Role of Gut Microbiota on Good Health

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Topics of Presentation

1. Gut Microbiota
2. Dysbiosis
   (imbalance of gut microbiota composition)
3. DOHaD and Dysbiosis
4. Gut-Brain Axis
5. Beneficial Effects of Breastfeeding

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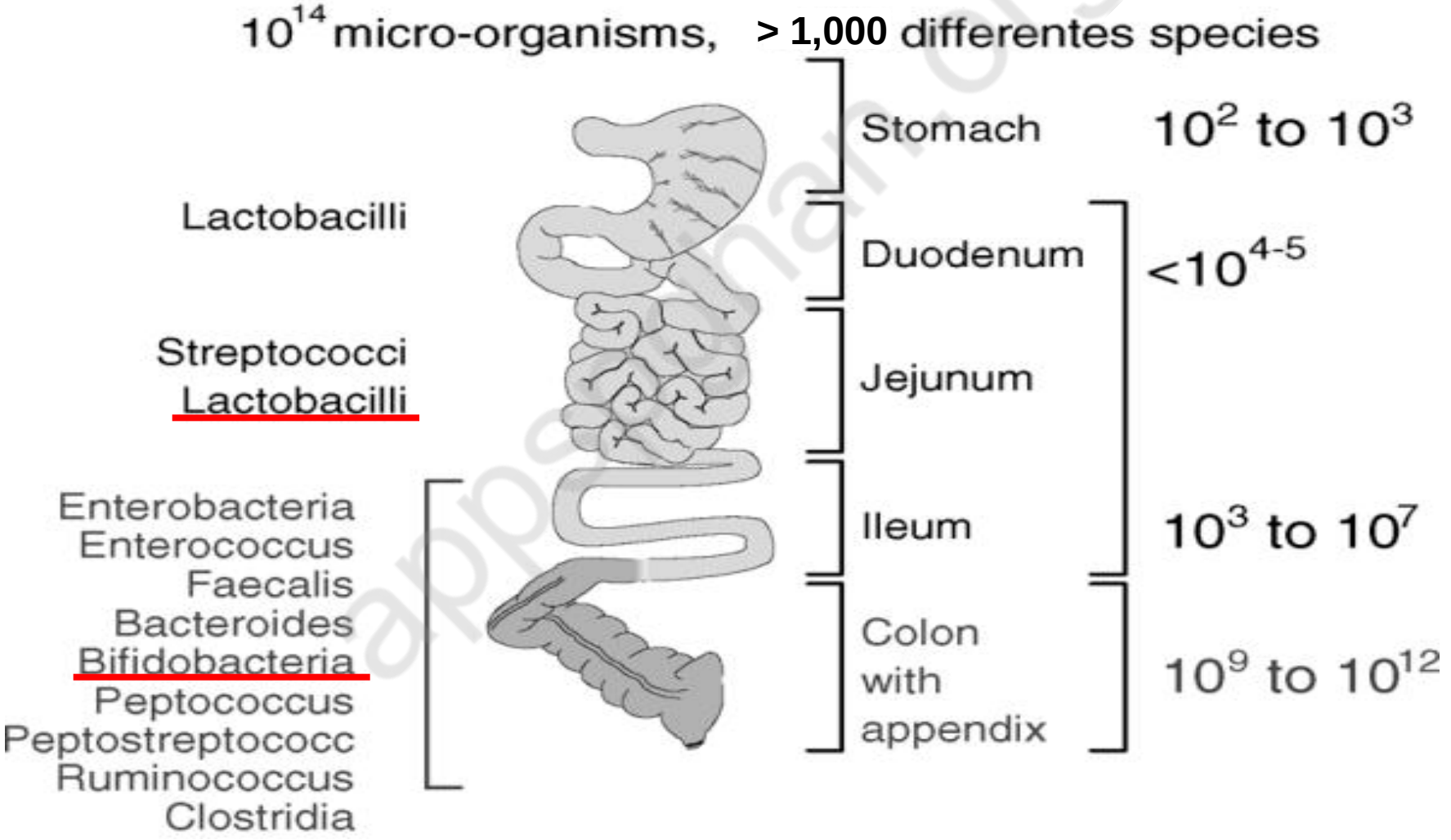
Gut Microbiota
— your best partner forever —



Transmission of beneficial bacteria including *Bifidobacterium* and *Lactobacillus* from Mother to Infant

Bifidobacterium

Lactobacillus

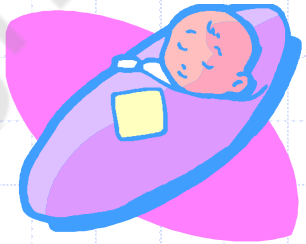
The birth canal

The maternal anus

Bifidobacterium

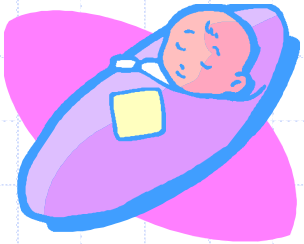
Lactobacillus

Delivery

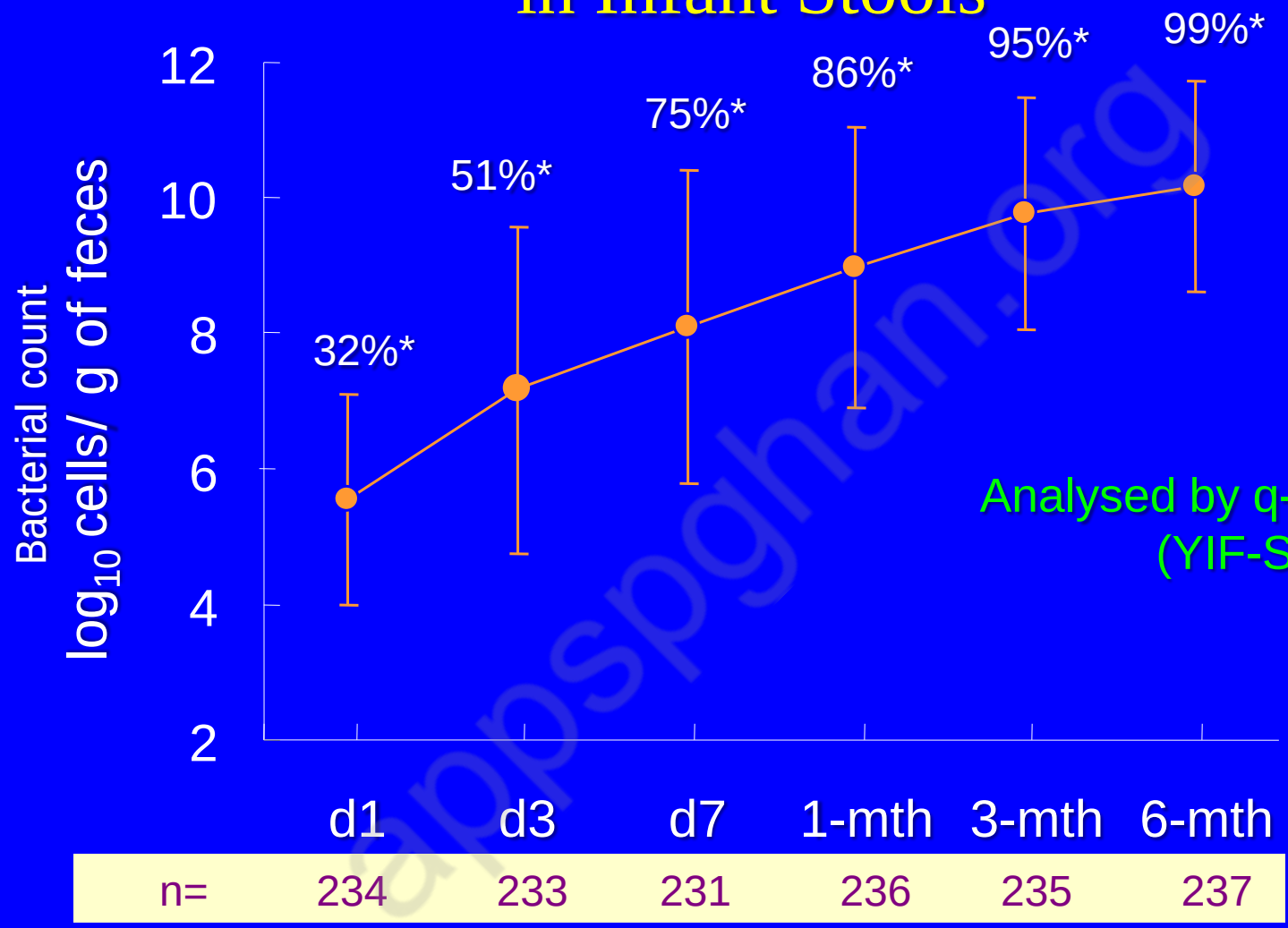


Breast milk

1 month



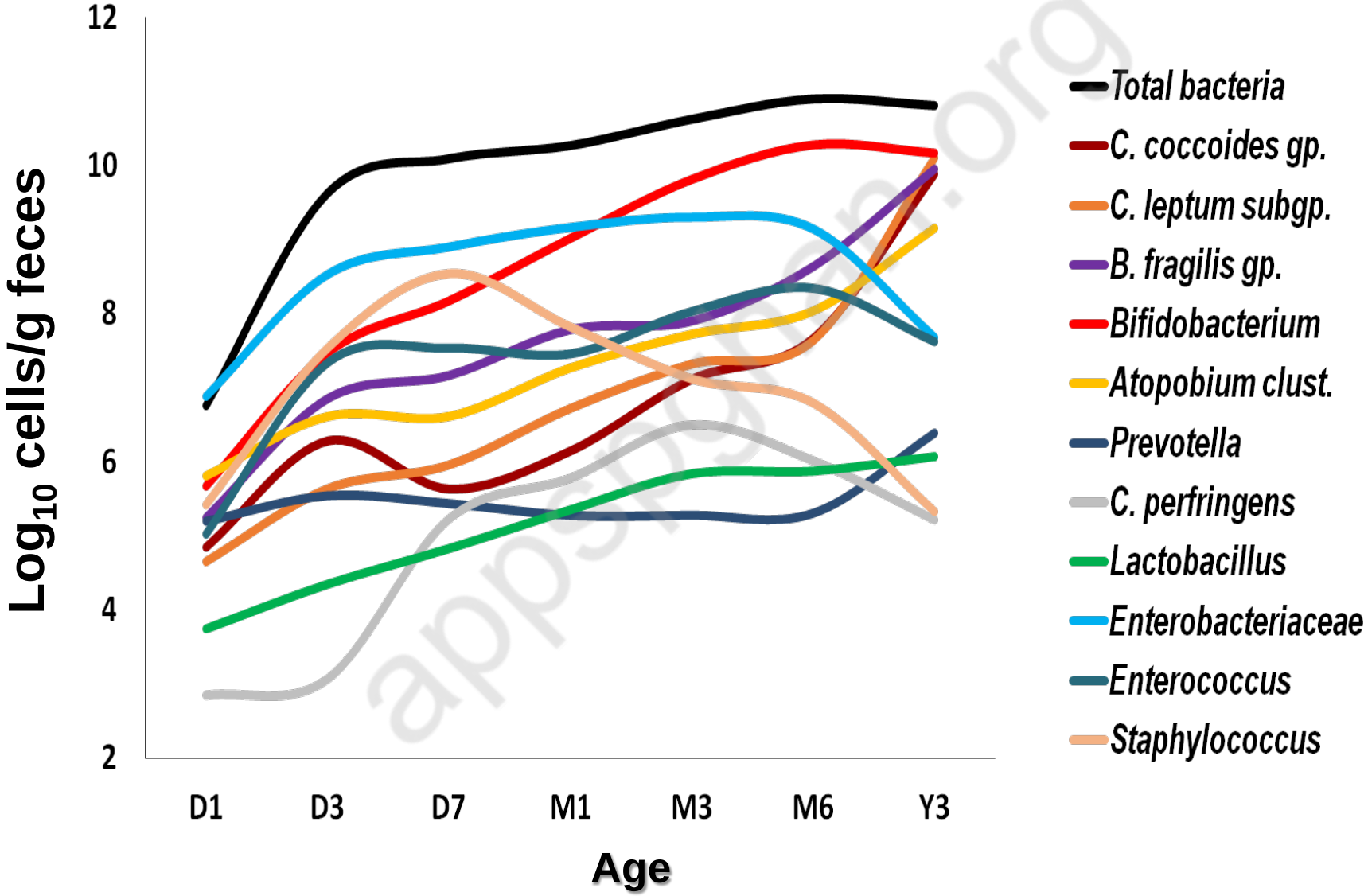
Changes in the population level of bifidobacteria in Infant Stools



