# Key Microbiome Populations for Improved Clinical Outcomes

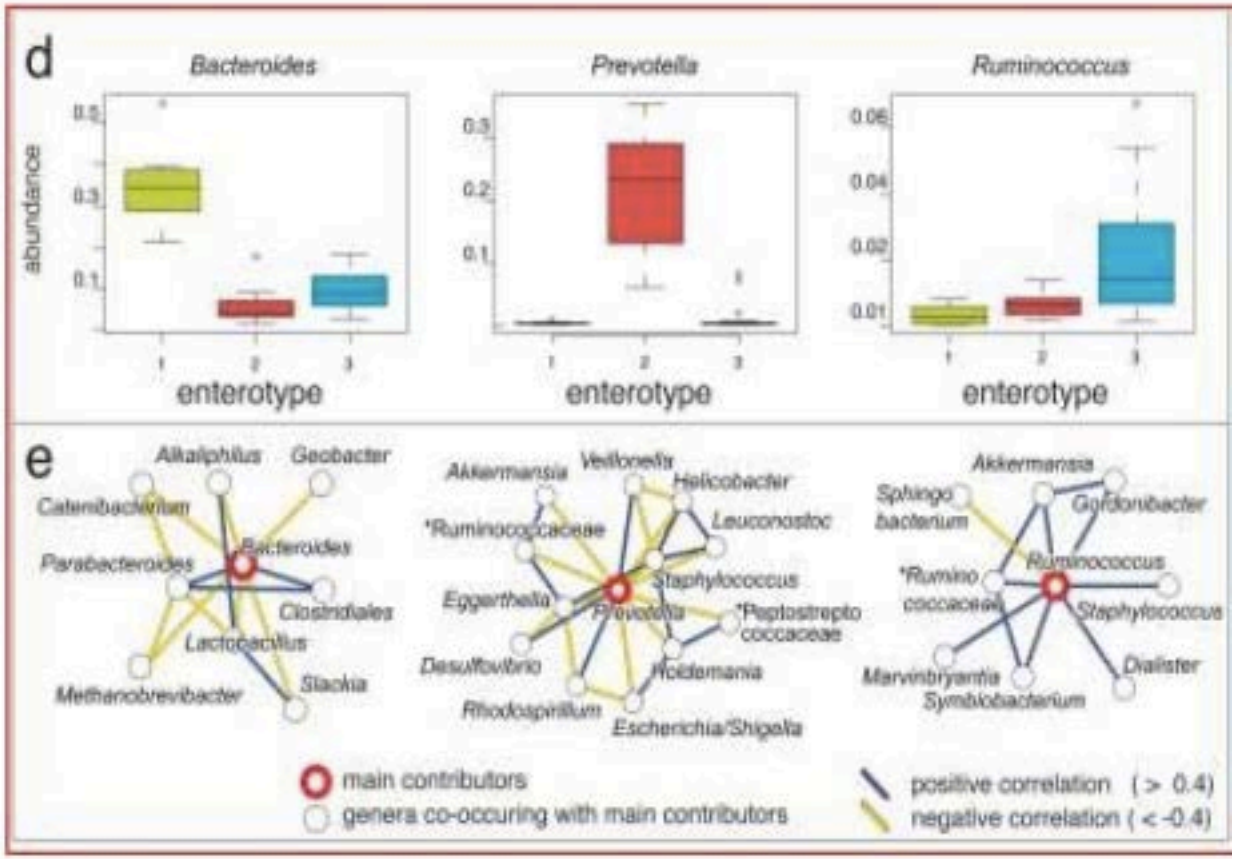
John Bagnulo MPH, PhD

# Human Microbiome projects: *3 main enterotypes*

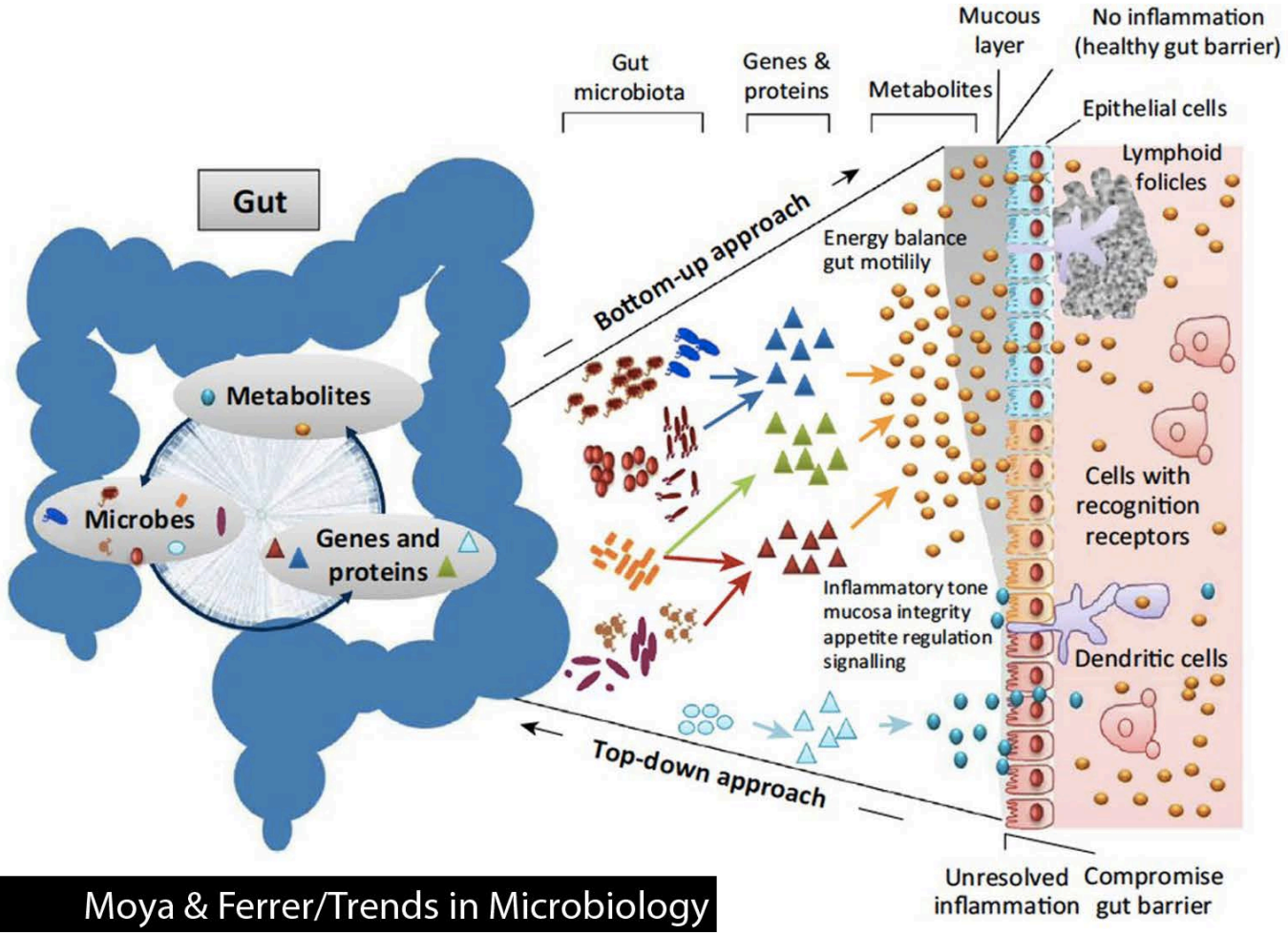
**ENTEROTYPE 1:**
**Bacteroides**

**ENTEROTYPE 2:**
**Prevotella**

**ENTEROTYPE 3:**
**Ruminococcus**




Arumugam – Nature 2011



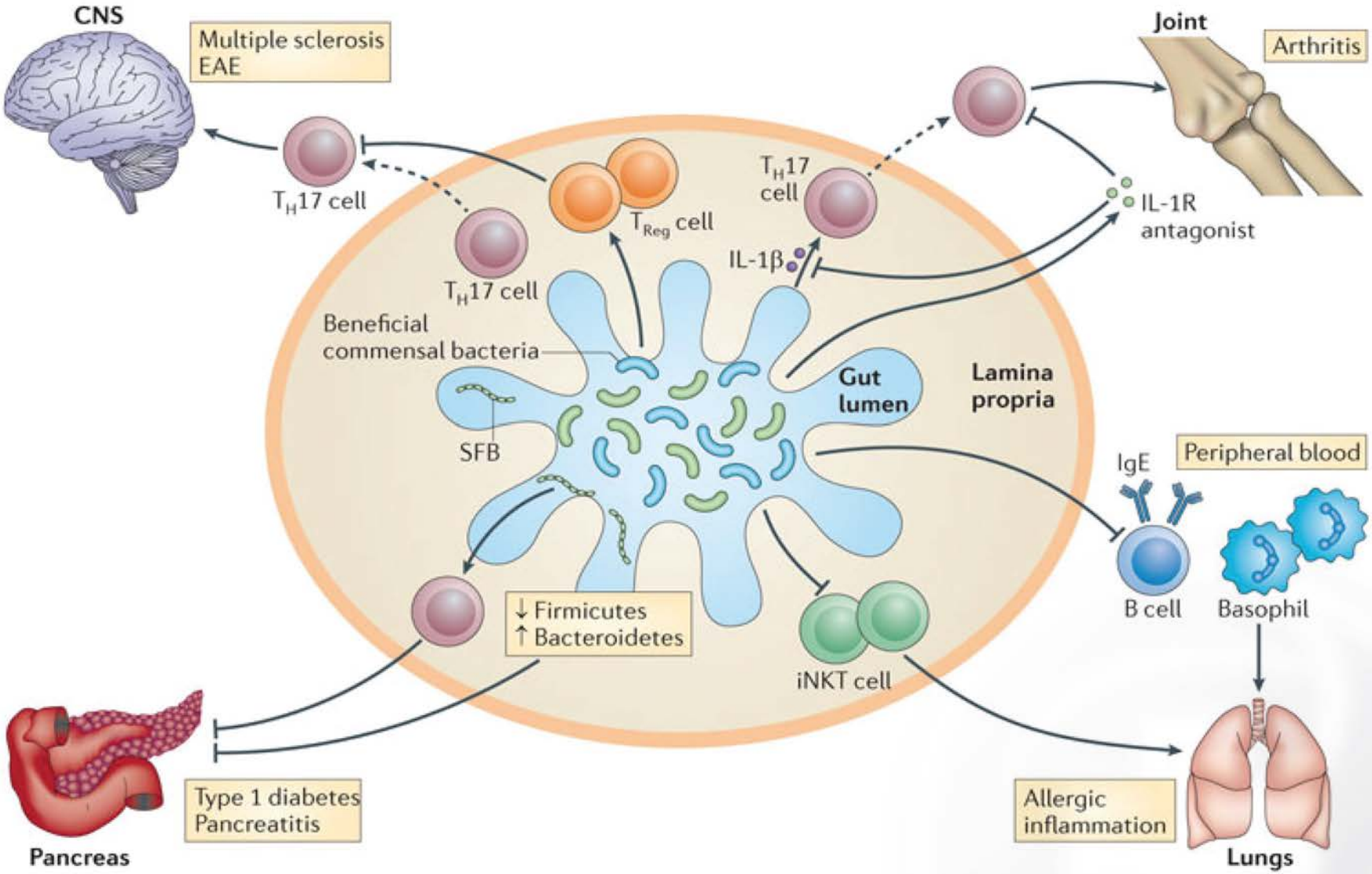

DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis. 2016;22(5):1137–1150.

Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms. 2019;7(1):14. Published 2019 Jan 10. doi:10.3390/microorganisms7010014

# Strains composing the RePOOPulate consortium.
# Composition of Stool Substitute (RePOOPulate)

Acidaminococcus intestinalis
Bacteroides ovatus
Bifidobacterium adolescentis (two different strains)
Bifidobacterium longum (two different strains)
Blautia producta
