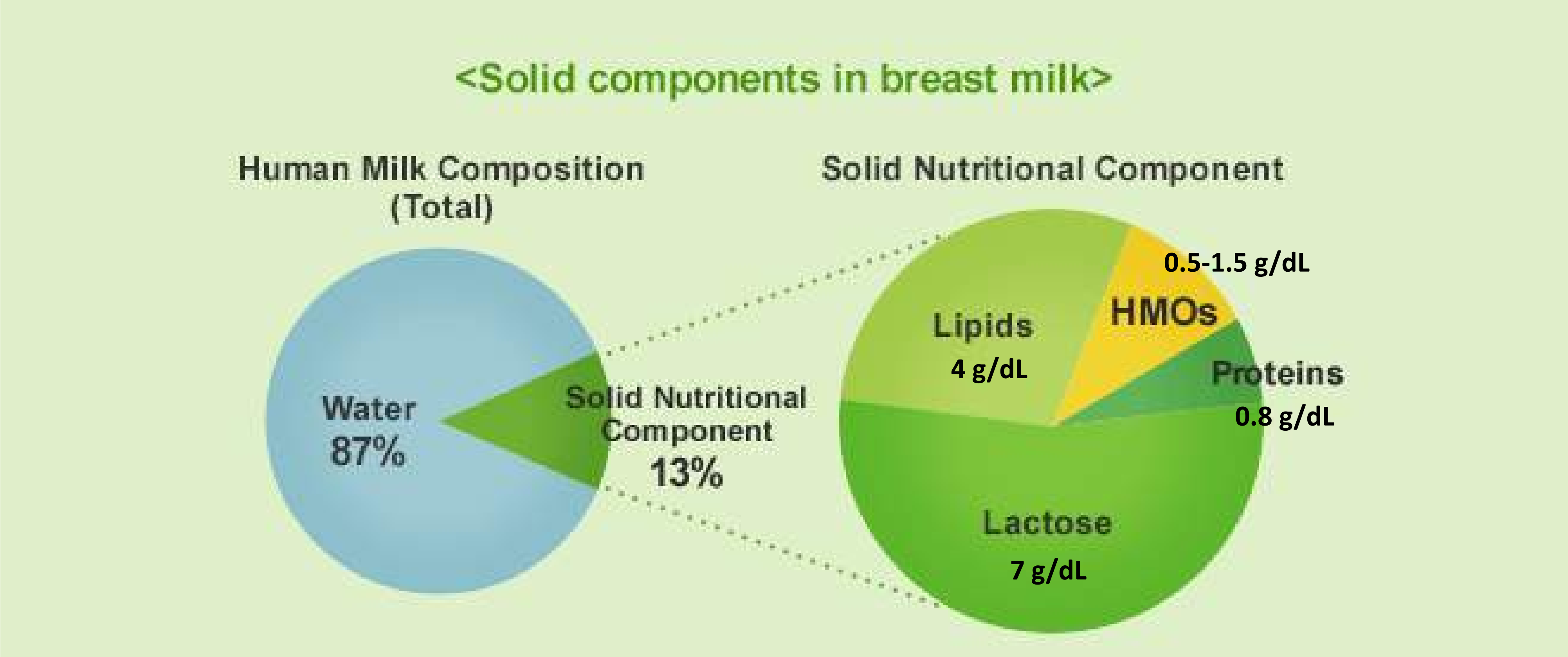
Adapted from Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology, Diagnosis, Management, 6e. Philadelphia, PA: WB Saunders; 1998

NB digestive enzyme



Adapted from Arch Dis Child 68:62–65, 1993.

MAJOR SOLID COMPONENT IN HUMAN MILK



Lactose

Mutarotation

β-lactose ⟶ *α*-lactose ⟶ absorbed

(in breast milk)　　(in small bowel)

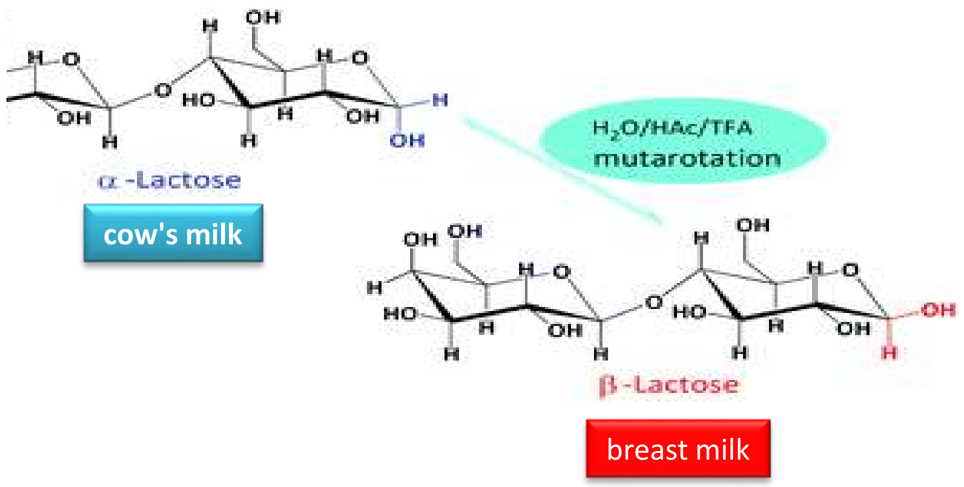
↓

not absorbed ⟶ fermentation by gut flora

↓

short-chain fatty acid + lactic acid

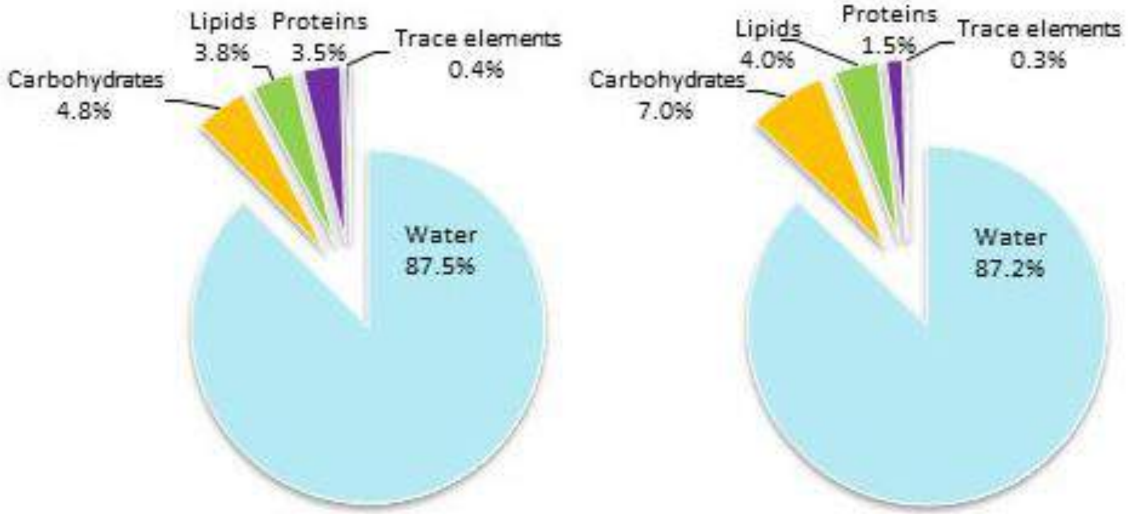
- acidic softer stool（pH: 5.0~6.5）
- more benefit bacterial fecal flora



Advantages of Lactose

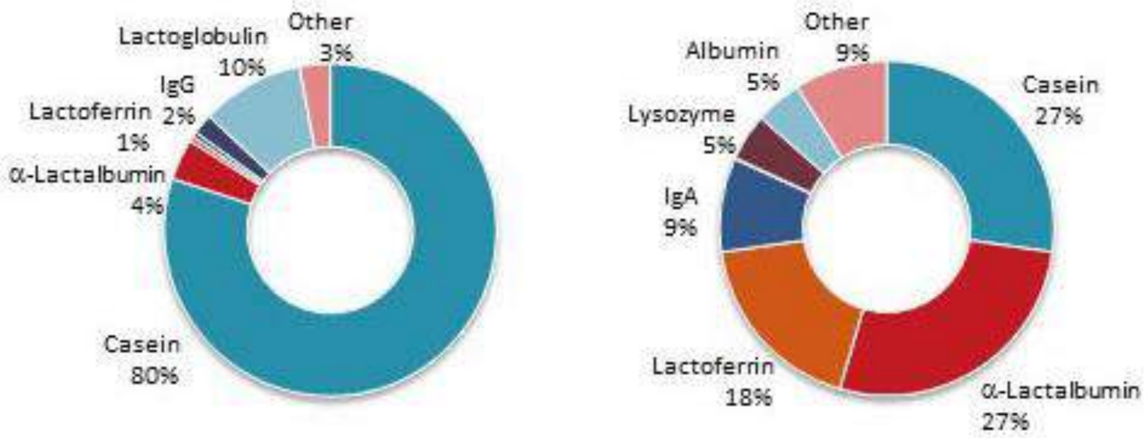
1. Energy source
2. **Brain cell development**: galactose
3. Enhanced absorption of:
   - Ca^{2+}
   - Mn^{2+}
   - Mg^{2+}
   - Cu^{2+}
   - Zn^{2+}
4. Enhanced lactobacillus growth
5. Other unknown benefits