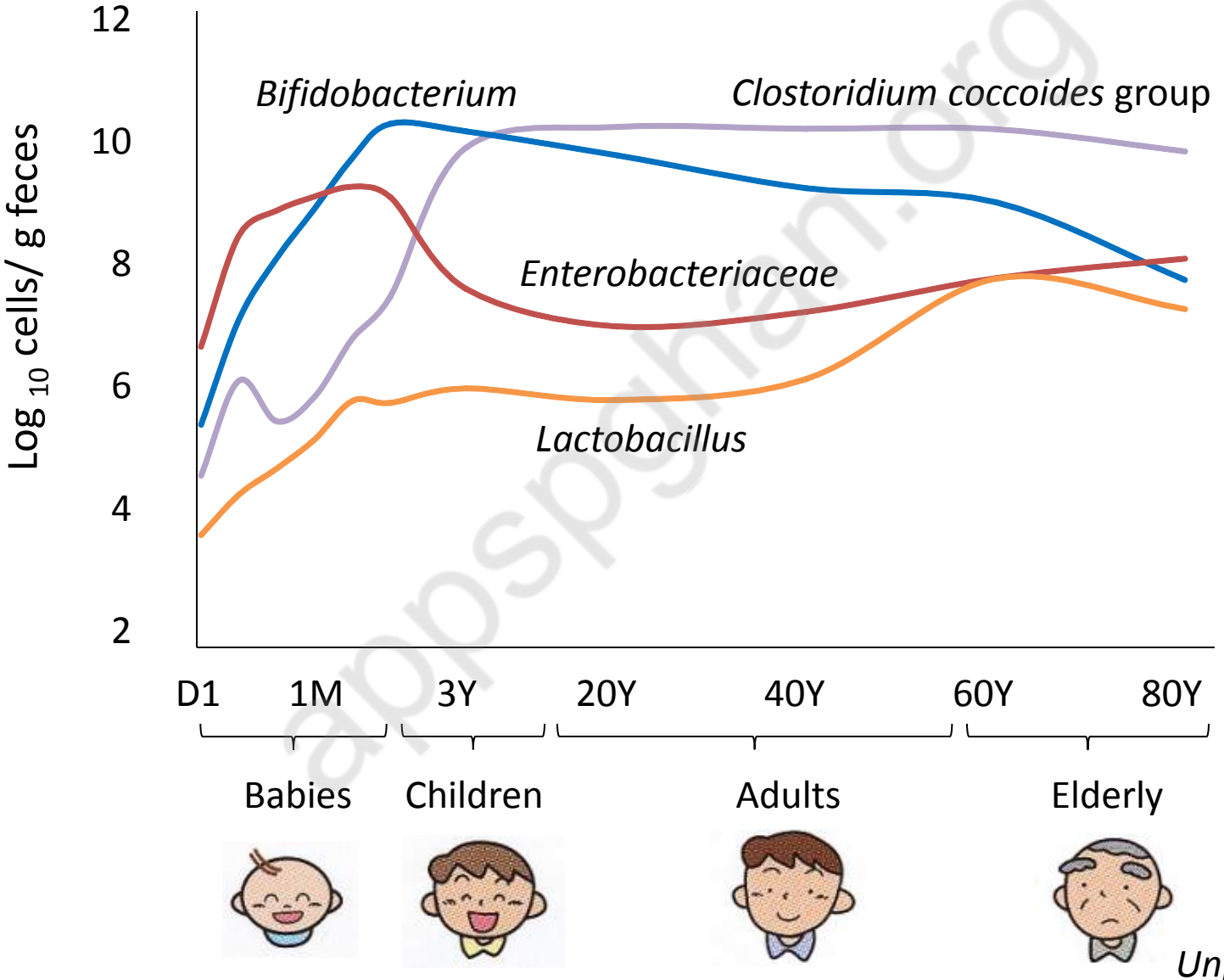
Results: mean ± SD, * Prevalence of bifidobacteria

（Tsuji, et al. 2012）

Bacterial count during the first 3 years of life



Gut microbiota continues to change over life from infancy to old age



Unpublished data

Roles of Intestinal Commensal Bacteria

1. Maintain the gut environmental and Eliminate pathogenic bacteria
2. Improve digestion and absorption of nutrients
3. Enhance the gut immune function
    1) Boost production of antibacterial proteins (e.g. defensins)
    2) Activate lymphocytes
4. Regulates host metabolism through the production of SCFAs from dietary fibers in the color.
5. Impact on Brain function and Behavior

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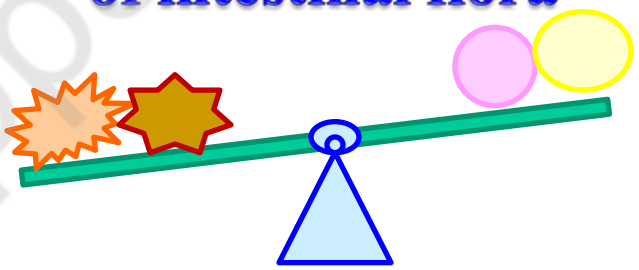
Factors contributing to the loss of balance of intestinal flora

Drugs (antibiotics)

Unbalanced diets, high fat diets, high calorie diets

Bacterial contamination

Disturbance of the balance of intestinal flora



gut dysbiosis

Stress, Overwork

Aging

Factors Influencing the Establishment of the Intestinal Flora in Newborns

1. Delivery mode
2. Drugs
3. Dietary changes
4. Stress

INTESTINAL MICROBIOTA IN PRETERM NEWBORNS

― Unique Feature of the Microflora ―

LBW Newborn

Most infants are born by Cesarean Section

↓

Lack of opportunities to obtain maternal bacteria (vaginal & fecal)