Clostridium cocleatum
Collinsella aerofaciens
Dorea longicatena (two different strains)
Escherichia coli
Eubacterium desmolans
Eubacterium eligens
Eubacterium limosum
Eubacterium rectale (four different strains)
Eubacterium ventriosum
Faecalibacterium prausnitzii
Lachnospira pectinoshiza
Lactobacillus casei/paracasei
Lactobacillus casei
Parabacteroides distasonis
Raoultella sp.
Roseburia faecalis
Roseburia intestinalis
Ruminococcus torques (two different strains)
Ruminococcus obeum (two different strains)
Streptococcus mitis

**Petrof EO, Gloor GB, Vanner SJ, et al. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: 'RePOOPulating' the gut. Microbiome. 2013;1(1):3. Published 2013 Jan 9.**




Nature Reviews | Immunology

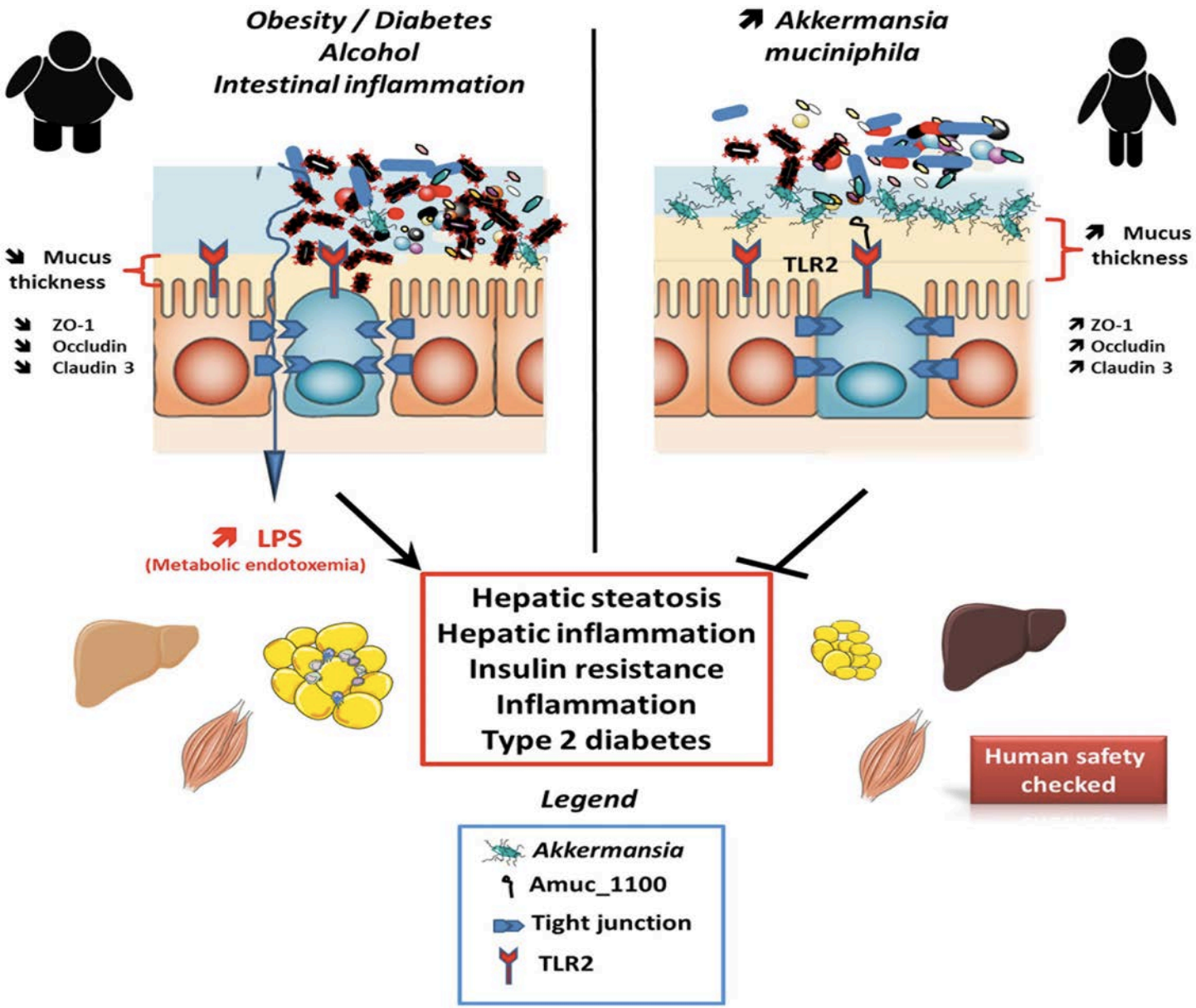
# Are there specific families of microbes that we can now see as essential difference makers?