Protein



Cow milk

Human milk

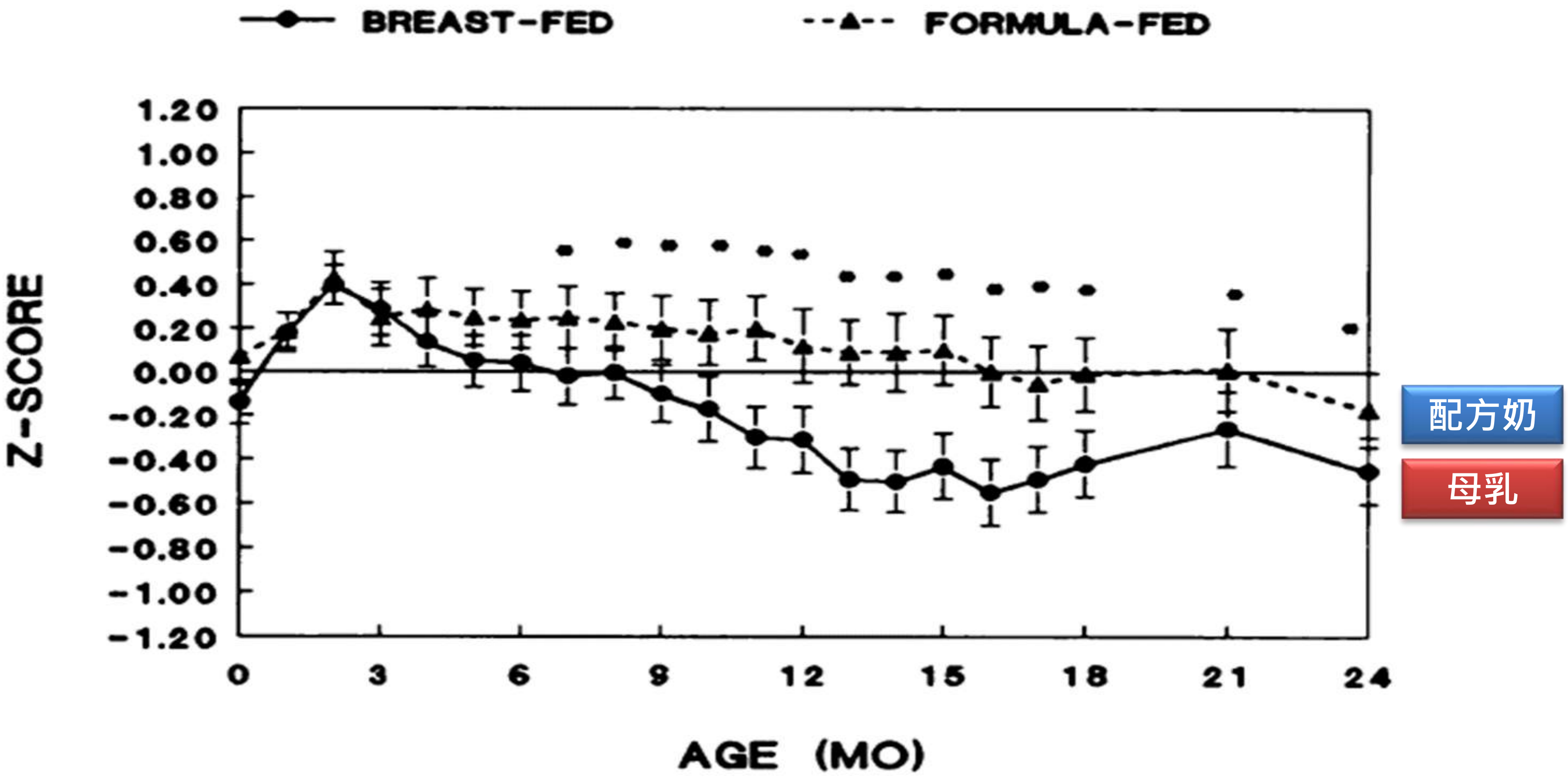


Human milk vs. Infant formula

Protein

- Mature breast milk:
  1.2-1.3 g/100 kcal (0.9-1.0 g/dL)
- Intact cow's milk protein–based formulas:
  1.8-3 g/100 kcal (1.4-1.8 g/dL)
  - ➢ designed to meet the needs of the youngest infants, but leads to excess protein intake for older infants
- Breast milk content varies over time to match protein needs at various ages.

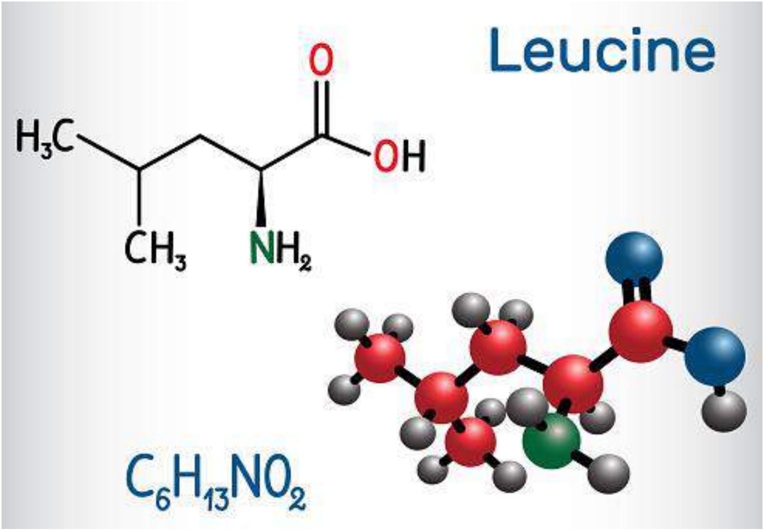
嬰兒配方與母乳嬰兒的生長



Leucine

- a unique amino acid linked with growth
- animals milk have higher levels of protein and leucine - grow quickly after birth (cows: 3.3% leucine; humans: 0.9% leucine)
- Calves: 2x BW- in 40 days

  Humans: 2x BW- in 4 months



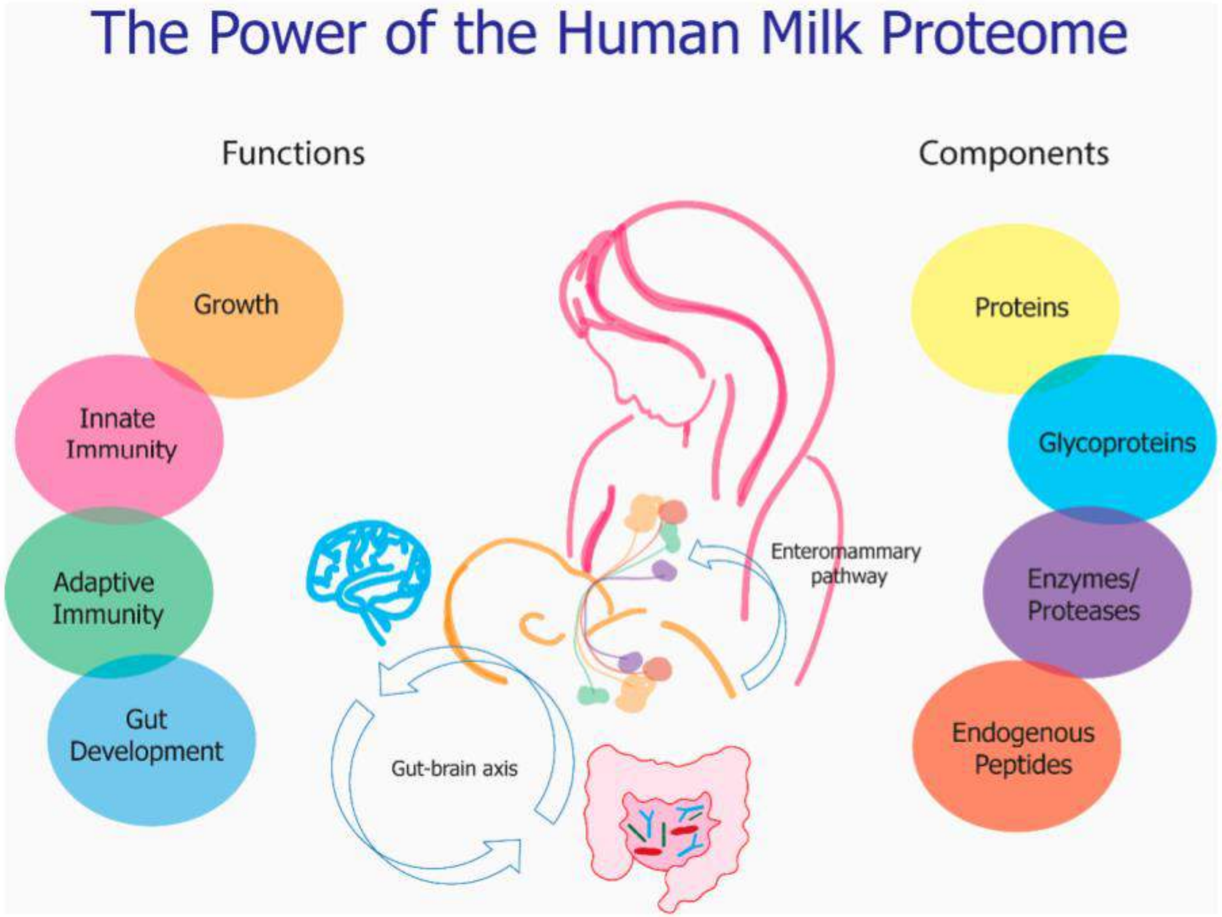
nutrients

Review

The Functional Power of the Human Milk Proteome

Jing Zhu [1,2] and Kelly A. Dingess [1,2,*]

Nutrients 2019, 11, 1834.