Int. microflora obtaining in NICU,

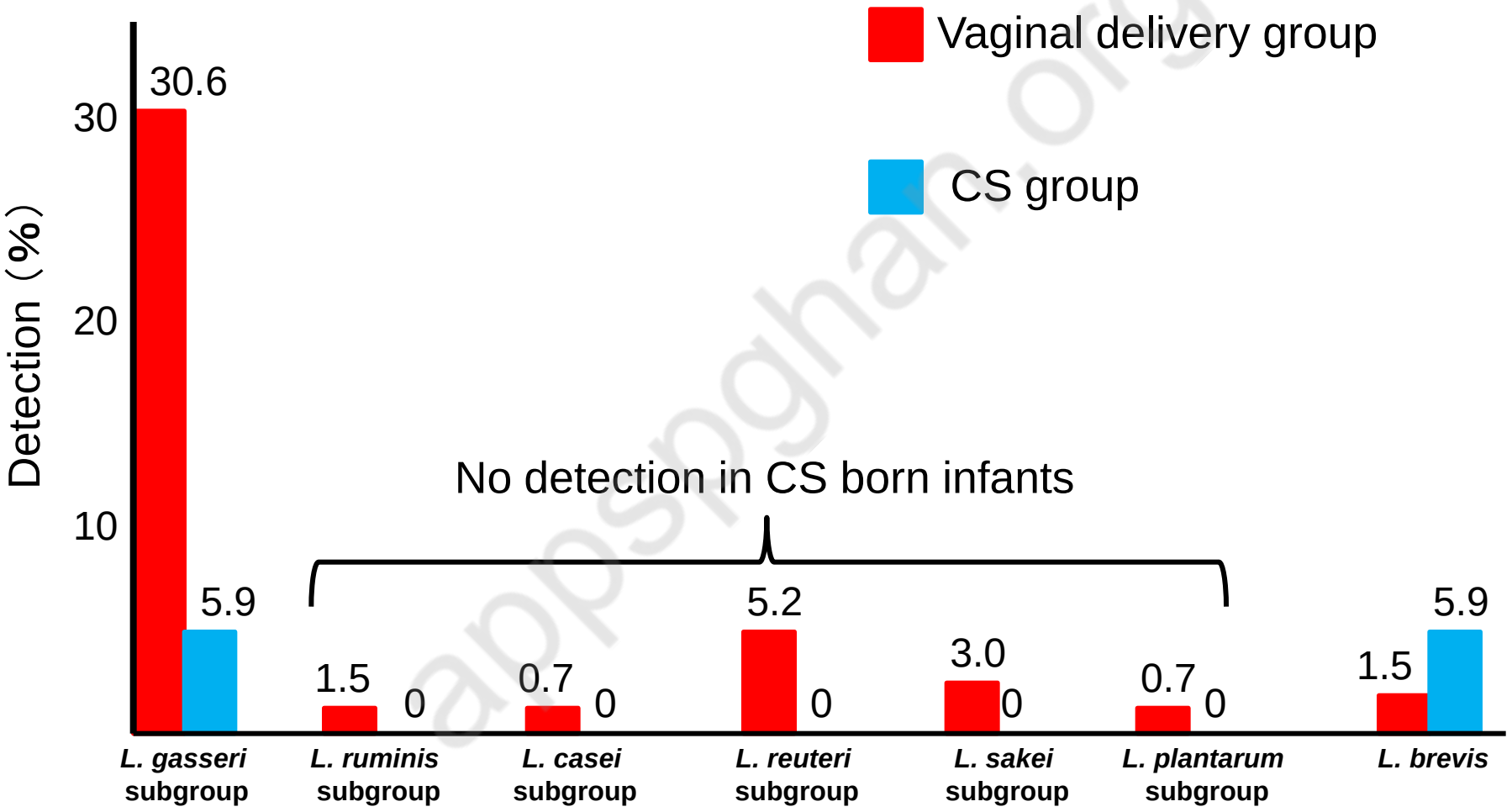
influenced by antibiotics

anaerobic ↓

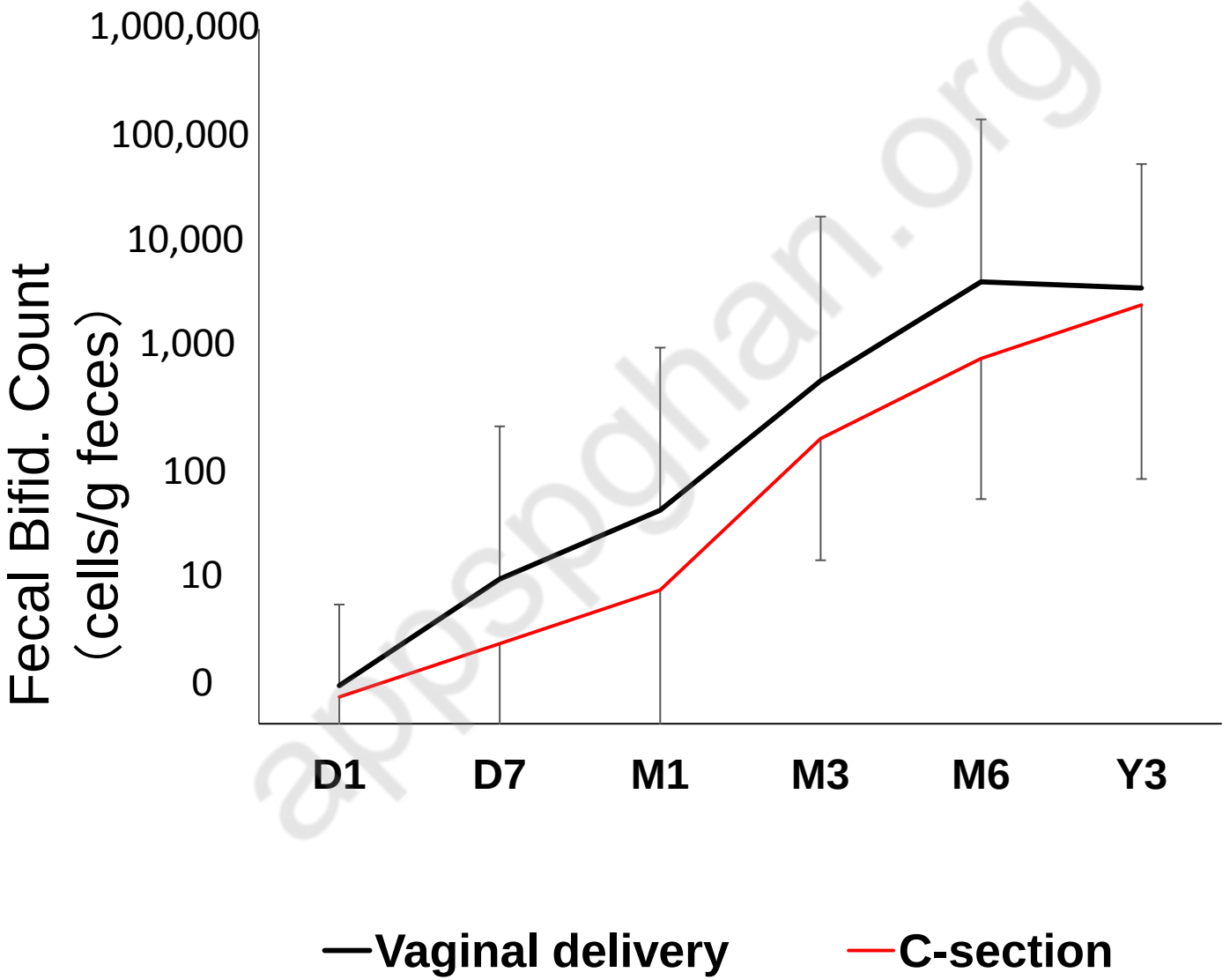
enterobacteria ↑ (klebsiella,Enterobacter,citrobacter),

pseudomonads ↑ , MRSA ↑

Prevalence of Lactobacillus subgroups/ species in the meconium of healthy Japanese infants



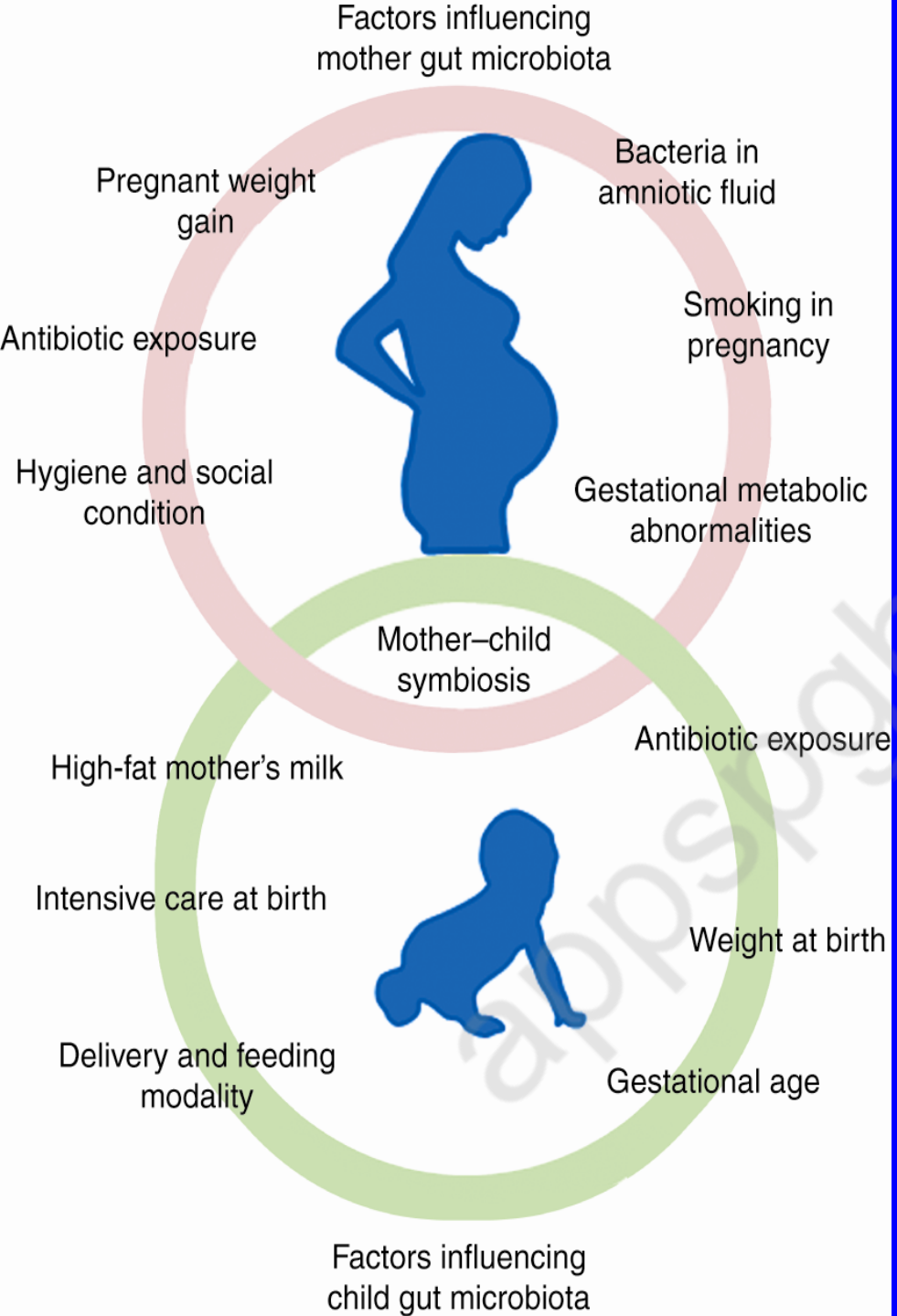
Differences in fecal Bifidobacterium carriage by delivery mode during first 6 months and at 3 yrs of life



Gut Flora of Cesarean-born Infants, Children & Young Adults
-in comparison to vaginally-born subjects- - our study

- less diversity
- Beneficial microbe:
  Obligate anaerobe: *Bifidobacterium*
  Bacteroides
  Facultative anaerobe: *Lactobacillus*
  } less count (Tsuji, et al. 2012)
- α-toxigenic & enterotoxigenic *C. perfrigens*
  - significantly higher in infants and children. (Nagpal, et al. 2015)

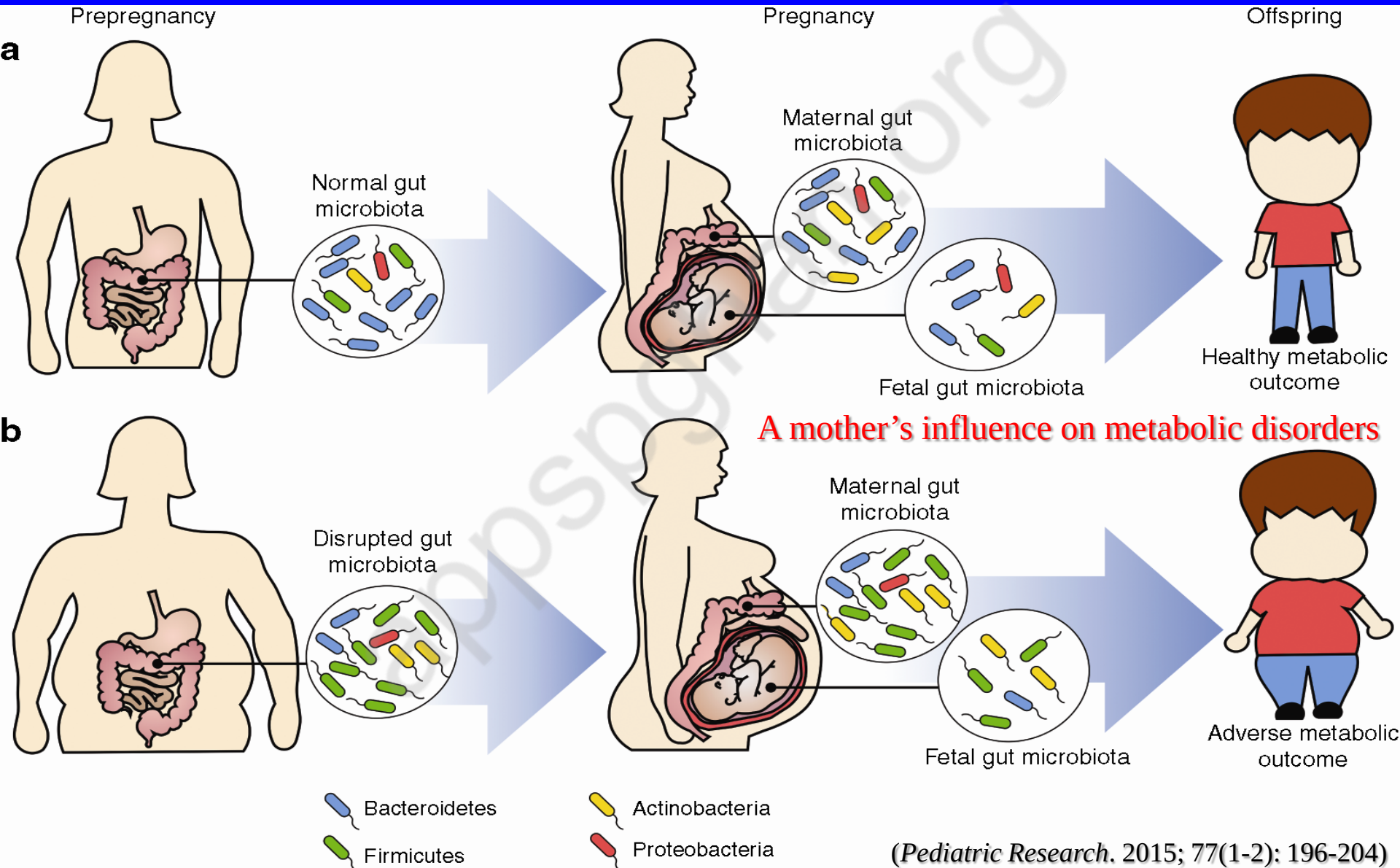
  C. difficile, corynebacterium
  Staphylococcus, propionibacteria
  } predoninat (reported by others)
- *Stephylococcus, Enterococcus*
  - significantly higher in young adults (Nagpal, et al. 2018)