**Protective/Favorable**

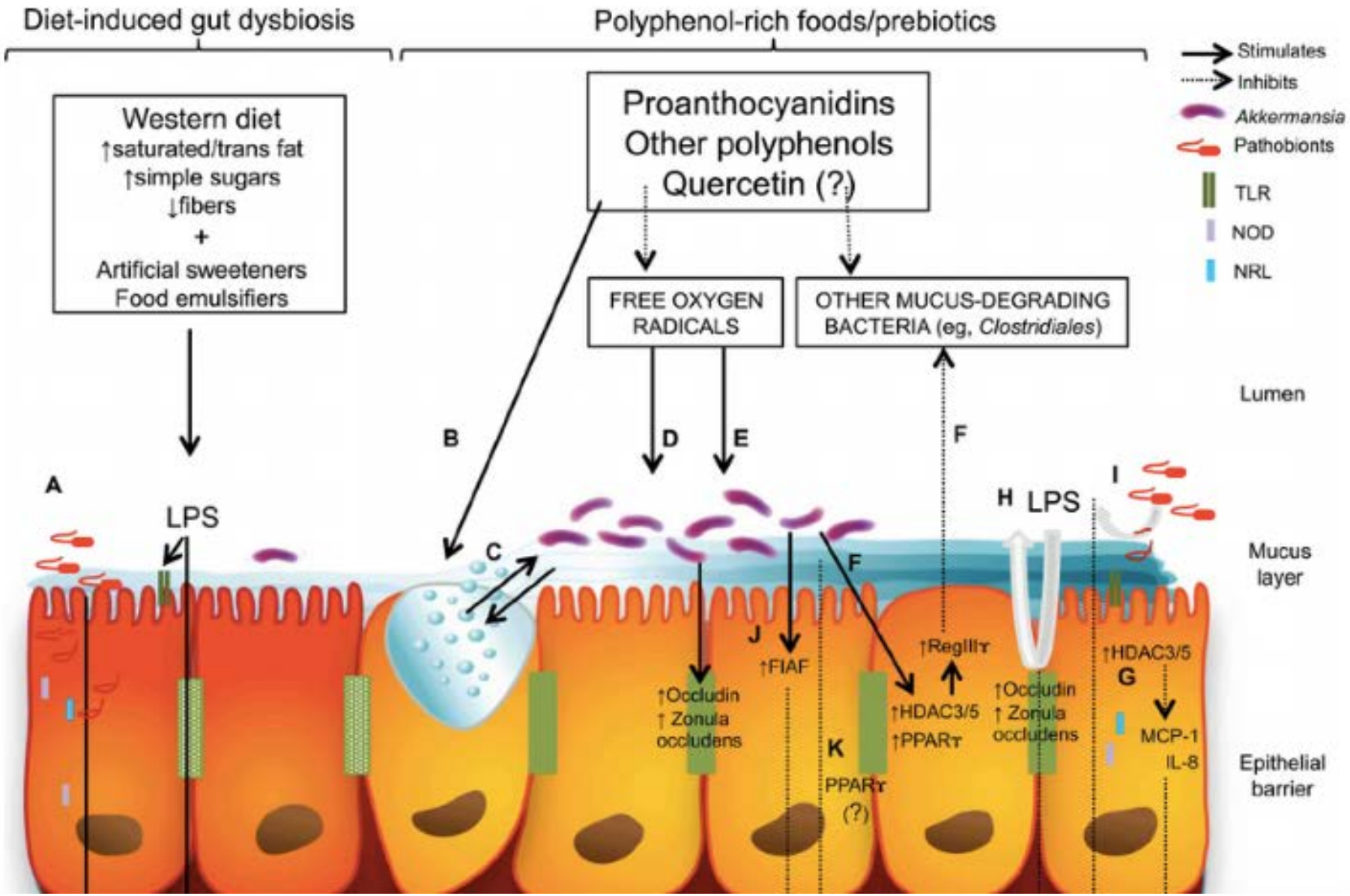
- Akkermansia
- Bacteroides fragilis
- Bifido species (longum, infantis, brevis, animalis)
- Faecalbacterium Prausnitzii
- Ruminococcus bromii
- Roseburia

**Higher levels of these species Associated with higher risk**

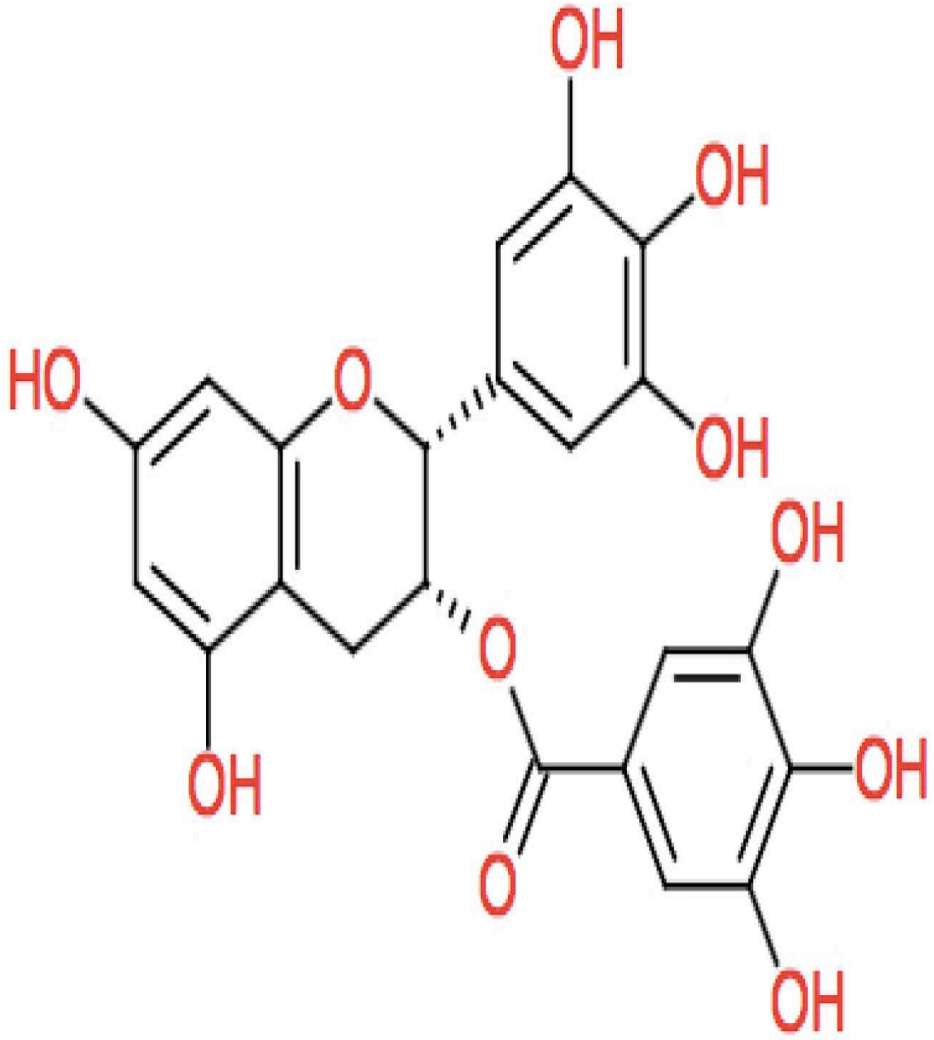
- Desulfovibrio
- Clostridiales
- Citrobacter
- Klebsiella




Cani PD, de Vos WM. Next-Generation Beneficial Microbes: The Case of Akkermansia muciniphila. Front Microbiol. 2017;8:1765. Published 2017 Sep 22. doi:10.3389/fmicb.2017.01765