母乳的脂肪結構

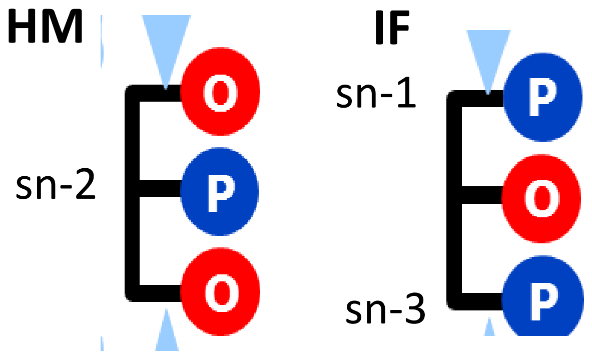
- 母乳中的脂肪酸以油酸(oleic acid, OA)和棕櫚酸(palmitic acid, PA)為主
- 棕櫚酸是母乳中為嬰兒提供約10%的能量供應
- 母乳中的棕櫚酸 70% 位於sn-2位置 (sn-2 PA)
- 傳統嬰兒配方添加palm olein，棕櫚酸鍵結位置主要為 sn-1及sn-3

Carnielli et al. JPGN. 1996
Bracco. Am J Clin Nutr 1994
Straarup et al. JPGN. 2006

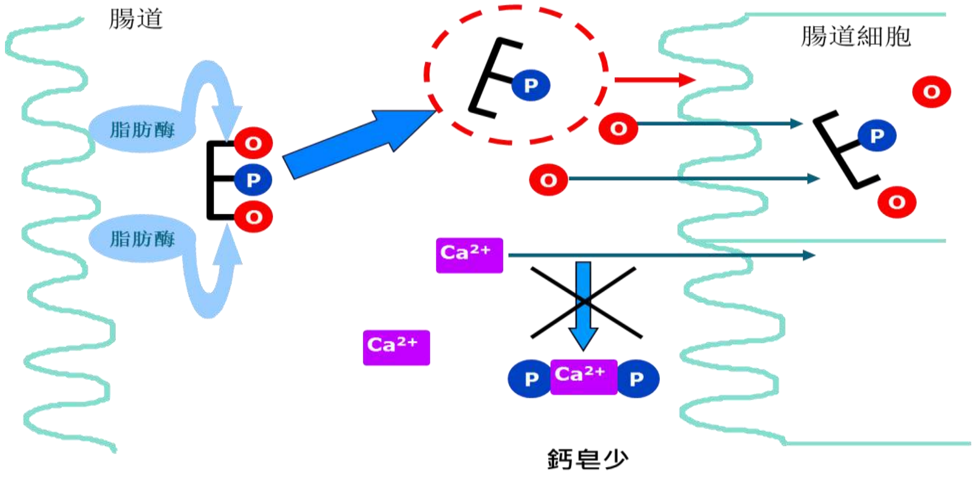
Table IV

Human Milk Fatty Acid Ranges

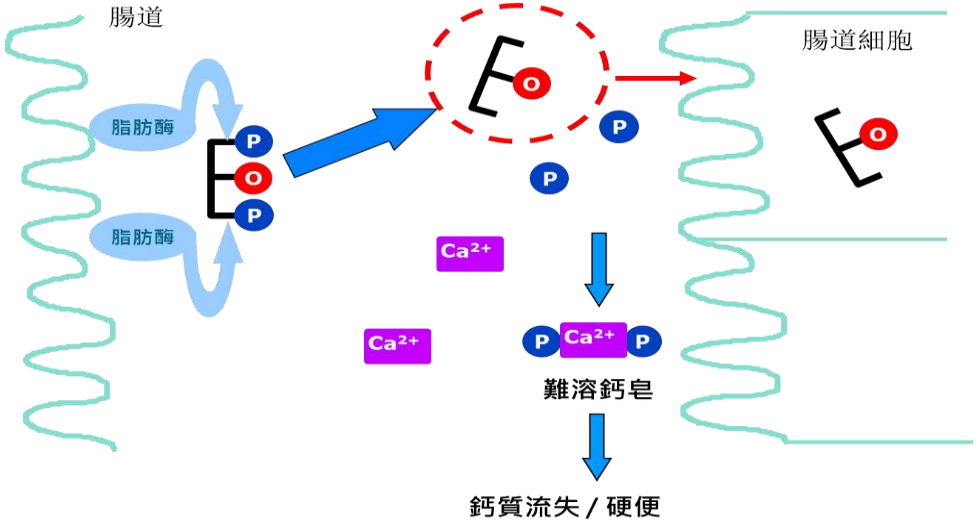
	Fatty Acid		Ranges Reported
	C8	Caprylic	0.1
	C10	Capric	0.8 - 1.6
	C12	Lauric	3.1 - 6.3
	C14	Myristic	5.1 - 7.4
2	C16	Palmitic	20.2 - 25.2
	C18	Stearic	5.5 - 10.4
	C16:1	Palmitoleic	3.7 - 4.1
1	C18:1	Oleic	29.4 - 46.9
	C18:2	Linoleic	7.2 - 15.6
	C18:3	Linolenic	0.7 - 2.0



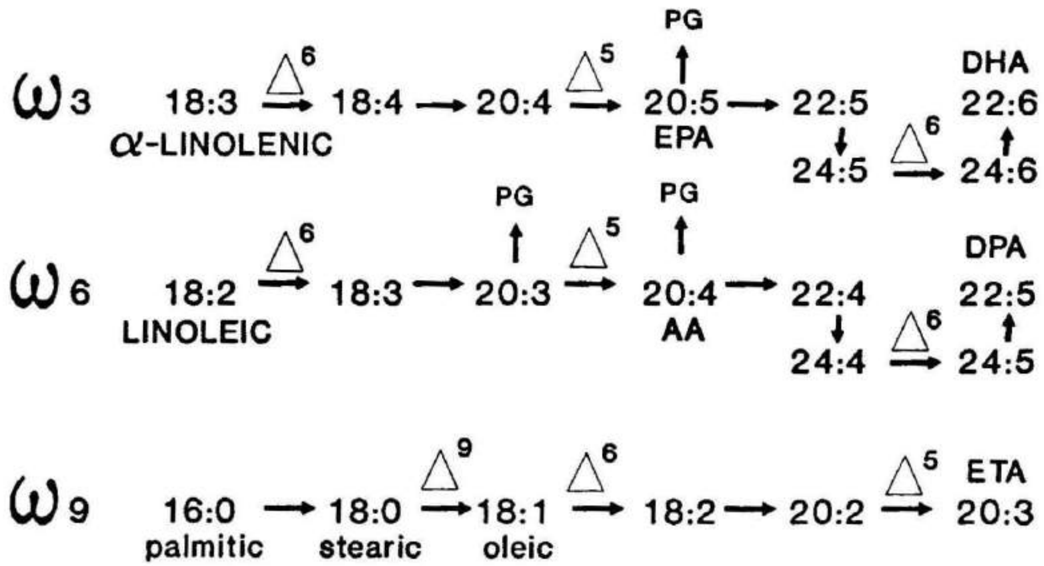
母乳 sn-2 棕櫚酸吸收較好



嬰兒配方 sn-1、-3棕櫚酸吸收較差



- **PUFA**: ω-3, ω-6 fatty acids; **DHA**, **AA**
  - ➢ **Linoleic** and **linolenic acids** play a role in **brain development** as a component of cell membrane.
    - ☐ > 0.3 gm/100kcal or 2.7% of total calories in formula

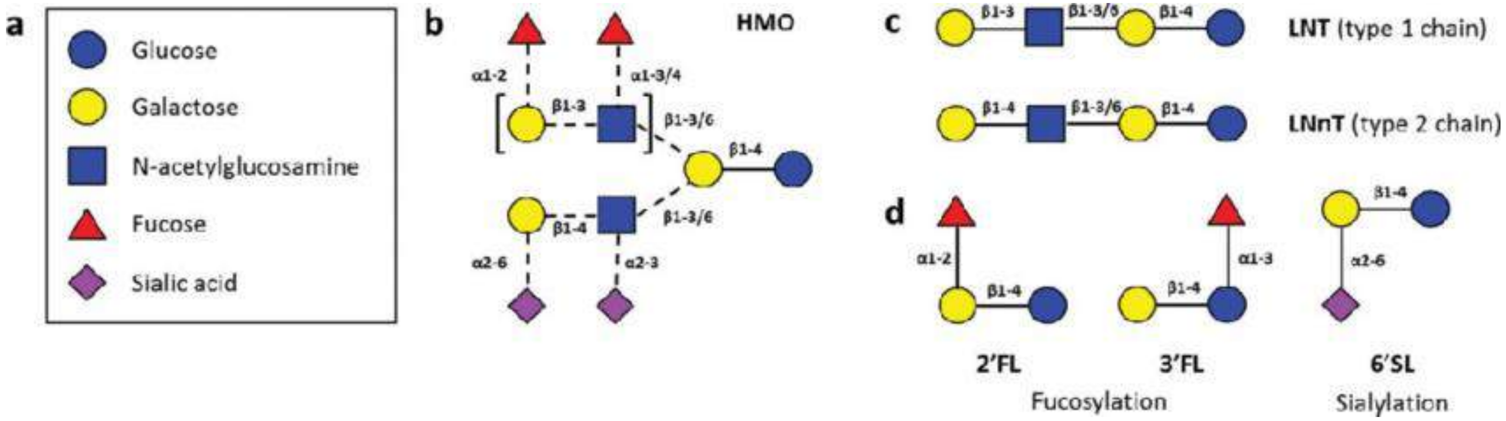


What are HMOs?

- **Human milk oligosaccharides (HMOs)** are specific bioactive compounds present in human milk.

Kunz,AdvNutr2012

- The amount and variety of oligosaccharides in human milk is unique and is not found in the milk of cows or other animals.