Mother–child symbiosis elements affecting the onset and modulation of the newborn gut microbiota

(*Pediatric Research*. 2014; 76(1): 2-10)

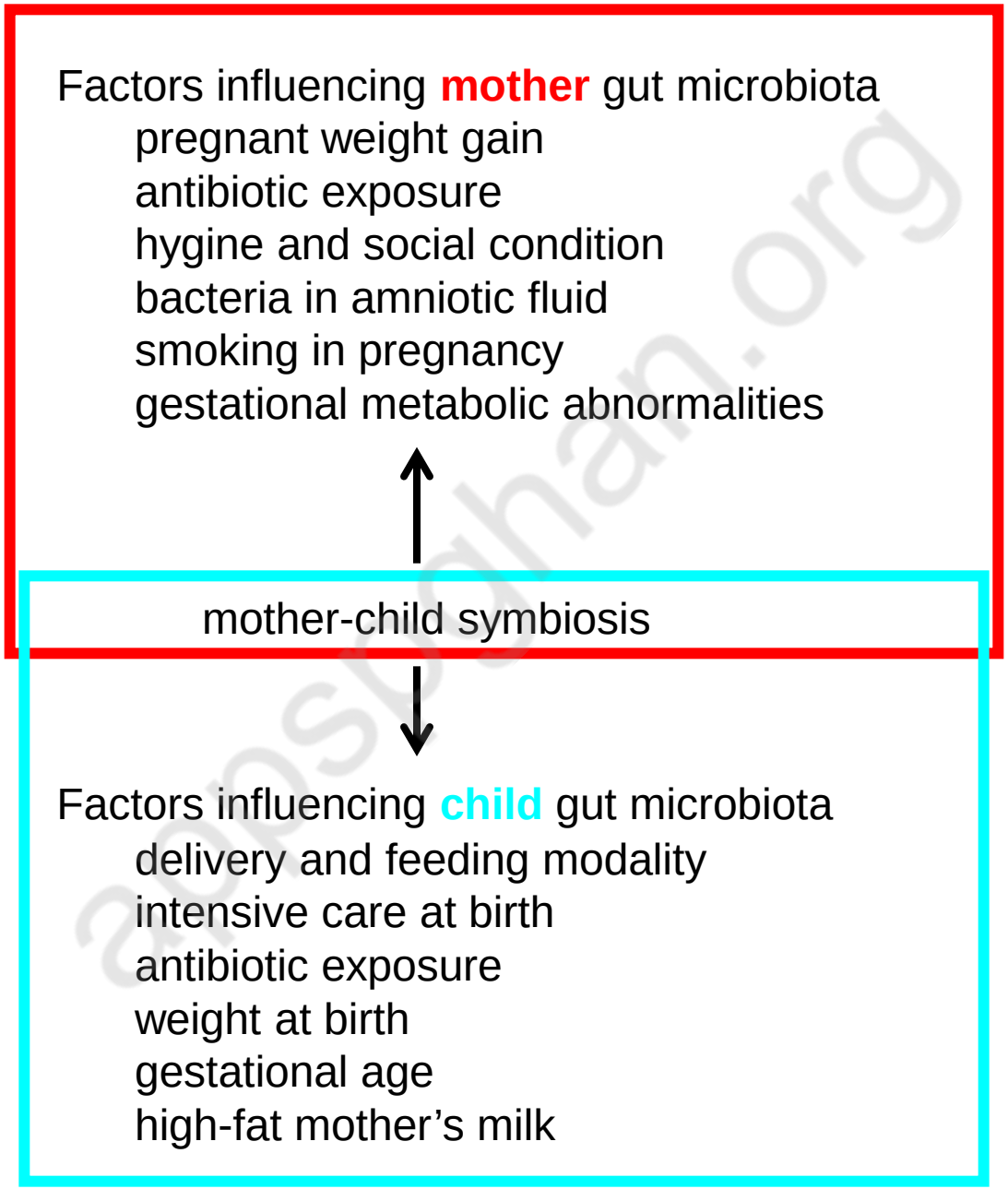
Overview of maternal gut microbiome modulation with pregnancy ±obesity



A mother's influence on metabolic disorders

(*Pediatric Research*. 2015; 77(1-2): 196-204)

Factors influencing child gut microbiota



(Putignani, et al)

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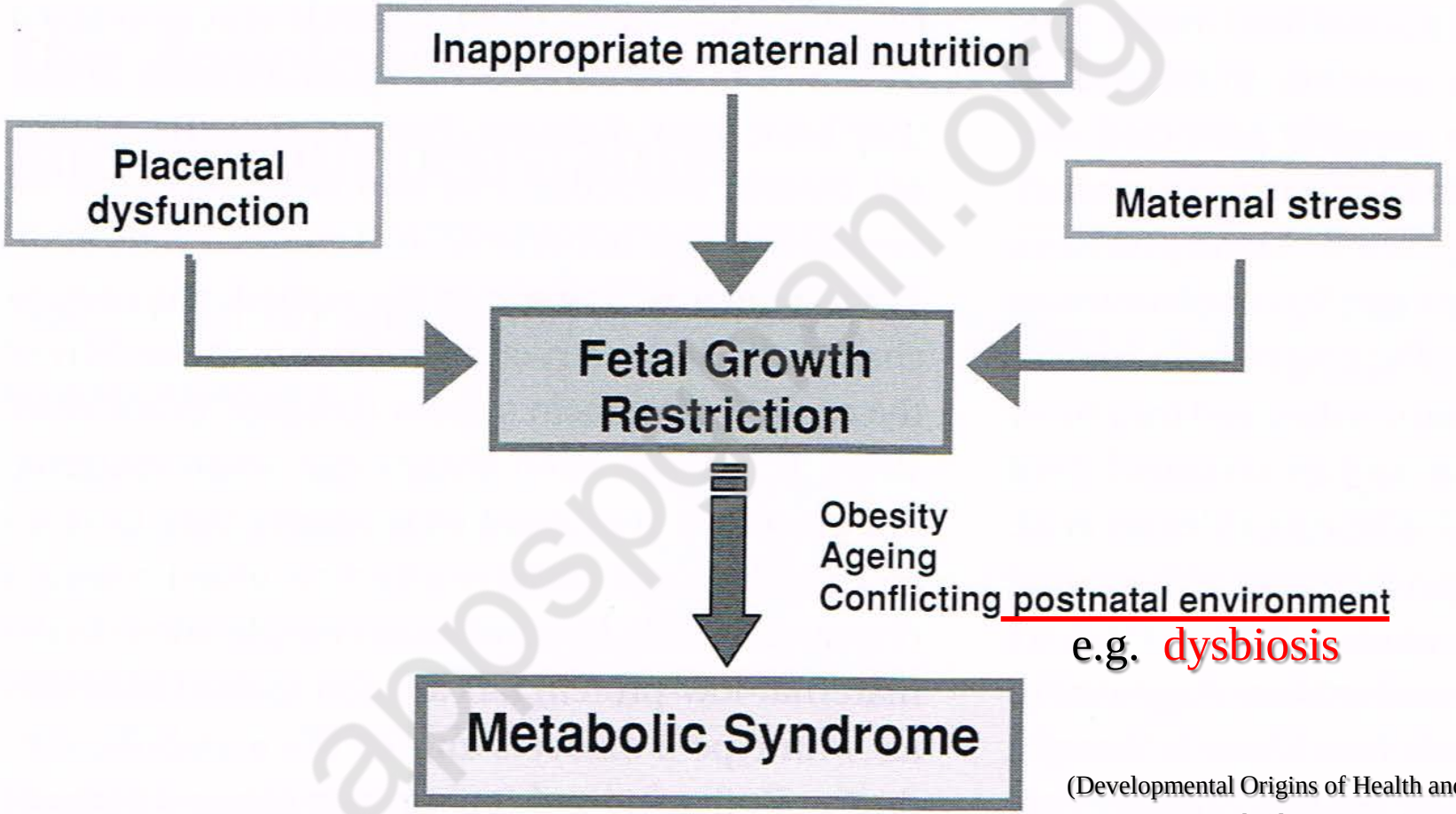
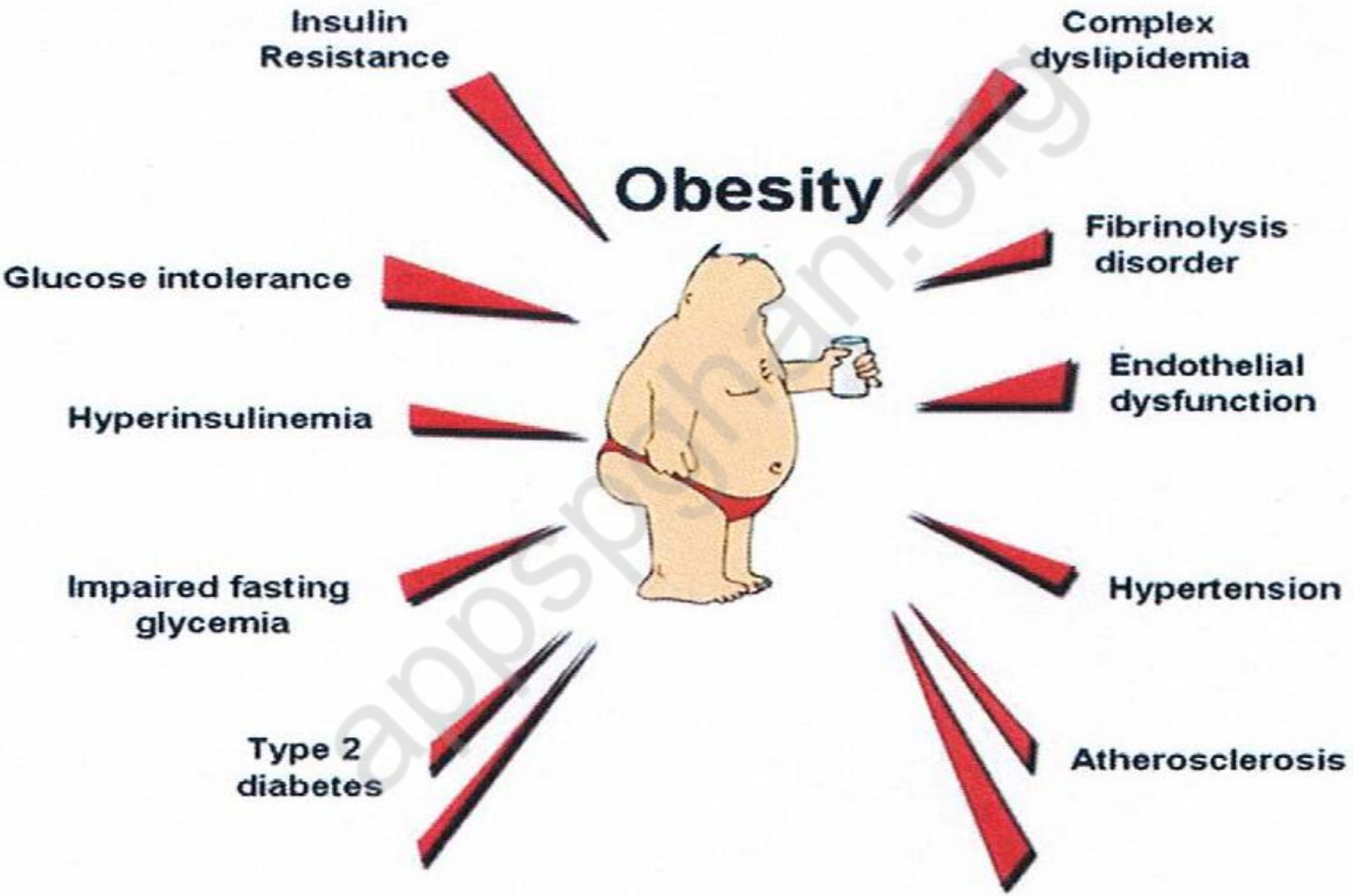
Developmental Origin of Health Disease (DOHaD)
Fetal origins of adult disease