**Forato Anhê, Fernando & Varin, Thibault & Le Barz, Mélanie & Desjardins, Yves & Levy, Emile & Roy, Denis & Marette, André. (2015). Gut Microbiota Dysbiosis in Obesity-Linked Metabolic Diseases and Prebiotic Potential of Polyphenol-Rich Extracts. Current Obesity Reports. 4. 10.1007/s13679-015-0172-9.**




**Wang L, Wu Y, Zhuang L, et al. Puerarin prevents high-fat diet-induced obesity by enriching Akkermansia muciniphila in the gut microbiota of mice. PLoS One. 2019;14(6):e0218490. Published 2019 Jun 24. doi:10.1371/journal.pone.0218490**

# Key Dietary and Lifestyle Factors Associated with Akkermansia

**Favorable/Increased Populations**

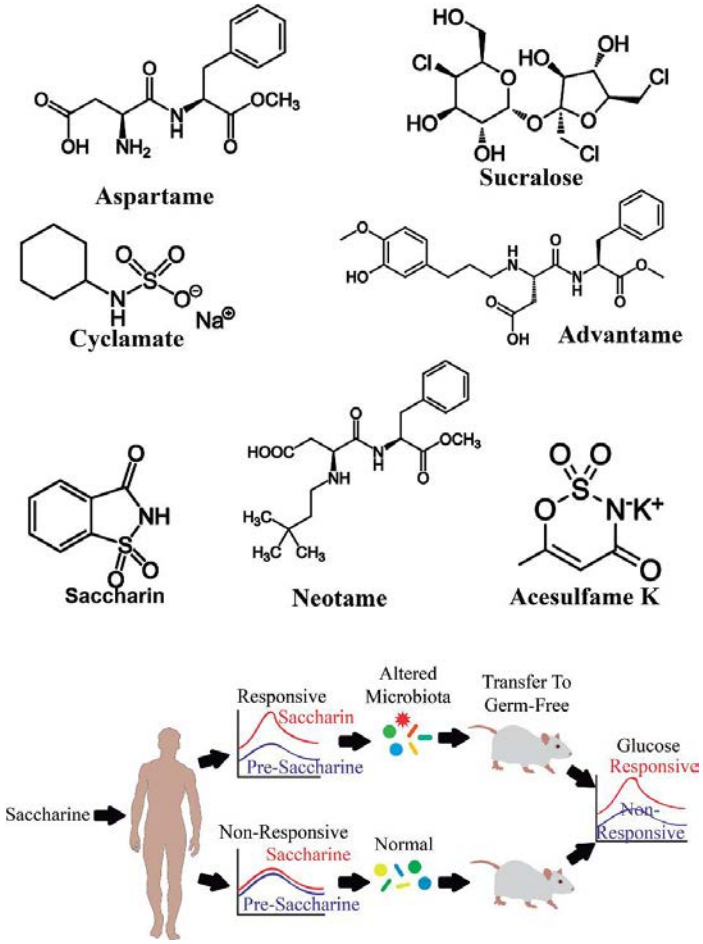
- Dietary polyphenolics
  - cranberries, vaccinium family
- Fasting
- Aerobic exercise
- Ketogenic diet

**Unfavorable/Decreased Populations**

- Low fiber
- High refined carbohydrate levels
- Frequent food intake
- Antibiotic use
- Artificial sweeteners
- Emulsifiers

**Verhoog S, Taneri PE, Roa Díaz ZM, et al. Dietary Factors and Modulation of Bacteria Strains of Akkermansia muciniphila and Faecalibacterium prausnitzii: A Systematic Review. Nutrients. 2019;11(7):1565. Published 2019 Jul 11. doi:10.3390/nu11071565**

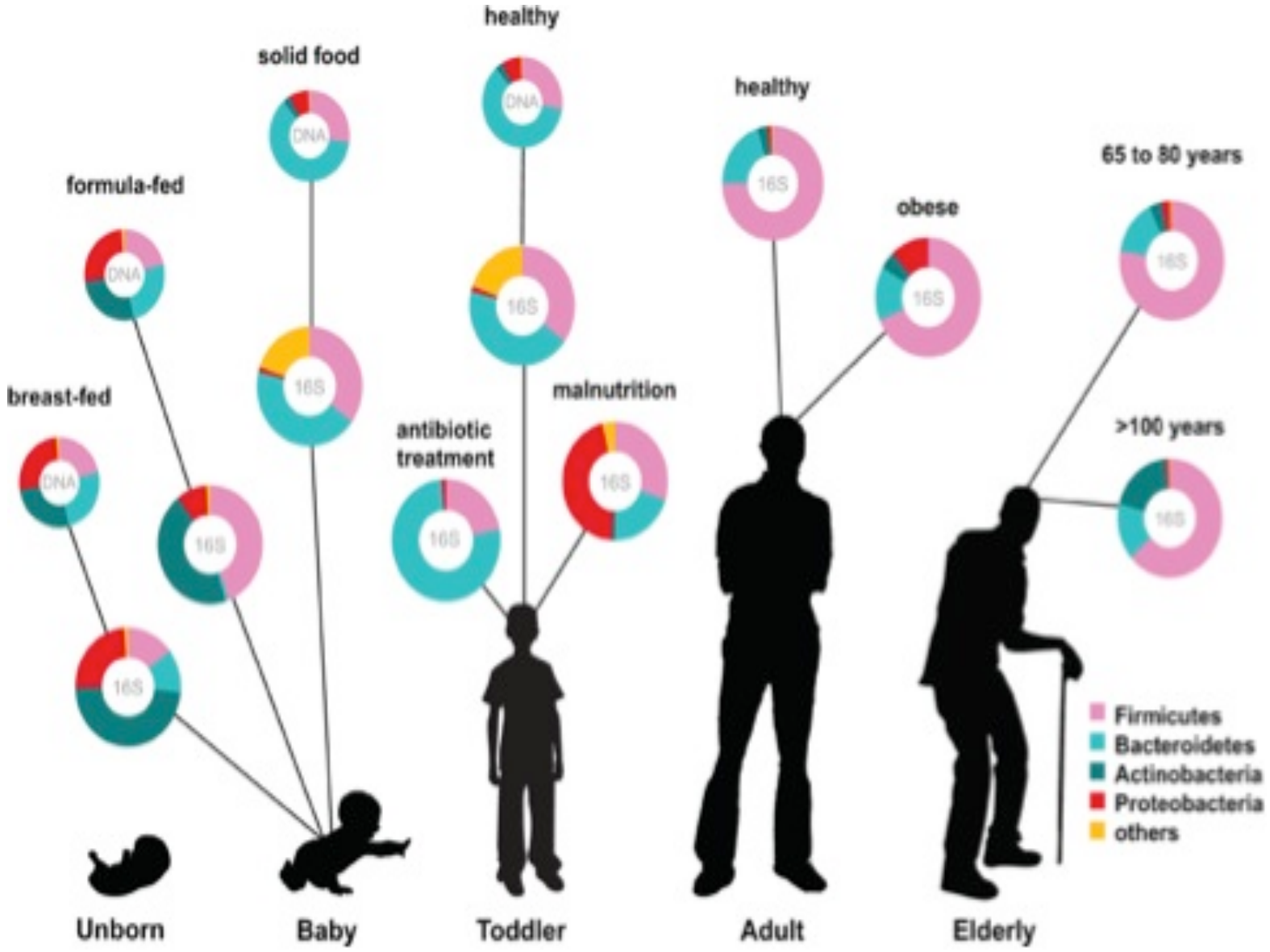
**FIGURE 1** Effects of artificial sweeteners and saccharin on gut microbiota. Animal studies have reported specific ...