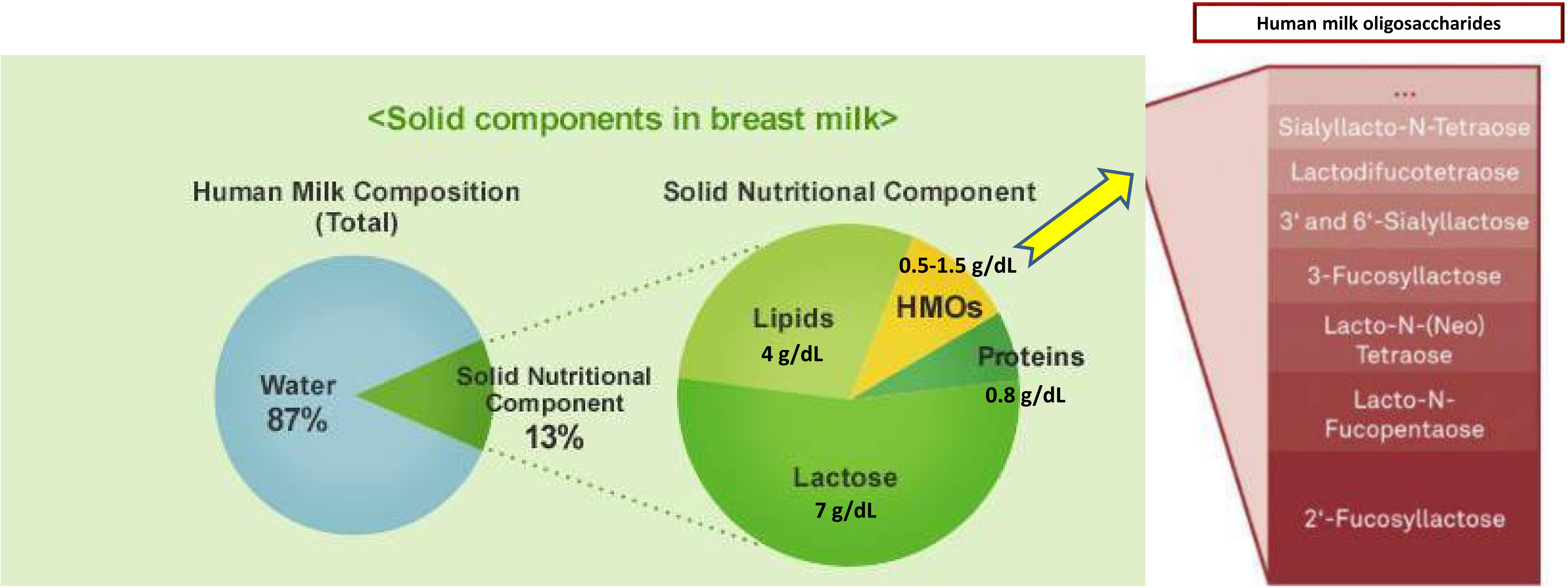


Ninonuevoetal. Pediatr Res 2008

Urashimaetal. Adv Nutr2012

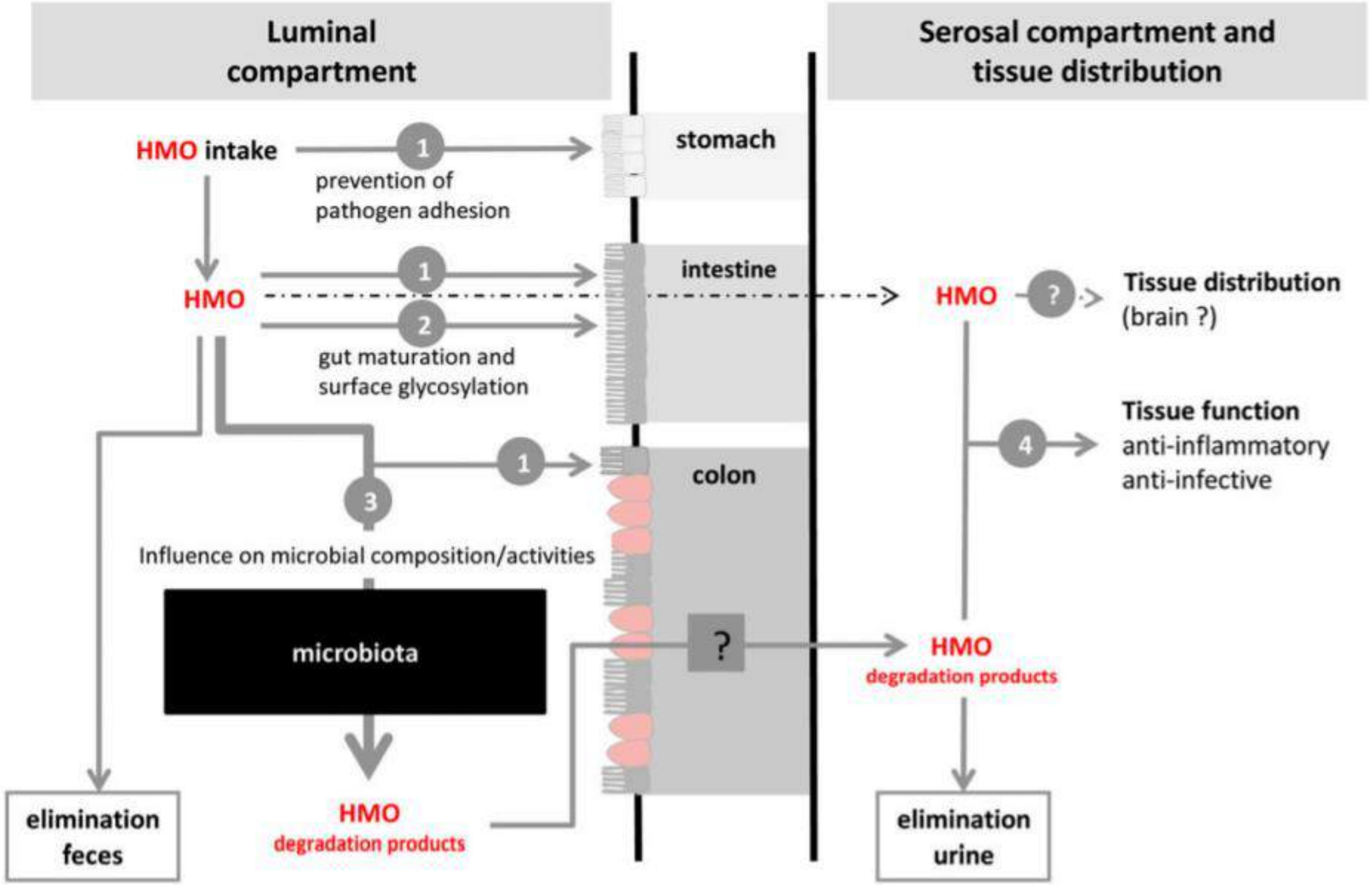
Ruhaaketal. Anal BioanalChem 2014

HMOs ARE THE 3RD LARGEST SOLID COMPONENT IN HUMAN MILK



2'FL is the most abundant HMO in breast milk

Main effects of HMOs



Luminal & mucosal effects

- Microbiota establishment & function
- Protection from infection
- Mucosal barrier function

Systemic effects

- Immunity - Allergy
- Brain
- Metabolic health

Adv. Nutr. 3: 398S–405S, 2012

HMOs and cognitive function

PLOS | ONE

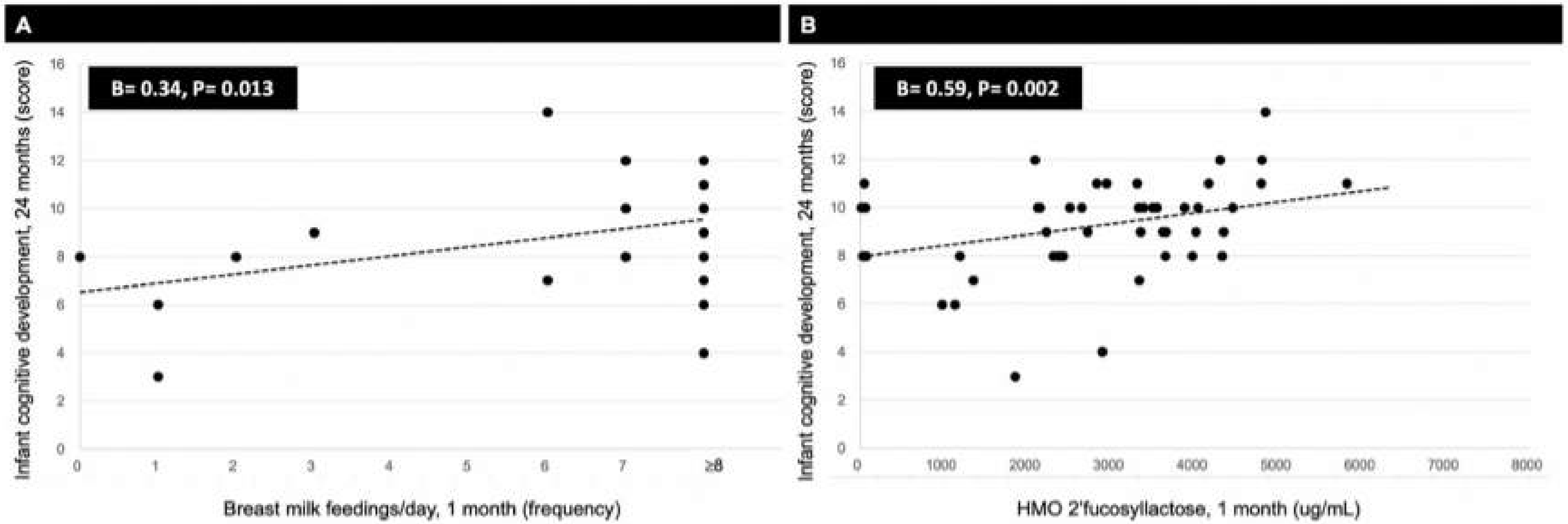
RESEARCH ARTICLE

PLoS One. 2020 Feb 12;15(2):e0228323.