(Developmental Origins of Health and Disease. Cambridge University Press. 2006)

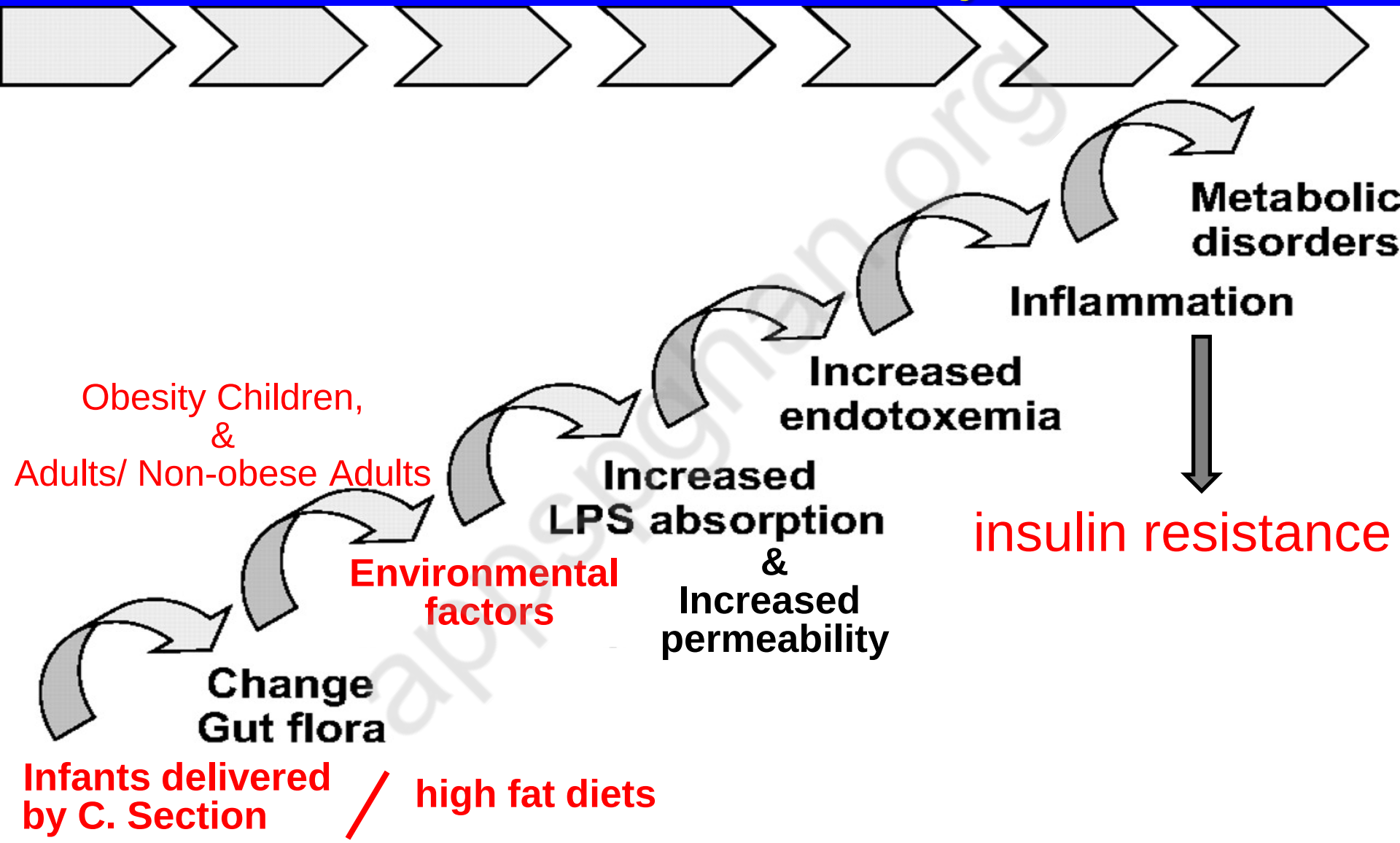
* Early-life environment factors can have lifelong effects and can manifest disease in later life

Obesity and associated metabolic disorders



(Patrice D. Cani, et al.
Current Pharmaceutical Design 2009)

Hypothesis for Gut Dysbiosis Induced Metabolic Disease
- based on DOHaD theory -



(Modified of Patrice D. Cani, et al. *Diabetes*. 2008; 57: 1470-1481)

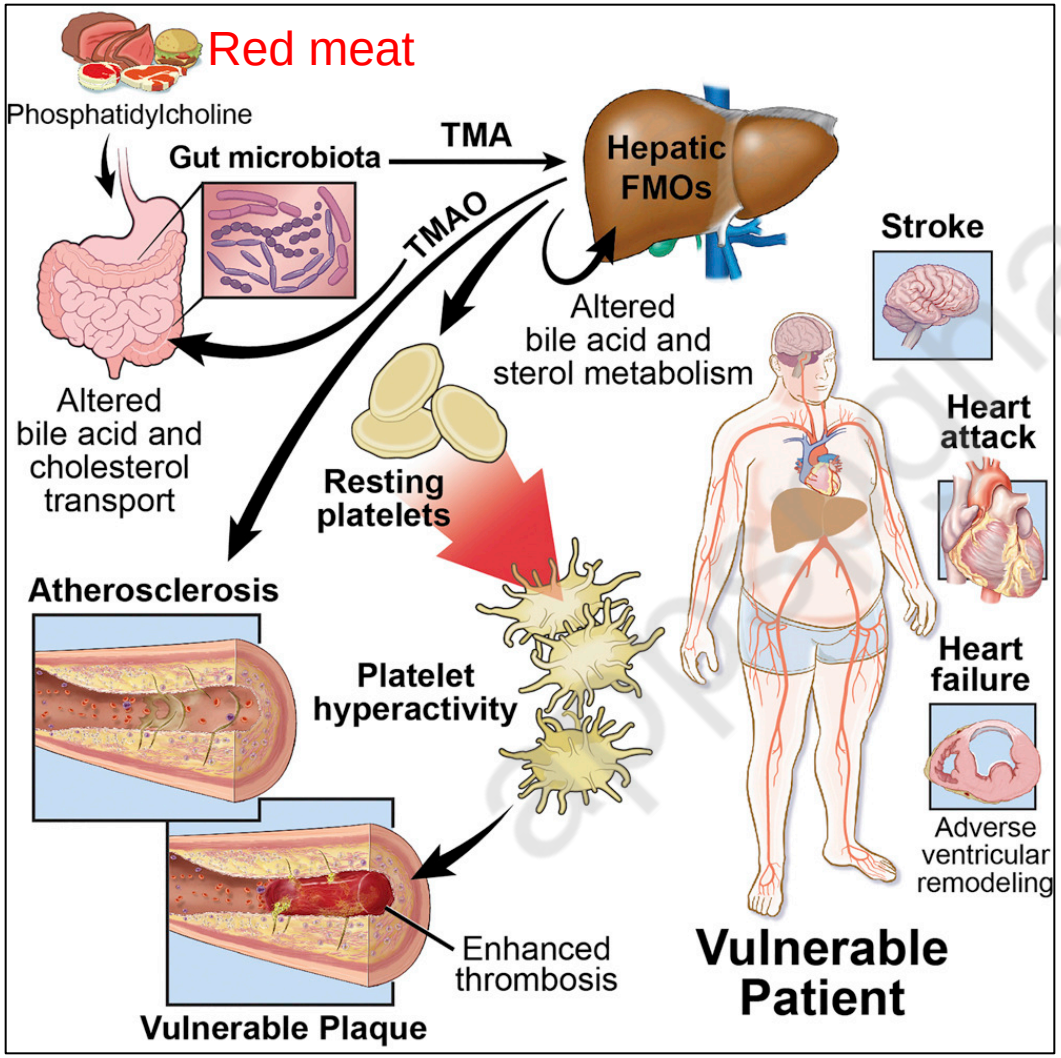
Gut Dysbiosis and Detection of "Live Gut Bacteria" in Blood of Japanese Patients With Type 2 Diabetes

Diabetes Care 2014;37:2343–2350 | DOI: 10.2337/dc13-2817

Junko Sato,[1] Akio Kanazawa,[1,2] Fuki Ikeda,[1] Tomoaki Yoshihara,[1] Hiromasa Goto,[1] Hiroko Abe,[1] Koji Komiya,[1] Minako Kawaguchi,[1] Tomoaki Shimizu,[1] Takeshi Ogihara,[1] Yoshifumi Tamura,[1,3] Yuko Sakurai,[1] Risako Yamamoto,[1] Tomoya Mita,[1] Yoshio Fujitani,[1,4] Hiroshi Fukuda,[5] Koji Nomoto,[6] Takuya Takahashi,[6] Takashi Asahara,[6] Takahisa Hirose,[7] Satoru Nagata,[8,9] Yuichiro Yamashiro,[8] and Hirotaka Watada[1–4,10]

Large Consumption of Red Meat Kills People

The nutrients in red meat, L-carnitine and phosphatidylcholine are metabolized by gut microbiota leading to cardiovascular events.



（Zhu W, et al. *Cell*. 2016;165:111-124）

- Elevated TMAO levels predict incident risk for thrombotic events in human subjects
  - TMA; trimethylamine,
  - TMAO; trimethylamine-N-oxide

Elevated plasma level of TMAO was associated increased risks of major adverse cardiovascular events and all-cause mortality (Meta analysis in USA).

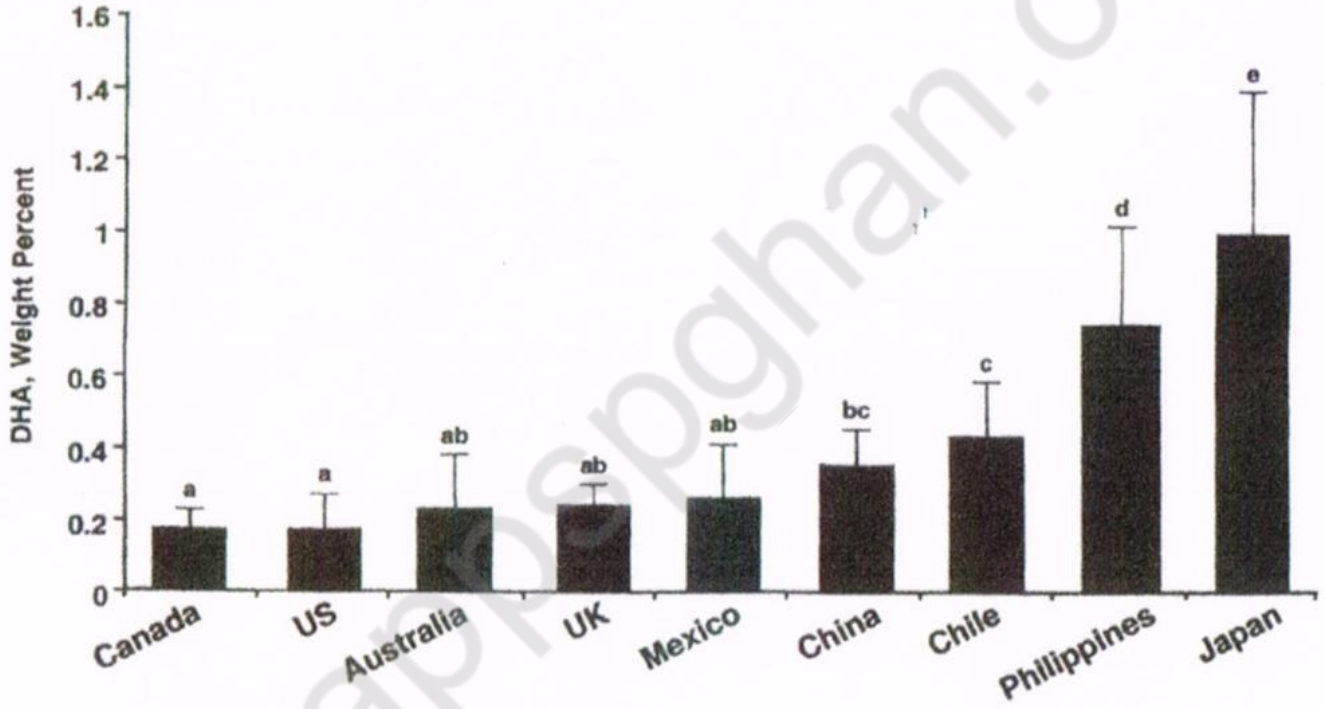
Yoriko Heianza, et al. 2017, *J Am Heart Assoc*.