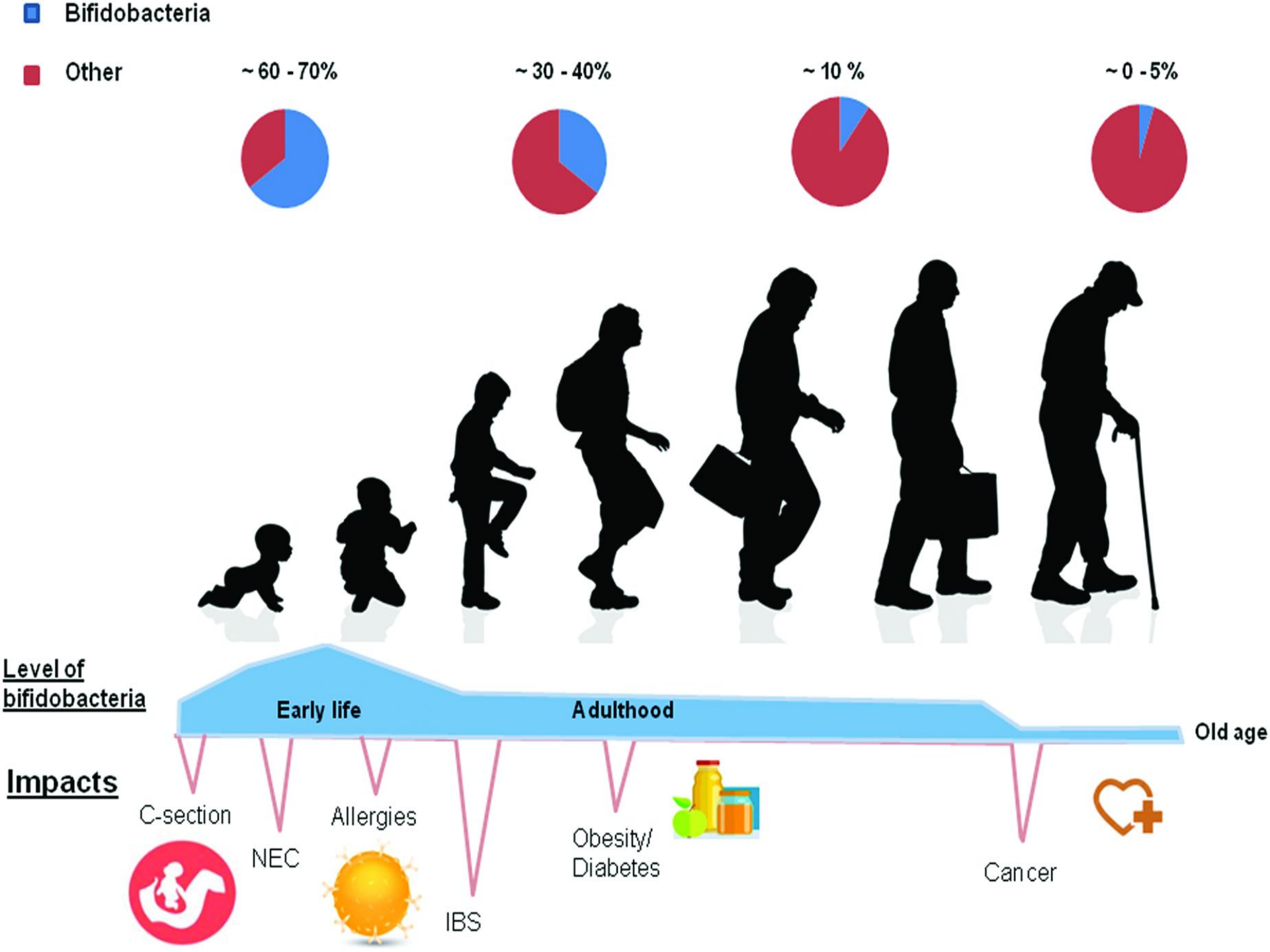



**Olivier-Van Stichelen S, Rother KI, Hanover JA. Maternal Exposure to Non-nutritive Sweeteners Impacts Progeny's Metabolism and Microbiome. Front Microbiol. 2019;10:1360. Published 2019 Jun 20. doi:10.3389/fmicb.2019.01360**

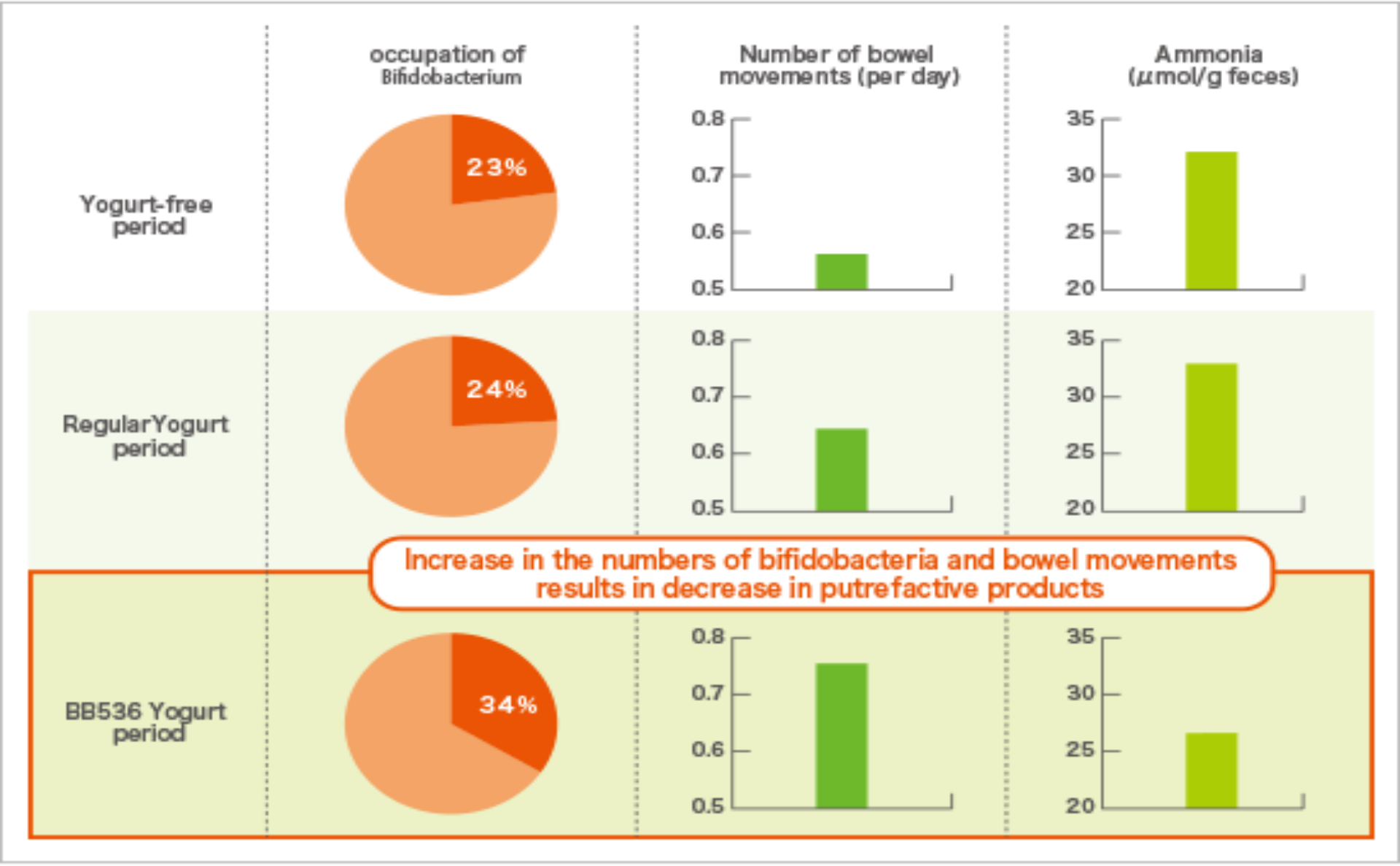
# Bifidobacterium Species

- B. longum
- B. infantis
- B. brevis
- B. animalis
- All are primary butyrate producers
- Comprise majority of all microbial species in early years of life
- Decline in composition associated with increased disease risk and aging