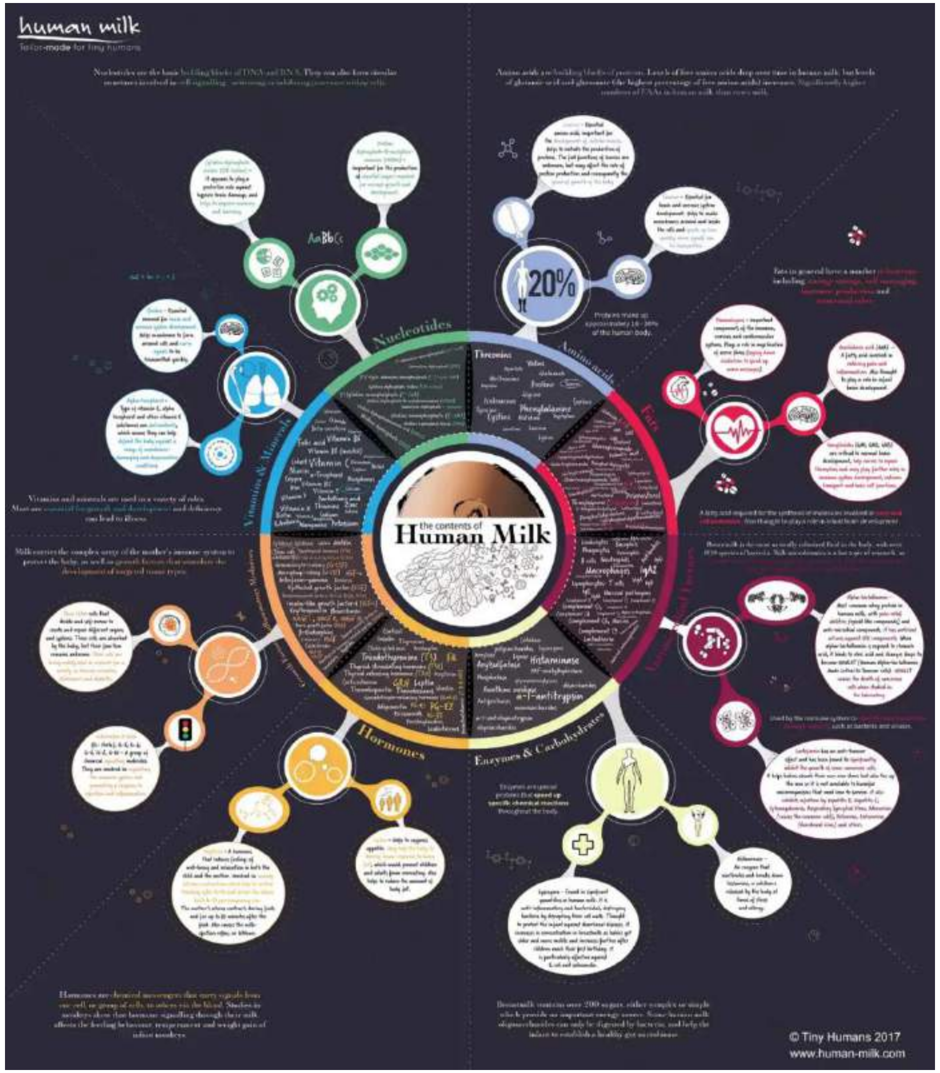
Human milk oligosaccharide 2′-fucosyllactose links feedings at 1 month to cognitive development at 24 months in infants of normal and overweight mothers

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]*

- mother-infant pairs (N = 50)
- Breast milk was collected at 1 and 6 months
- Infant cognitive development score was assessed with the Bayley-III Scale at 24 months
- 母乳中2-FL含量與認知發展指數呈正相關



? Enough

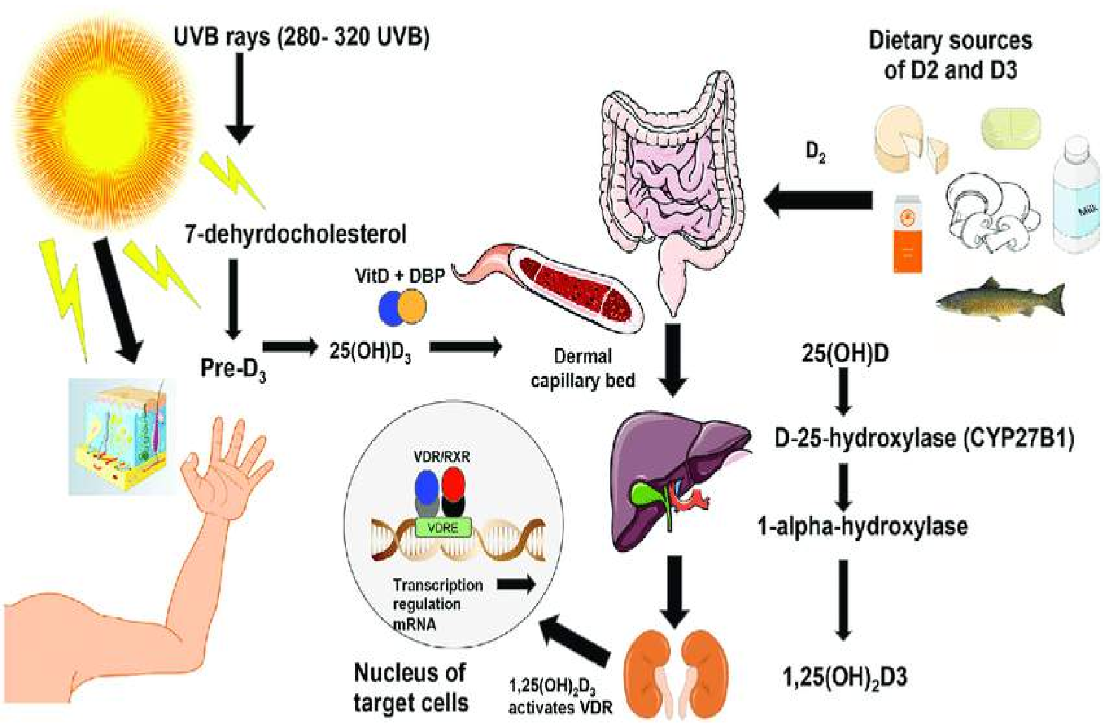


- Mean intakes of human milk provide sufficient **energy** and **protein** to meet mean requirements during the first 6 months of infancy.

Vitamin A and Vitamin B6

- In well-nourished populations the amounts of **vitamins A** and **B6** in human milk are adequate to meet the requirements for infants during the first 6 months of life.
- In populations deficient in vitamins A and B6, the amount of these vitamins in human milk will be sub-optimal and corrective measures are called for, either through maternal and/or infant supplementation, or complementary feeding for infants.

Vitamin D



- ◻ The vitamin D content of human milk is **insufficient** to meet infant requirements.
- ◻ Infants depend on sunlight exposure or exogenous intakes of vitamin D.
- ◻ If these are inadequate, the risk of vitamin D deficiency rises with age as stores become depleted in the exclusively breastfed infant.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

The current AAP recommendation is that all infants and children should have a minimum intake of 400 IU (International Units) of vitamin D per day beginning soon after birth.

- **If your baby is exclusively or partially breastfed:** He or she receive 400 IU of supplemental vitamin D daily, beginning in the first few days of life. Supplementation should continue until he or she is weaned to at least 1 qt (1 L) of whole milk per day. Whole milk should not be used until after 12 months of age.

- **If your baby is on infant formula:** All formulas sold in the United States have at least 400 IU/L of vitamin D; so if your baby is drinking at least 32 ounces of formula, vitamin D supplementation is not needed. Whole milk should not be used until after 12 months of age.

臺灣兒科醫學會
Taiwan Pediatric Association

2012年3月15日制訂
2013年8月19日第一次修訂
2016年5月20日第二次修訂

維生素D的補充：

- 維生素D的補充：純餵母乳有引起維生素D缺乏與佝僂症（rickets）的報告。
- 為了維持嬰兒血清中維他命D的濃度，台灣兒科醫學會建議純母乳哺育或部分母乳哺育的寶寶，從新生兒**開始每天**給予400 IU口服維生素D。
- 使用配方奶的兒童，如果每日進食少於1,000毫升加強維生素D的配方奶或奶粉，需要每天給予400 IU口服維生素D。
- 維生素D 的其他來源，例如加強維生素D的食物，可計入400 IU的每日最低攝取量之中。

Calcium

- The calcium content of human milk is fairly constant throughout lactation and is not influenced by maternal diet.
- Human milk meets the calcium requirements of infants during the first 6 months of life.

Iron and Zinc

- The iron endowment at birth meets the iron needs of the breastfed infant in the first half of infancy, i.e. 0 to 6 months.
- If an exogenous source of iron is not provided, exclusively breastfed infants are at risk of becoming iron deficient during the second half of infancy (> 6 mo).
- Net zinc absorption from human milk falls short of zinc needs, which appear to be subsidized by prenatal stores.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

Where We Stand: Iron Supplements

Full-term healthy babies receive enough iron from their mothers in the third trimester of pregnancy to last for the first four months of life.

- **If your baby is breastfed:** Human milk contains little iron, so infants who are exclusively breastfed are at increased risk of iron deficiency after four months of age. The AAP clinical report, *Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children 0 Through 3 Years*, recommends giving breastfed infants 1 mg/kg/day of a liquid iron supplement until iron-containing solid foods are introduced at about six months of age. When you add solid foods to your baby's diet, continue breastfeeding until at least 12 months. Check with your child's pediatrician about the duration of iron supplements during the first year.
- **If your baby is partially breastfed:** The iron recommendation remains the same as that for fully breastfed babies if more than half of the daily feedings are from human milk and the child is not receiving iron-containing complementary foods.
- **If your baby is on infant formula:** It is recommended that you use iron-fortified formula (containing from 4 to 12 mg of iron) from birth through the entire first year of life.
- **Premature babies** have fewer iron stores, so they often need additional iron beyond what they receive from breastmilk or formula.

Universal Screening

In 2010, the AAP began recommending all babies be screened at 12 months of age for iron deficiency and iron deficiency anemia. *See Anemia and Your Child: Parent FAQs for more information.*

2012年3月15日制訂

2013年8月19日第一次修訂
2016年5月20日第二次修訂

鐵及鋅的補充：

- 含有鐵及鋅的副食品可在4-6個月時開始添加
- 4個月後尚未使用副食品之前，應開始每天補充口服鐵劑 1 mg/kg/day

Am Psychol. 2001 Jan;56(1):**5-15**.

Developmental science and the media. Early brain development.

Thompson RA[1], Nelson CA.