Median per capita daily consumption (g/day) of egg, fish and meat based on 2009-2011 FAO Food Balance Sheets

Countries	Egg	Fish, seafood	Bovine, meat	Mutton Goat, meat	Poultry, meat	Pig meat	Meat, other	Total meat
European Union	29.8	49.9	40.7	3.1	52.0	85.0	4.2	185.0
Australia & New Zealand	19.0	42.7	82.5	37.4	86.5	50.8	5.0	262.2
USA & Canada	30.3	36.9	80.3	1.7	102.0	62.7	1.1	247.8
China	45.3	75.5	11.9	7.1	31.7	87.9	2.8	141.4
Japan	51.3	130.0	22.4	0.5	45.5	50.6	0.3	119.3
Developing Countries (GNI 2-4)	10.5	23.9	16.3	3.5	30.3	11.3	1.2	62.6

（*Ann Nutr Metab*. 2016;68(4):258-67.）

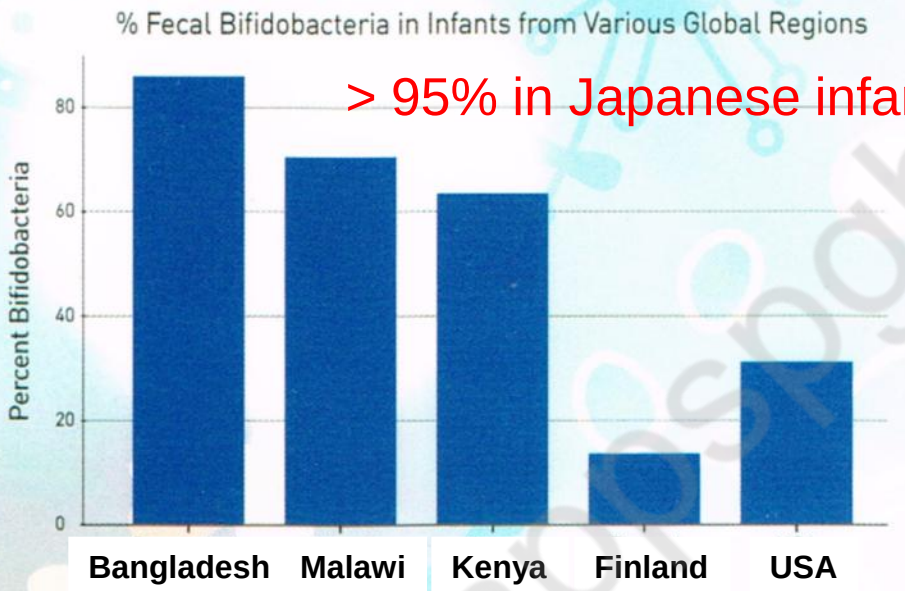
DHA in Breast Milk 9 in countries (DHA/AA: Lowest in Japan)



DHA as weight percent of total FA in mature human milk of women from nine countries. Values are means ± SEM with 44 to 54 samples per group. Means with different superscripts are statistically different ($P < 0.05$).

Lipids, Vol. 41, no. 9 (2006)

Levels of Bifidobacteria in Infants in the United States Have Fallen Well Below Those in Developing Countries[1-5]



- Differences in bifidobacteria are due to increased rates of C-section delivery, antibiotic use, and feeding practices other than exclusive breast-feeding
- Lower levels of bifidobacteria in the infant gut have been linked to increased incidence of metabolic and inflammatory disorders

References:
1. Bangladesh: Huda et al. *Pediatrics*. 2014;134.2:e362-e372.
2. Malawi: Grzeskowiak et al. *JPGN*. 2012;54.6:812-816.
3. Kenya: Jaeggi et al. *Gut*. 2015;64.5:731-742.
4. Finland: Yassour et al. *Sci Transl Med*. 2016;8.343:343ra81.
5. USA: Lewis et al. *Microbiome*. 2015;3.1:1.

Tripling of T2Diabetes in USA

"A staggering tripling of diagnosed cases of diabetes in the USA: from 6·2 million cases in the late 1980s to 21·1 million cases in the early 2010s."

Lancet

Volume 391 · Number 10138 · Pages 2389-2474 · June 16-22, 2018

	Overweight & Obesity in Children	Average (M&F) lifespan in 2016
U S A	35%	78.5 y (34th)
Japan	10%	84.2 y (Top)

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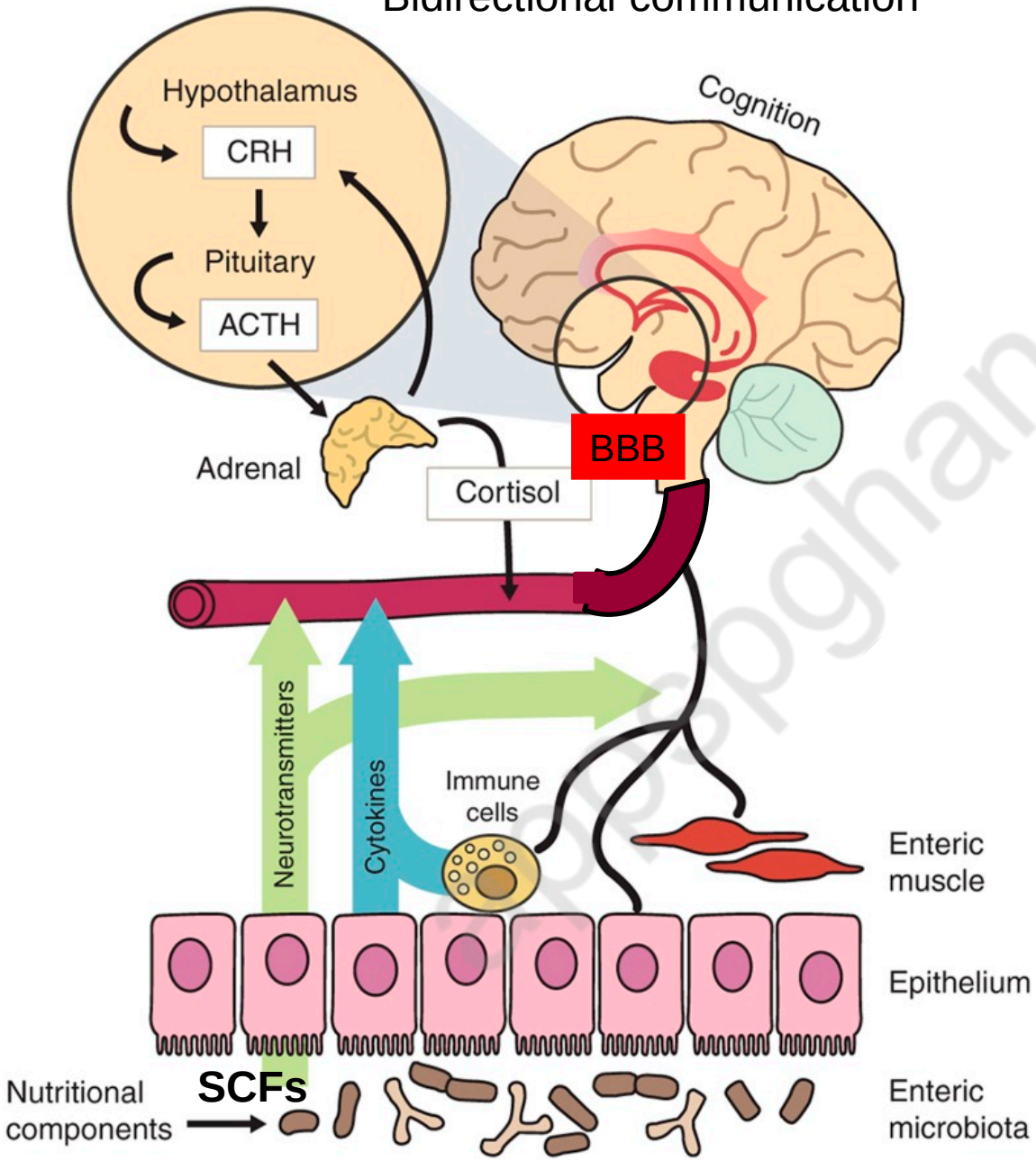
Gut Brain Axis

— Bidirectional communication —



Gut Microbiota Affects Blood-Brain Barrier Permeability in both the Fetal and Adult Brain

The reciprocal interaction between gut microbiota and the brain. Gut microbiota may modulate brain function and development through immune signaling (e.g., pro- and anti-inflammatory cytokines, chemokines, and immune cells), endocrine, and neural pathways.

Gut Microbiota Affects Blood-Brain Barrer Permeability in both the Fetal and Adult Brain

Maternal Gut Microbiota during Gestation

↓

B B B

Tight Junction (claudins, tricellulin, ZO-1)

Restricting diffusion of substances from blood to the Brain

Physiological & Pathophysiological conditions

Infants of Preterm & C-section born

Gut Microbiota

SCFAs, metabolite

↓

Dysruption of tight junction

↓

Metabolic synd
Ageing

Inflammatory cytokines

↓

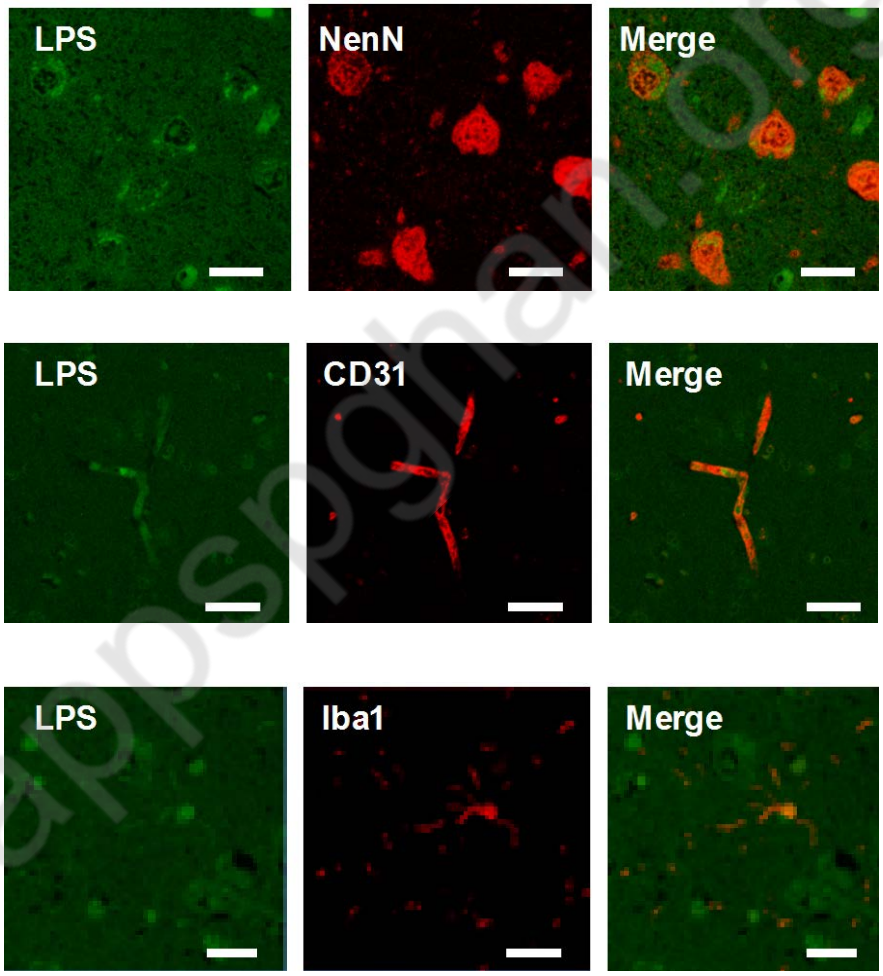
Increased Permeability of BBB (Impaired **BBB** function)