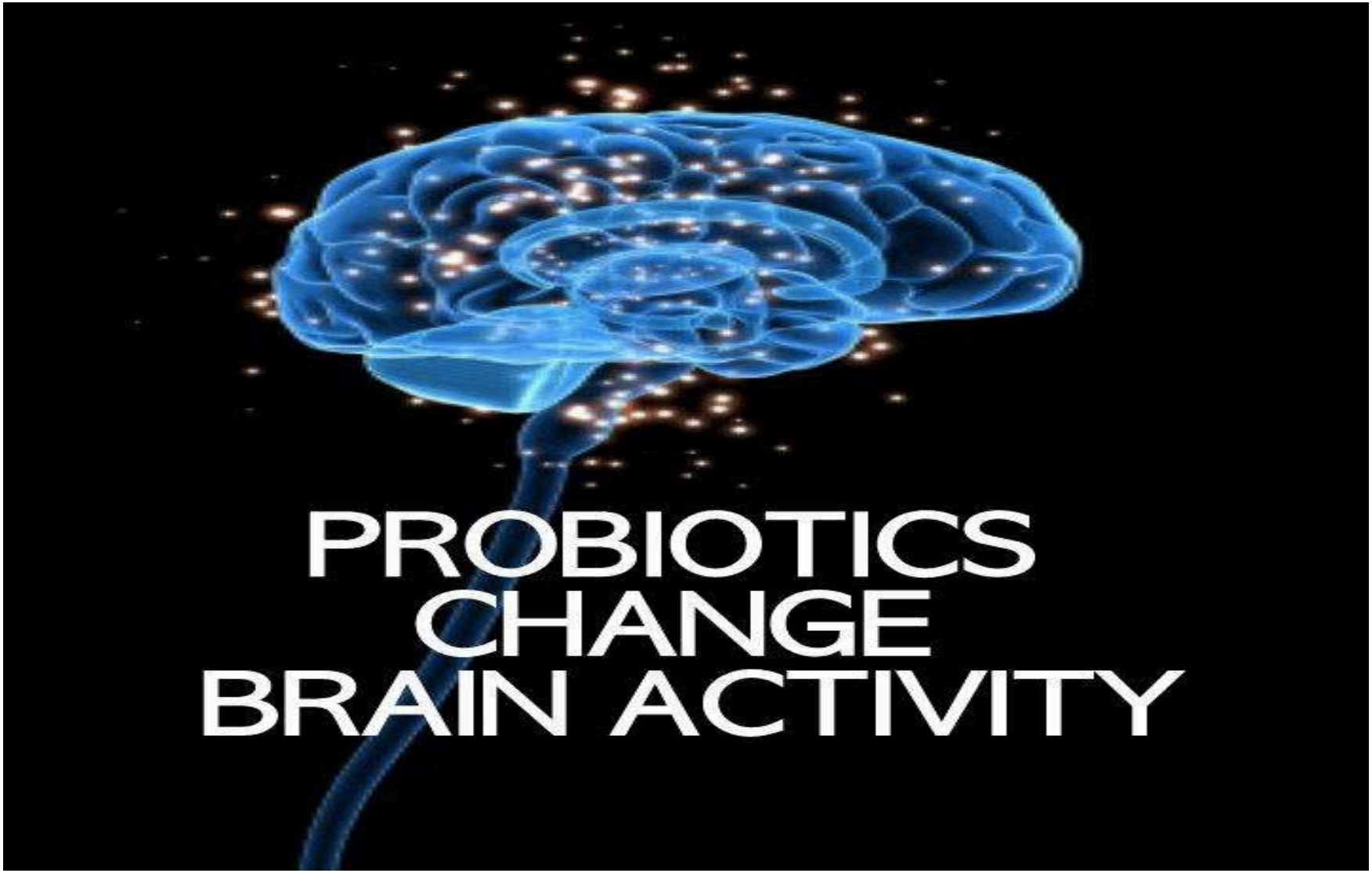

healthy
solid food
formula-fed
breast-fed
DNA
16S
antibiotic treatment
malnutrition
healthy
obese
65 to 80 years
>100 years
Firmicutes
Bacteroidetes
Actinobacteria
Proteobacteria
others
Unborn
Baby
Toddler
Adult
Elderly


Bifidobacteria
Other
~ 60 - 70%
~ 30 - 40%
~ 10 %
~ 0 - 5%
Level of bifidobacteria
Early life
Adulthood
Old age
Impacts
C-section
NEC
Allergies
IBS
Obesity/ Diabetes
Cancer

## Differences in the effects of maintaining intestinal health when consuming yogurt




(Yaeshima T. *et al*, Bioscience Microflora, 1997)




**Wang H, Braun C, Murphy EF, Enck P. Bifidobacterium longum 1714™ Strain Modulates Brain Activity of Healthy Volunteers During Social Stress. Am J Gastroenterol. 2019;114(7):1152–1162.**

# Microbes Associated with MDD

**Associated w/Risk Reduction**

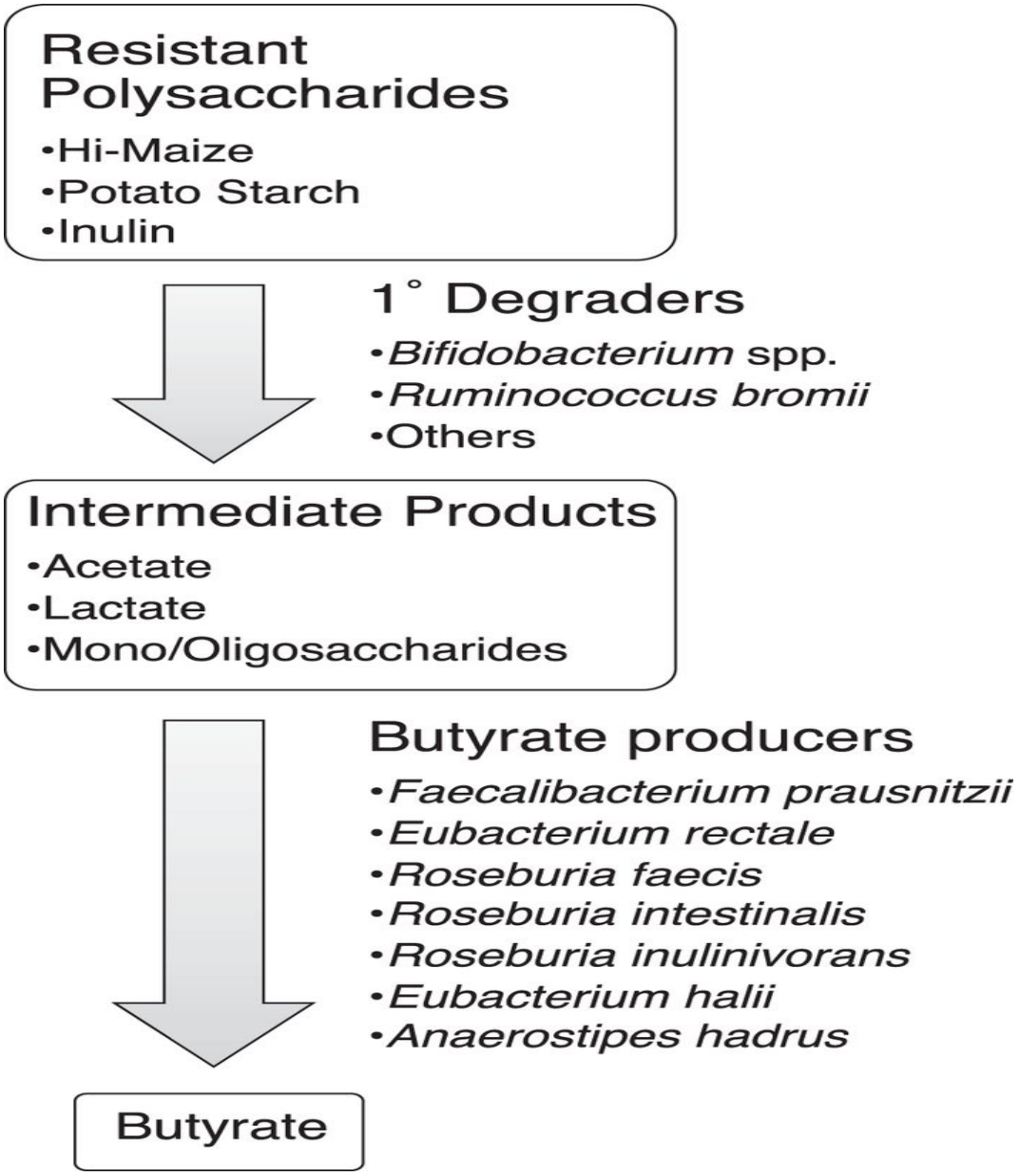
- Bifidobacterium species
- Dialister
- Faecalbacterium Prauznitzi
- Ruminococcus
- Roseburia