Author information

1 Department of Psychology, 238 Burnett Hall, University of Nebraska-Lincoln, Lincoln, NE 68588-0308, USA. rthompson1@unl.edu or canelson@tc.umn.edu

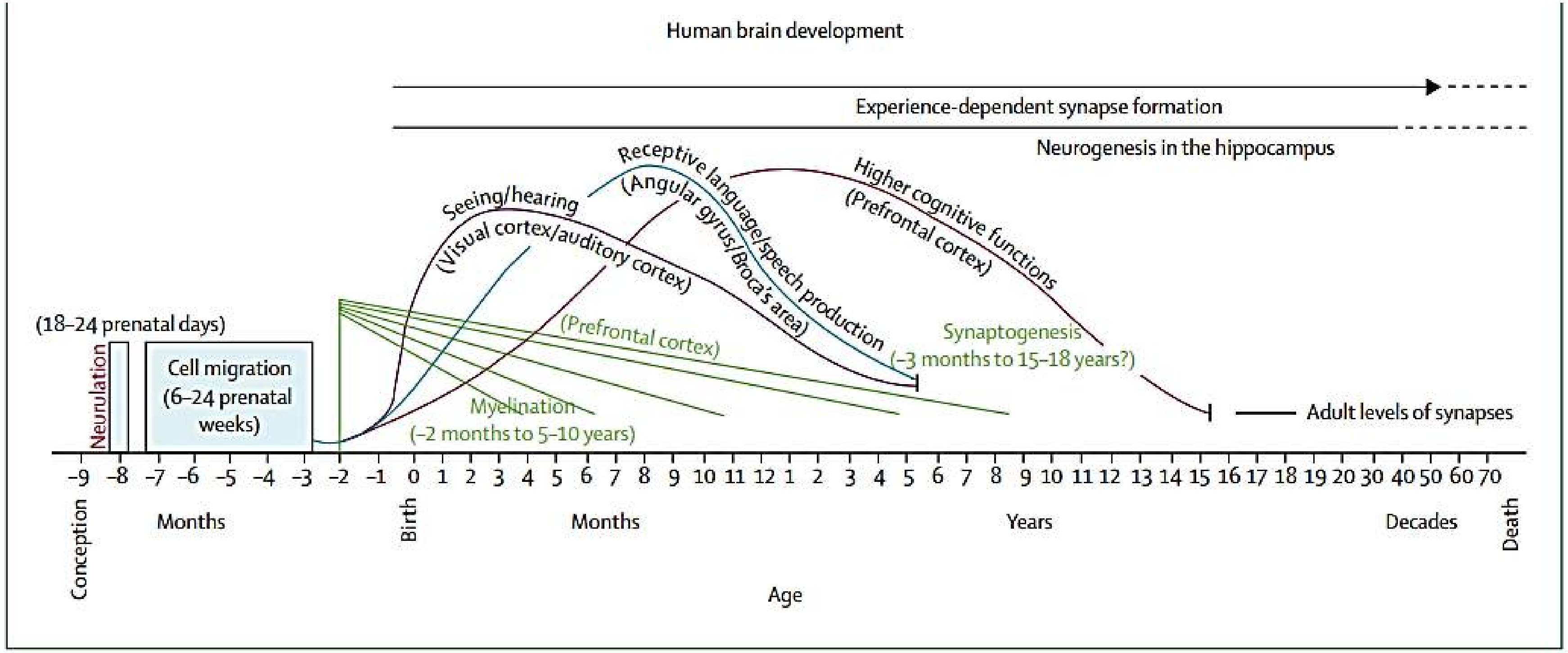


Figure **1: Human brain development**
Reproduced with permission of authors and American Psychological Association[17] (Thompson RA, Nelson CA. Developmental science and the media: early brain development. *Am Psychol* 2001; **56:** 5–15).

J. Nutr. 140: 348–354, 2010.

The Journal of Nutrition
Community and International Nutrition

Weight Gain in the First Two Years of Life Is an Important Predictor of Schooling Outcomes in Pooled Analyses from Five Birth Cohorts from Low- and Middle-Income Countries[1,2]

Reynaldo Martorell,[3*] Bernardo L. Horta,[4] Linda S. Adair,[5] Aryeh D. Stein,[3] Linda Richter,[6] Caroline H. D. Fall,[7] Santosh K. Bhargava,[8] S. K. Dey Biswas,[9] Lorna Perez,[10] Fernando C. Barros,[4] Cesar G. Victora,[4] and Consortium on Health Orientated Research in Transitional Societies Group[11]

[3]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA 30322; [4]Universidade Federal de Pelotas, Pelotas 96090-790, Brazil; [5]Department of Nutrition, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27516-2524; [6]Birth to Twenty Research Programme, University of the Witwatersrand and the Human Sciences Research Council, Durban 4014, South Africa; [7]MRC Epidemiology Resource Centre, University of Southampton, Southampton S016 6YD, UK; [8]S.L. Jain Hospital, Delhi 464551, India; [9]Indian Council of Medical Research, New Delhi 138648, India; and [10]Office of Population Studies Foundation, University of San Carlos, Cebu 6000, Philippines

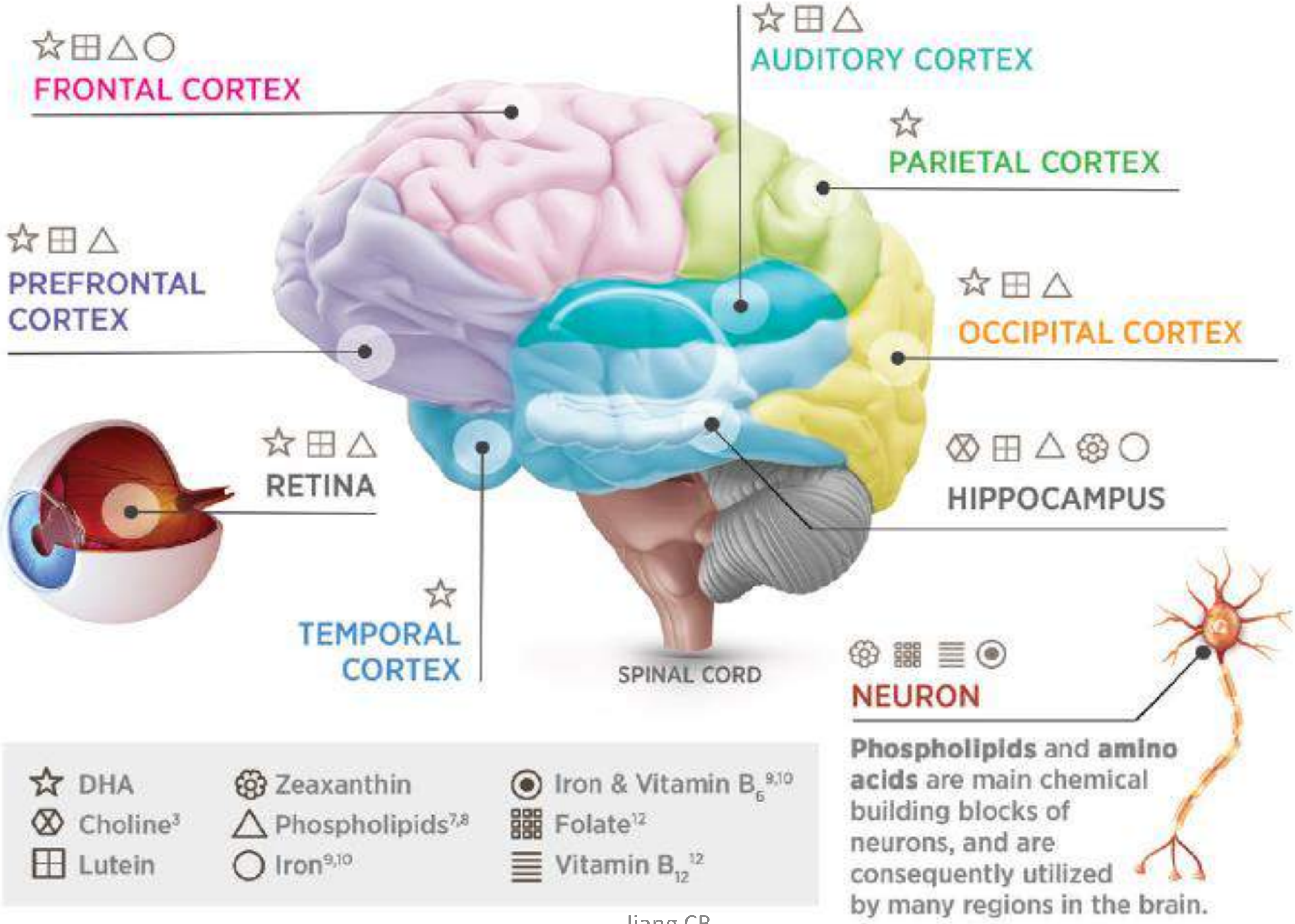
TABLE 1 Characteristics of the COHORTS Studies

Study	Design	Cohort recruitment	Age at recruitment	Initial sample	Age at last visit, *y*	Examined in the last visit, *n*
Pelotas Birth Cohort, Brazil	Prospective cohort	1982	Birth	5914	21–23	4297
INTCS, Guatemala	Community trial	1969–1977	Birth–7 y	2392	26–41	1571
New Delhi Birth Cohort Study, India	Prospective cohort	1969–1972	Before pregnancy	8181	26–32	1583
CLHNS, Cebu Philippines	Prospective cohort	1983–1984	Gestation	3080	21.4	2032
Bt20 cohort, Soweto-Johannesburg, South Africa	Prospective cohort	1990	Gestation	3273	15	2100

Abstract

upper tertile. Relationships with age at school entry were inconsistent. In conclusion, weight gain during the first 2 y of life had the strongest associations with schooling followed by birthweight; weight gain between 2 and 4 y had little relationship to schooling. Catch-up growth in smaller babies benefited schooling. Nutrition interventions aimed at women and children under 2 y are among the key strategies for achieving the millennium development goal of universal primary education by 2015. J. Nutr. 140: 348–354, 2010.