↓

Compromising the CNS

Detection of LPS in the peri-infarct area of a patient with stroke by immunofluorescence staining

Stroke patient

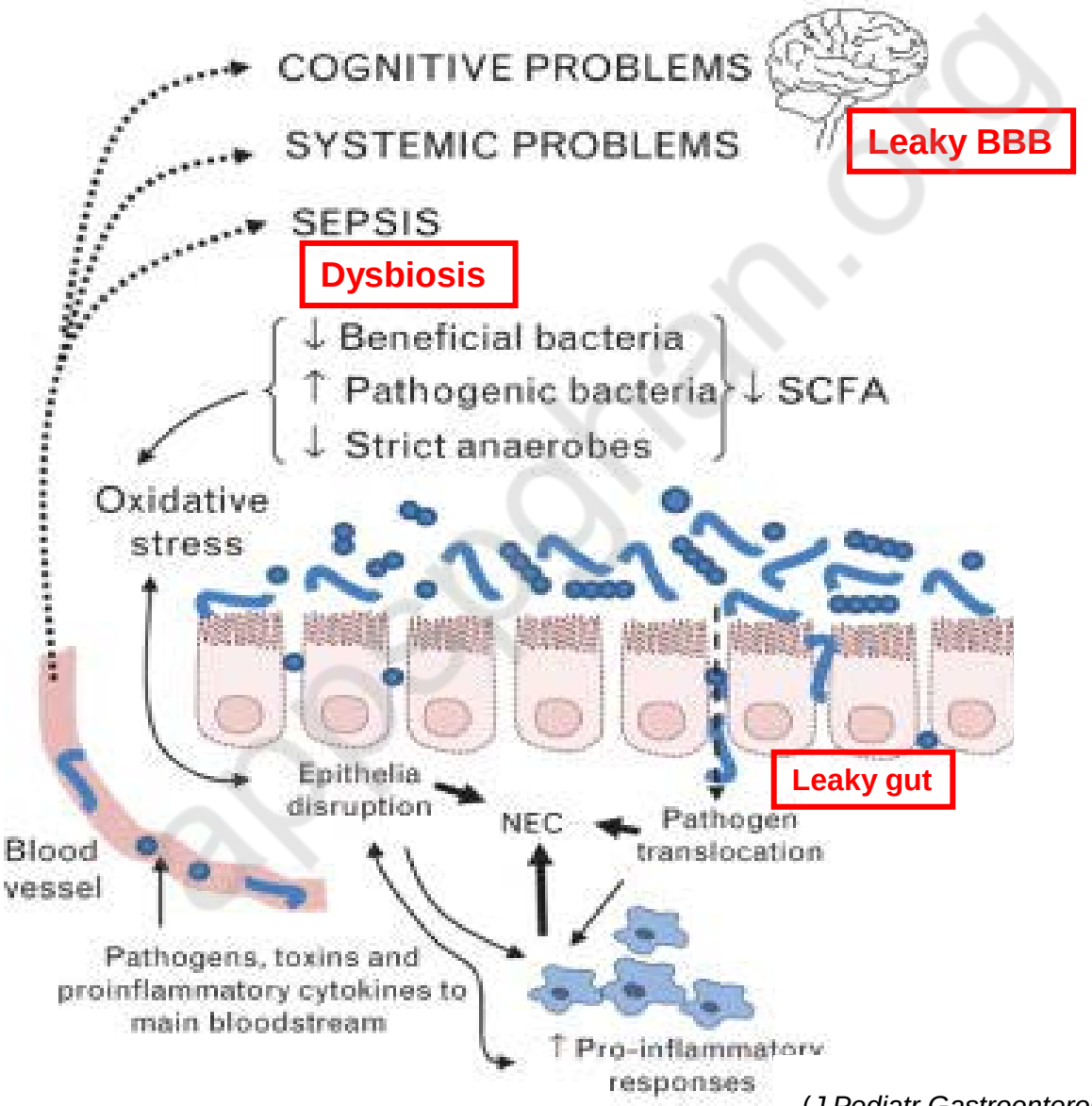


NeuN, Neuron; CD31, endothelial cells; Iba-1, microglia

Scale bar = 20μm

Gut Ecosystem

Preterm Infants



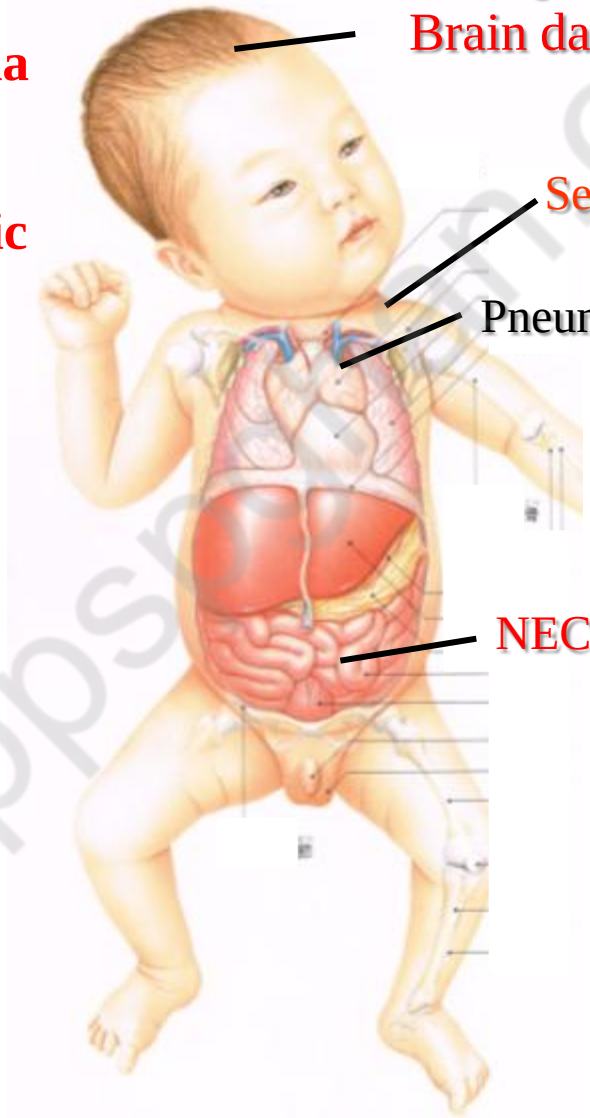
(*J Pediatr Gastroenterol Nutr*. 2016; 63(6): e193-e203.)

Association of Dysbiosis with Diseases in the Inside & Outside of GI tract

【Infant】

Periventricular leucomalacia (PVL)

Periventricular hemorrhagic infaction (PVHI)



meningitis

Brain damage (CP)

Sepsis

Pneumonia

NEC

abnormality of gut microbiota (dysbiosis)

IBS

IBD

mucositis

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Beneficial Effects of Breastfeeding on Gut Microbiota

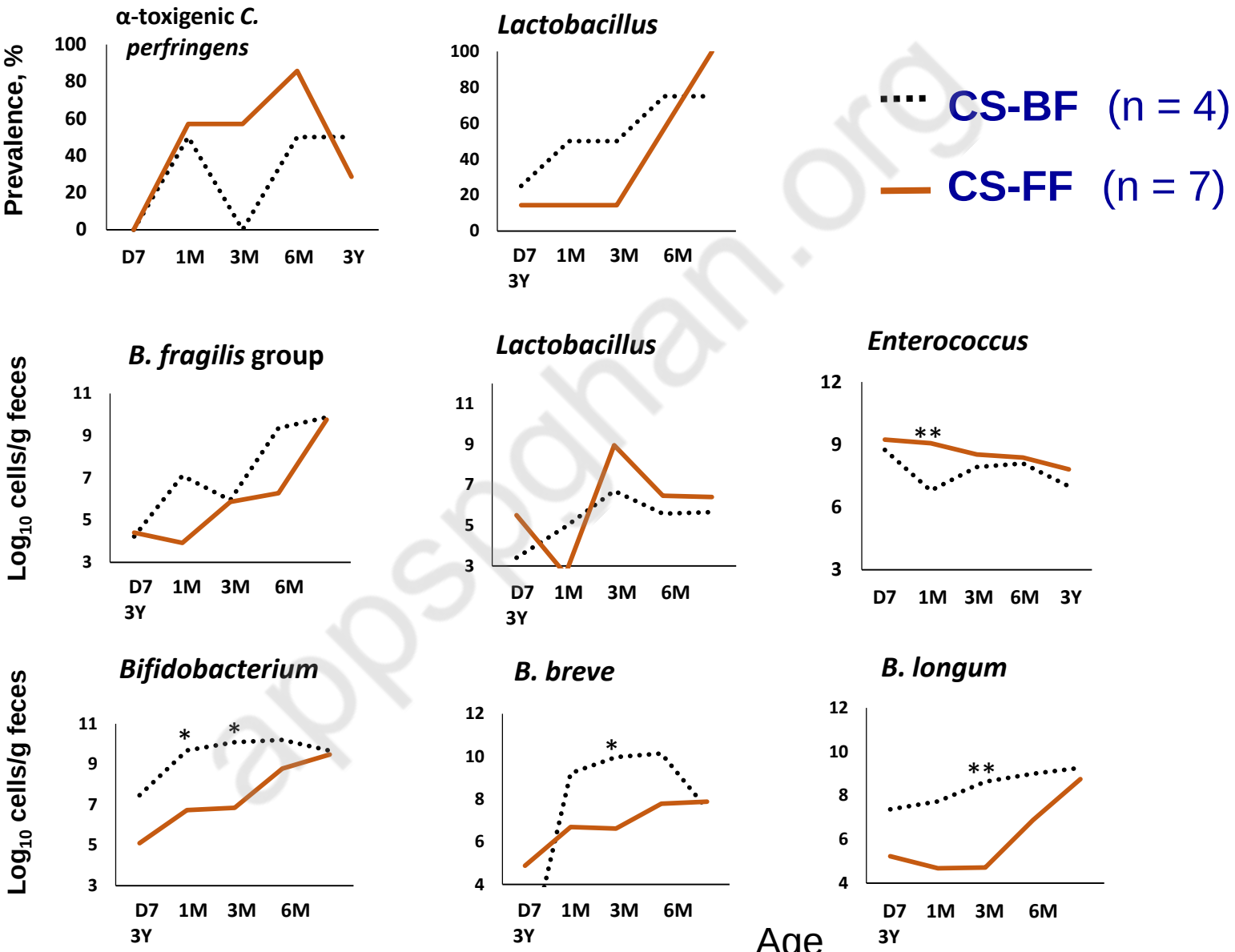
- Stimulates the active proliferation of *bifidobacteria*,
  → Bifidogenic effect by HMOs*
  also *lactobacillus*, *bacteroides*, *clostridia* by SCFAs**

- Breast milk provides beneficial microbiota:
  lactobacillus, *bifidobacteria*

- Prebiotics role of human milk:
  by the effect of the dominant fucosylated digosacharides
  → growth of *bfidobacteria*, *bacteroides*

*Human milk digosaccharides
** short-chain fatty acids (acerate, propoonate, butyra

Breast-feeding might ameliorate the gut dysbiosis associated with cesarean delivery



*P < 0.05 vs FF. CS, cesarean born; BF, exclusively breast-fed; FF, Formula-fed.