**Increased Risk**

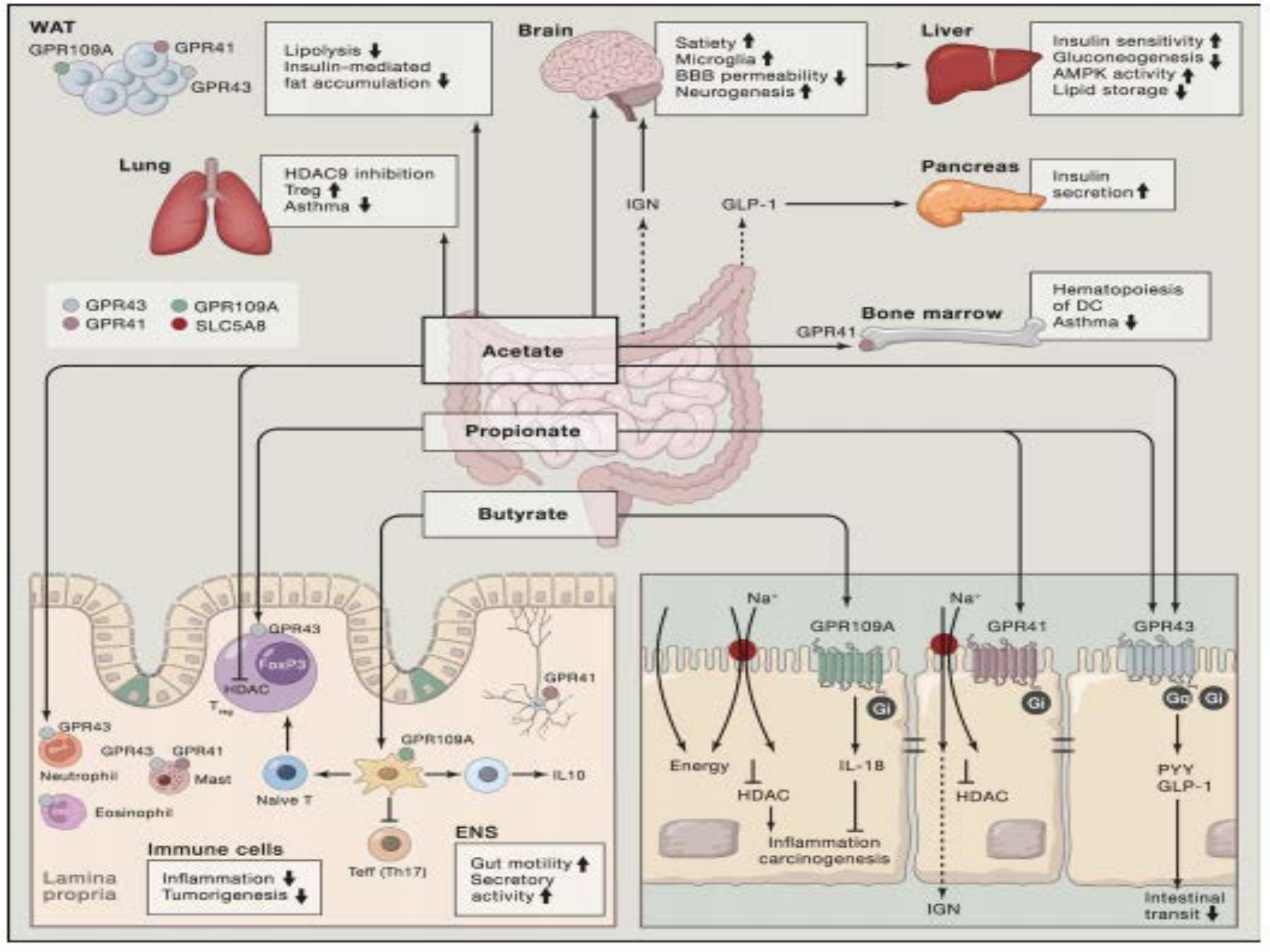
- Klebsiella
- Clostridium
- Lachnospiracea
- Parabacteroides
- Streptococcus

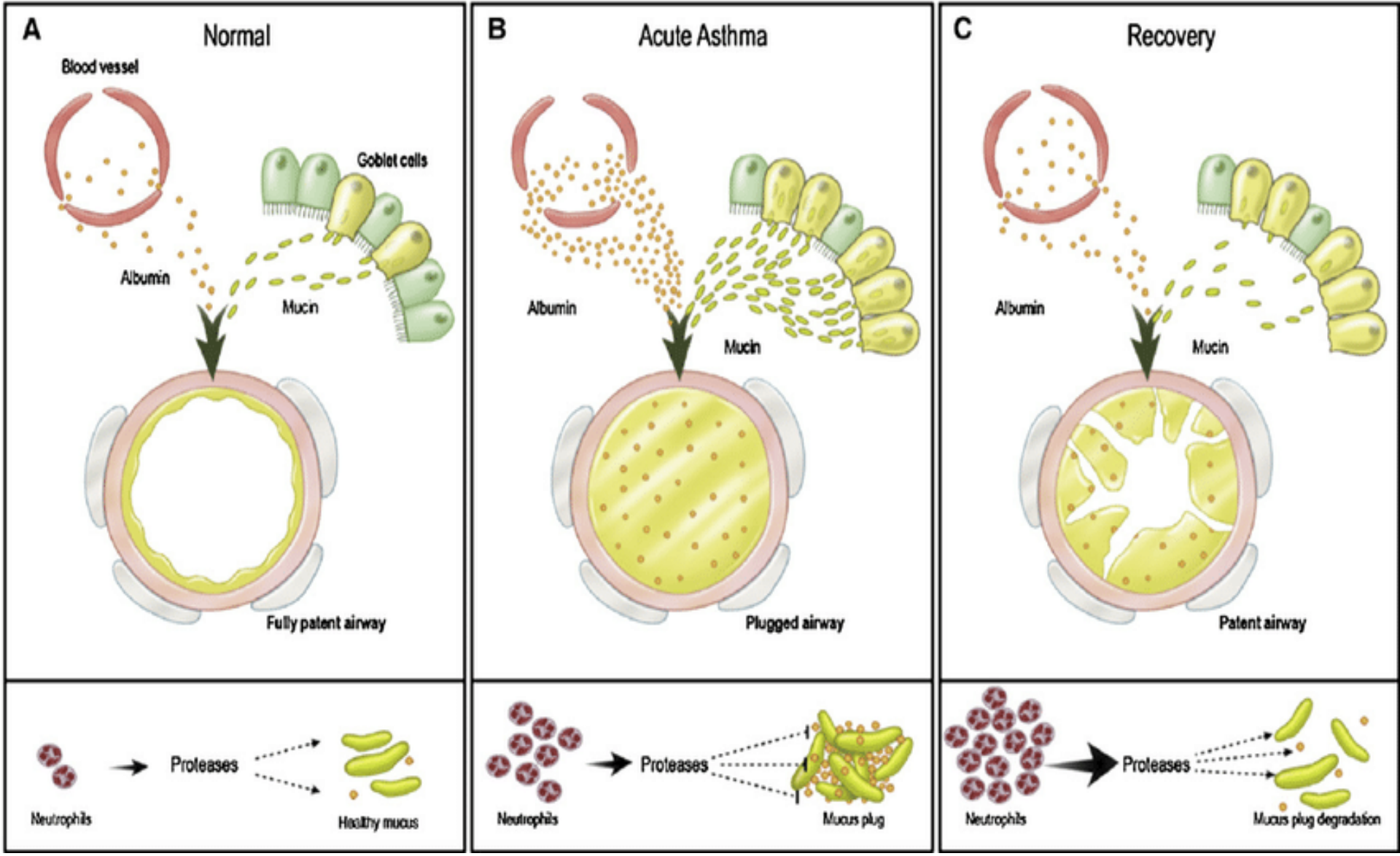
**Cheung SG, Goldenthal AR, Uhlemann AC, Mann JJ, Miller JM, Sublette ME. Systematic Review of Gut Microbiota and Major Depression. Front Psychiatry. 2019;10:34. Published 2019 Feb 11. doi:10.3389/fpsyt.2019.00034**