Key nutrients in the brain support cognitive development



The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days"

Sarah E. Cusick, PhD and
Assistant Professor of Pediatrics, University of Minnesota School of Medicine

Michael K. Georgieff, MD
Professor of Pediatrics, University of Minnesota School of Medicine

Critical Processes During Neurodevelopment Affected by Specific Nutrients

J Pediatr. 2016 August ; 175: 16–21.

Neurologic Process	Cell Type	Function	Nutrient Example	At Risk During Late Gestation and 0–3 y
Anatomy				
	Neuron	Division (Neurogenesis) Migration Differentiation (Neurite outgrowth; synaptogenesis)	Protein, Carbohydrates, Iron, Copper, Zinc, LC-PUFA, Iodine, Vitamin A, Vitamin B6, Vitamin D, Vitamin C	Global, Hippocampus, Striatum, Cortex, Retina
	Oligodendrocyte	Myelination	Protein, Carbohydrates, Iron, Iodine, Selenium, Zinc, Vitamin B6, Vitamin B12	Global
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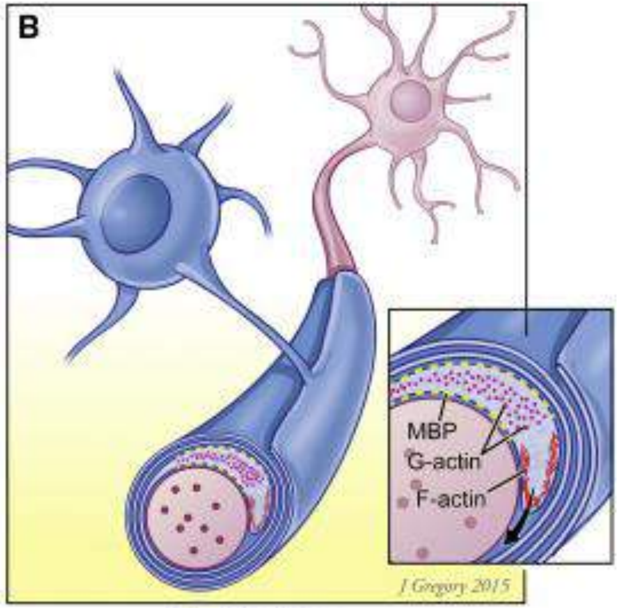
Physiology & Metabolism				
	Neuron Oligodendrocyte	Electrical Efficiency	Glucose, Protein, Iron, Iodine, Zinc, Choline, Copper	Global

The brain developmental trajectories



Myelination

- **Myelination** abruptly increases at 32 weeks gestation and is most active in the first 2 postnatal years.

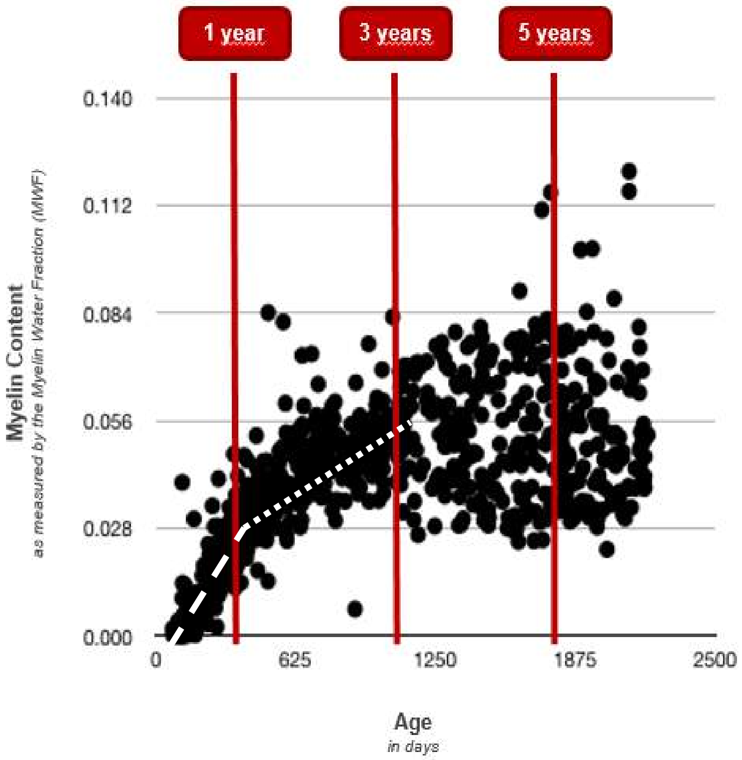
  Child Development. 2010; 81:28–40.

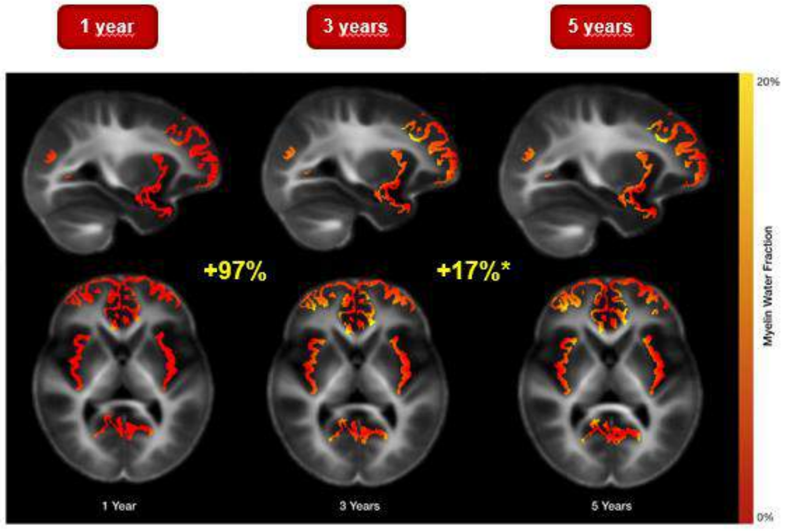
- The monoamine neurotransmitter systems involved in mediating reward, affect, and mood begin their development pre-natally, continuing at a brisk pace until at least age 3 years.

  Infant Behavior and Development. 2008; 31:590–593.

神經髓鞘化 (myelination)

- 髓鞘形成包圍神經元軸突的過程
- 神經髓鞘化使訊息有效率地(速度又快、又準確)傳遞， 是腦部網絡連結發展的必要過程。
- 嬰兒出生後，神經髓鞘化迅速增加，是腦部發展的一個重要標誌。





(more yellow = more myelin in colored areas)

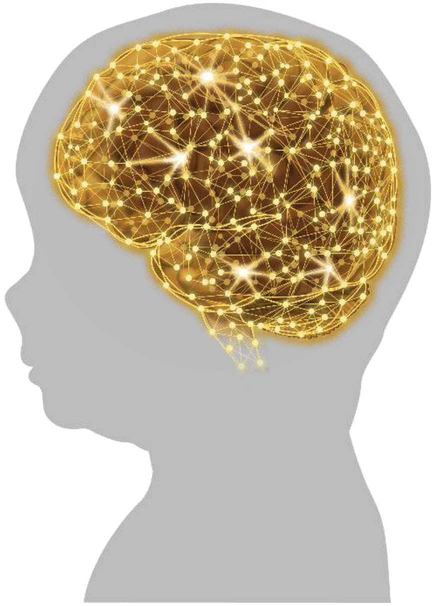
Images: Unpublished data (Prof. Sean Deoni) based on ECHO cohort, N_{1year} =97, N_{3years} = 112, N_{5years} = 84

神經髓鞘化加速大腦網絡發展，與認知能力有關

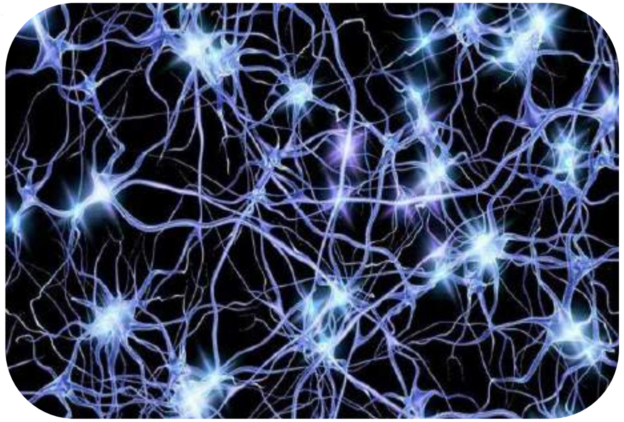
- 一般認知能力
- 語言及閱讀
- 記憶
- 處理速度
- 感官反應

→ **學習的重要技能**

大腦網絡發展**低**:
學習表現較差



大腦網絡發展**高**:
學習表現較好



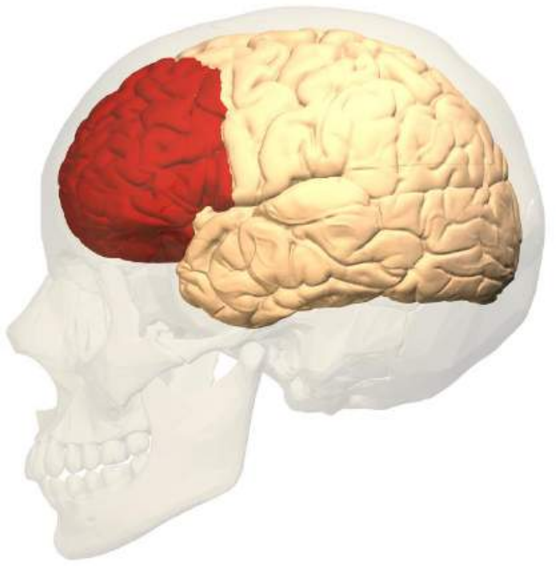
關鍵營養
加速大腦網絡發展

The brain developmental trajectories

- The prefrontal cortex, which orchestrates more complex processing behaviors, such as attention and multi-tasking, has the onset of its growth spurt in the first 6 postnatal months.