Probiotics supplementation

1. To expectation Mothers

   Supplementation with *L. rhamnosus* GG during late pregnancy of the mother are more colonized with Bifidobacteria in the intestine of infants born via C-section.

2. To Infants

   Supplementation with B. breve to infants born via C-section immediately after birth can confer beneficial effects.

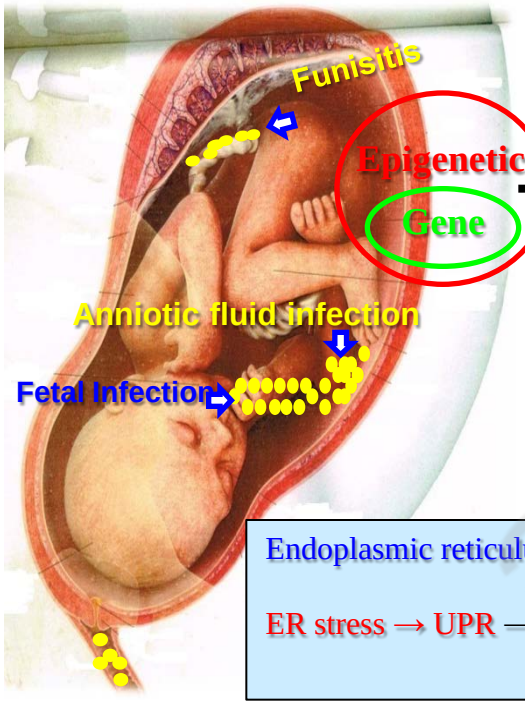
Developmental Origin of Health and Disease: DOHaD

Nutrition → Catch-up Growth → Obesity → **NCDs**※

(under/excess) (Obesogenic HFD)

Fetal adaptive responses to a suboptimal intrauterine environment

Developmental plasticity (Development mismatch)



Thrifty metabolic programming

Inflammatory responses

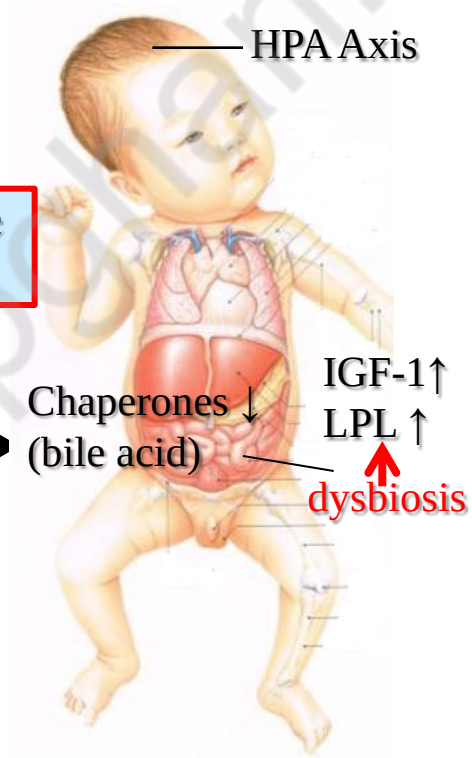
Endoplasmic reticulum

ER stress → UPR → PERK, ATF6, IRE1

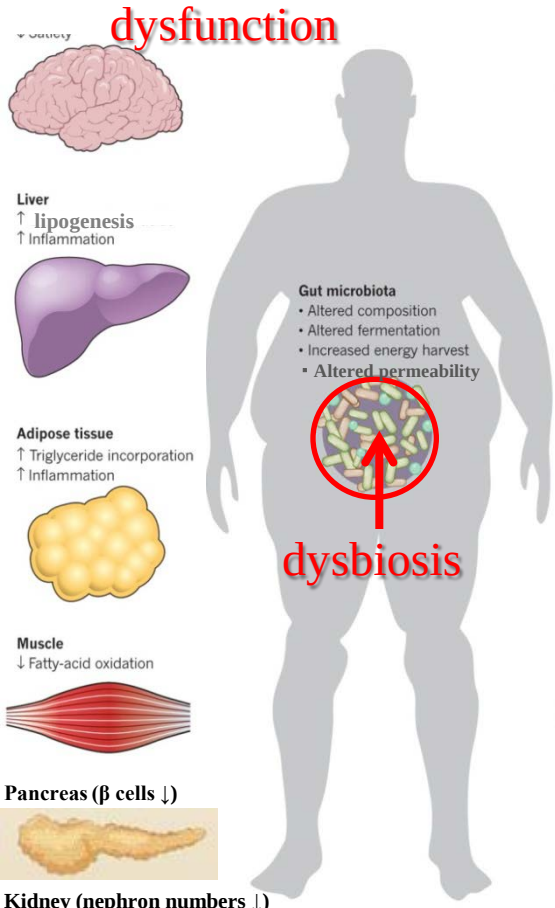
LPS

IUGR

Environment (gut dysbiosis, pathogen)



Low birth weight



※ NCDs: non-communicable diseases

Yamashiro Y

Summary

1. Gut microbiota play an important role in human health.
2. The early development and establishment of the gut microbiota during infancy is influenced by numerous factors.
3. C-section-born infants acquire a different gut microbiota profile (dysbiosis) than vaginally born infants.
4. Dysbiosis is now known as a high risk factor for NCDs and brain dysfunction.

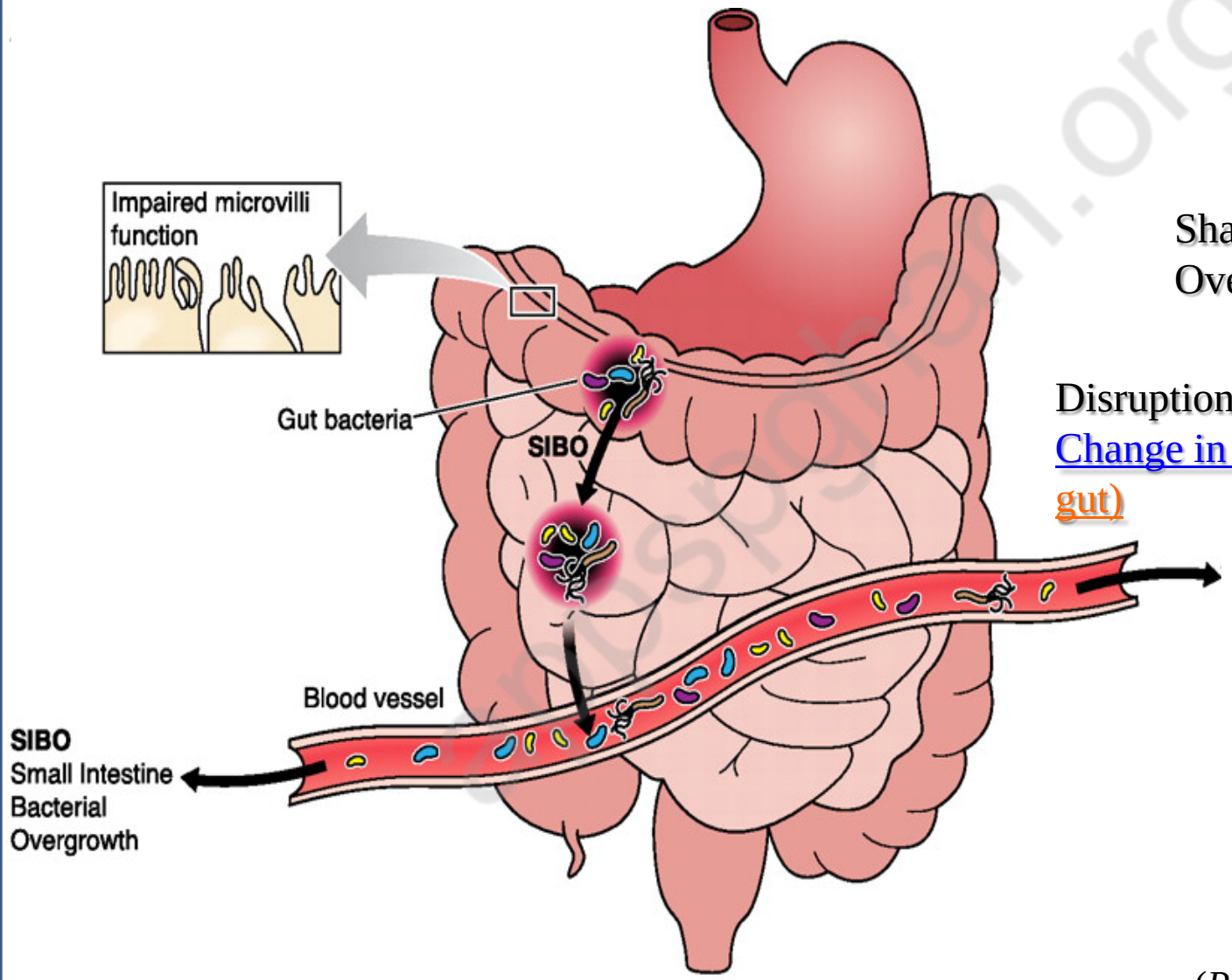
Conclusion

Based on the concept of DOHaD, gut bacteria related to early nutrition can have life long effects on the health.

Thank you for your attention.

Bacterial Translocation and Disease

As the Root of Systemic Complications



GI tract Inflammation

↓

Shall Intestinal Bacterial Overgrowth & Dysbiosis

↓

Disruption of Gut Homeostasis

Change in gut permeability (leaky gut)

↓

Translocation and initial systemic complications

(*Physiol Rev* 2010;90:859-904)

Unnecessary Cesarean S has been increasing worldwide (WHO2010)
-Recommended upper limit of C S rate is 15%, suggested by WHO in 1985-

Cesarean Section rates

Country	< 10%
India	8.5
Pakistan	7.3
Indonesia	6.8
Bangladesh	7.5
Cambodia	1.8
Philippines	9.5
Viet Nam	9.9
Mongolia	5.0

Country	> 15%
China	25.9
Korea	37.7
Japan	17.4
USA	37.8
UK	22.0
France	18.8
Germany	27.8
Italy	38.2

Features and Function of *Bifidobacterium*

- The most predominant gut microbe, colonizing from neonatal days,
- Play various important physiological role promoting metabolism, activating immune functions, suppressing of pathologic micro-organisms, Leading to a great contribution to maintaining the health of the host.
- Growth is stimulated by HMOs.
- HMOs inhibit infection by pathogens and suppress inflammatory cytokines.