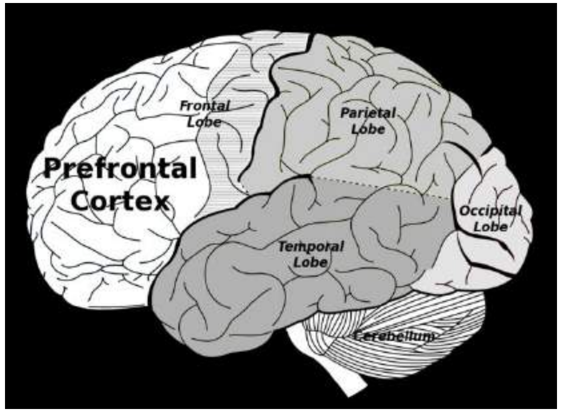
Environmental Health Perspectives. 2000; 108:511–533.

Child Development. 2010; 81:28–40.



- Developmental trajectory is critical to ensure time-coordinated development of brain areas that are designed to work together as circuits that mediate complex behaviors.

Neurobiology of Learning & Memory. 2002; 77:125–184.



- Early life events, including nutritional deficiencies and toxic stress, can have differential effects on developing brain regions and processes based on the timing, dose, and duration of those events.

American Journal of Clinical Nutrition. 1996; 63:997S–1001S.

- The importance of timing in particular should be underscored.

Arch Ped Adolesc Med. 2012; 155:481–482.

Critical period & Sensitive period

- **Critical periods** are typically conceptualized as early-life epochs when alterations to brain structure or function by an environmental factor (eg, nutrition) result in **irreversible** long-term consequences

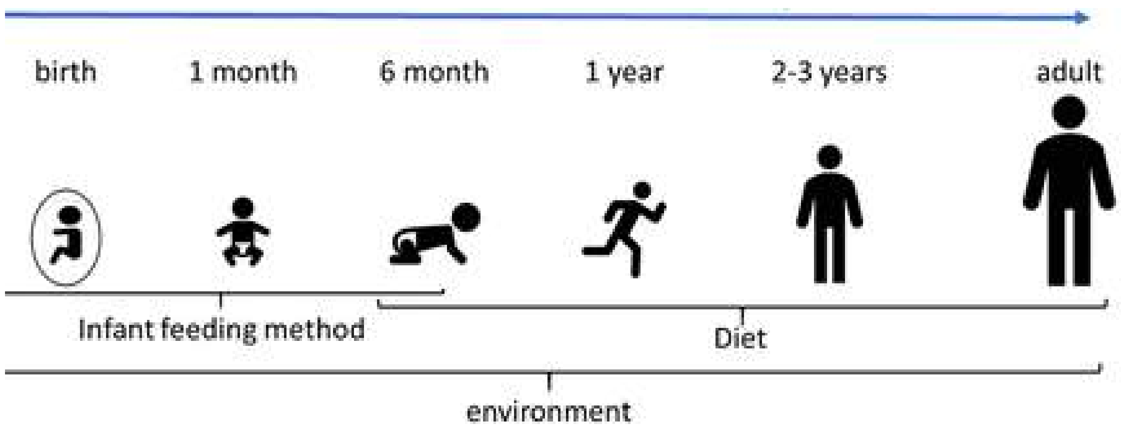
Psychological Bulletin. 1989; 105:179–197.

- **Sensitive periods** imply an epoch when the brain (or brain region) is more vulnerable to environmental factors, including nutrient deficiencies. /It can also be used in a positive manner to describe times when the brain may be particularly receptive to positive nutritional or social stimulation.

Psychological Bulletin. 1982; 91:260–275.

- Either concept emphasizes the need for pediatricians to focus on making sure the child is receiving **adequate nutrition** to promote normal **brain development** in a **timely** fashion.

Prog Brain Res. 2013; 207:3–24.
Development and Psychopathology. 2015; 27:411–423.



- **All nutrients are important for brain growth and function.**
- But certain ones have particularly significant effects during early development.
- **Key nutrients** for brain development are defined as those for which deficiency that is concurrent with sensitive or critical periods early in life results in long-term dysfunction.

Critical Processes During Neurodevelopment Affected by Specific Nutrients

J Pediatr. 2016 August ; 175: 16–21.

Neurologic Process	Cell Type	Function	Nutrient Example	At Risk During Late Gestation and 0–3 y
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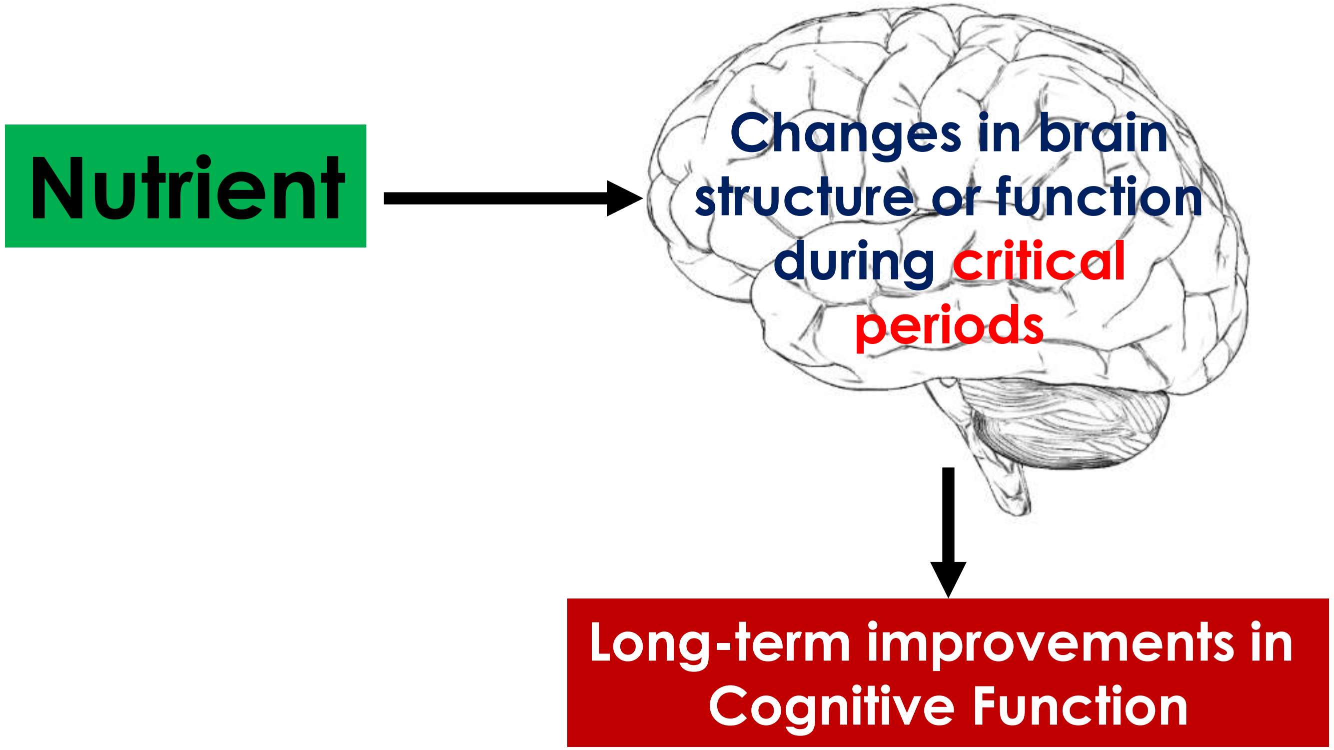
Physiology & Metabolism				
	Neuron Oligodendrocyte	Electrical Efficiency	Glucose, Protein, Iron, Iodine, Zinc, Choline, Copper	Global

The Role of Nutrition in Cognitive Development

Direct effects of nutrition on the brain



4大關鍵營養 幫助神經髓鞘化加速大腦網絡發展

3

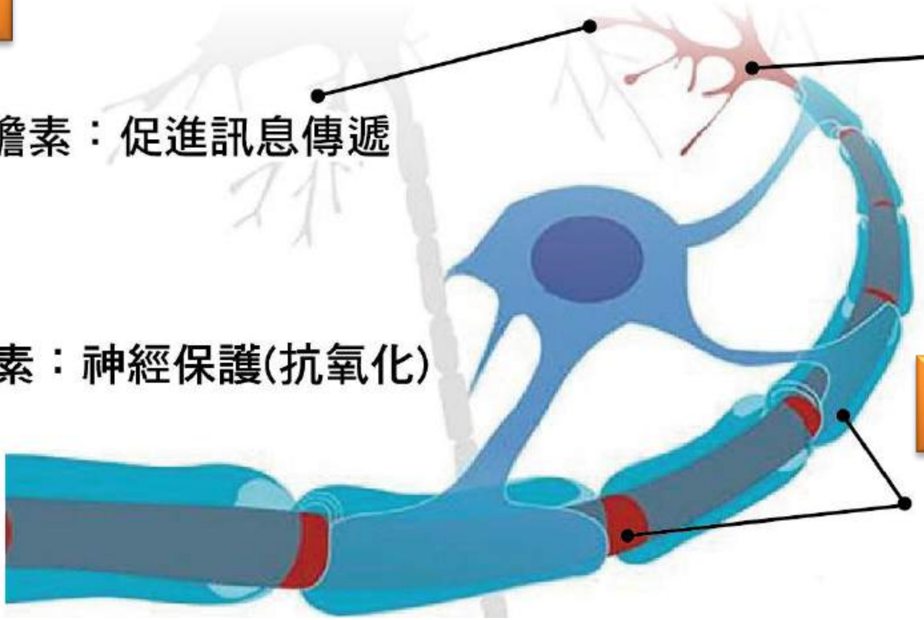
DHA：參與神經生成

4

膽素：促進訊息傳遞

5

葉黃素：神經保護(抗氧化)



1

神經鞘磷脂：髓鞘的構成成份，
保護神經細胞，支持效率傳遞訊息

2

gangliosides Milk Origin-乳源神經節苷脂