**Proposed model of metabolites and microbes that catalyze the flow of carbon from resistant polysaccharides to butyrate.**

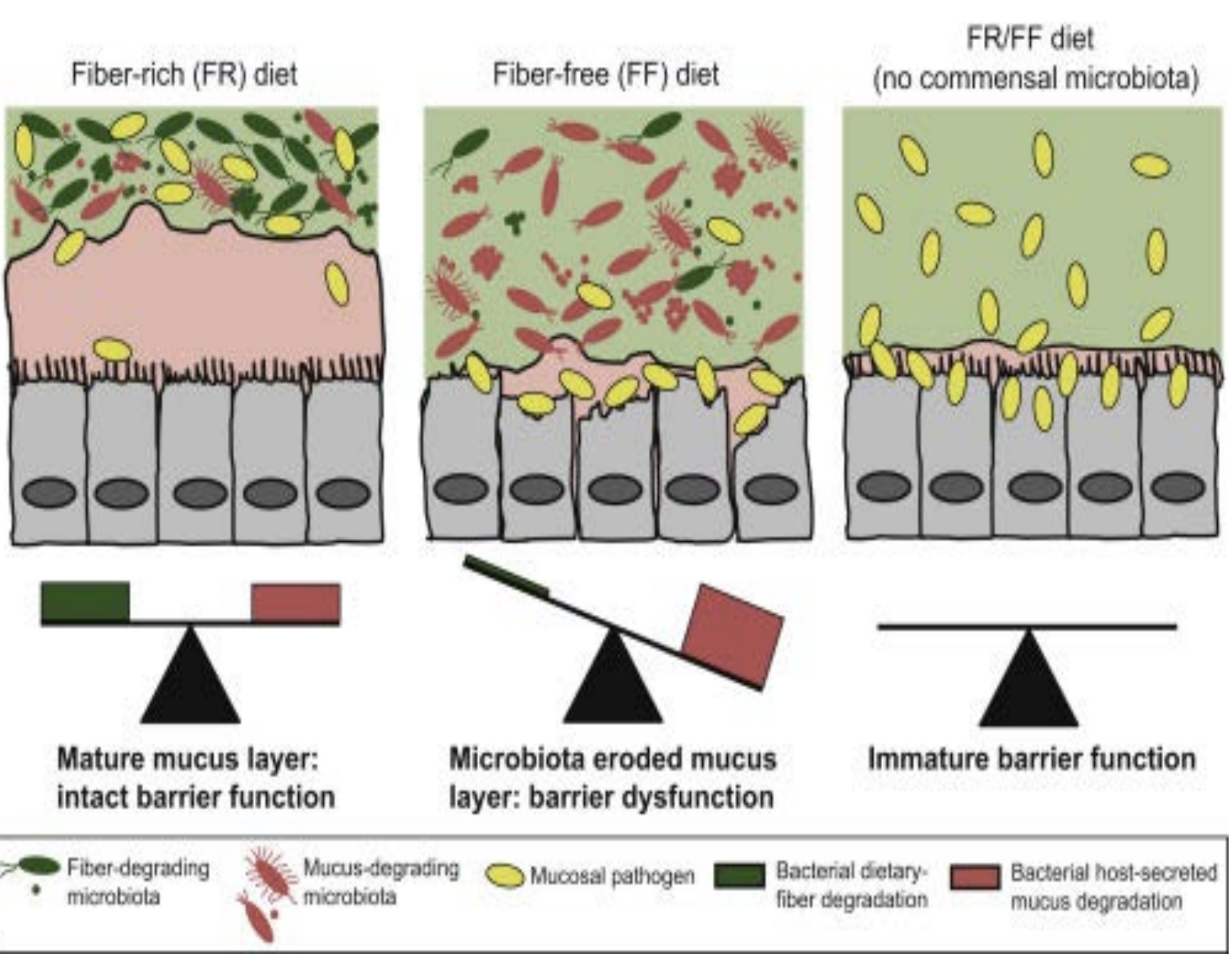


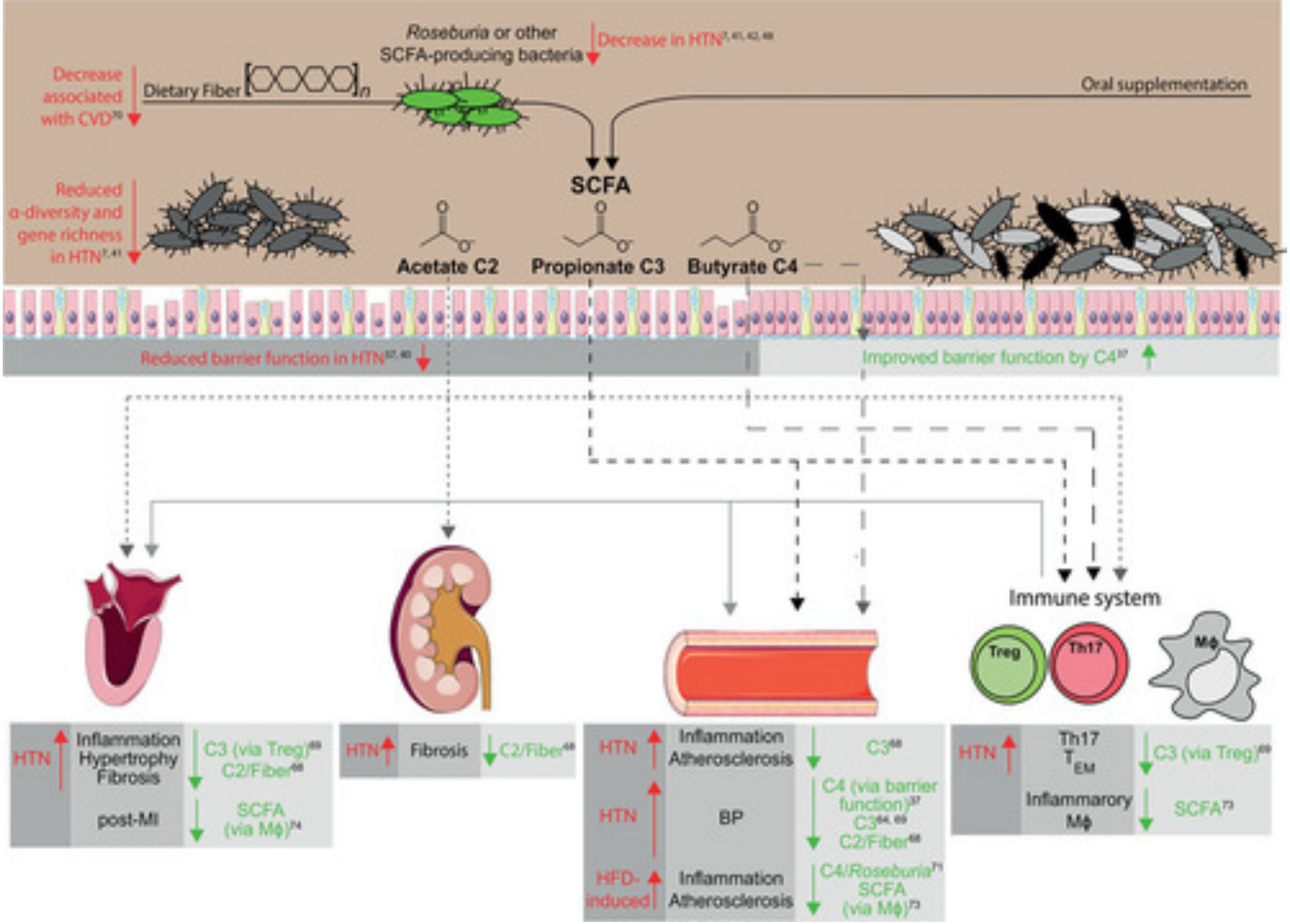

Nielson T. Baxter et al. mBio 2019; doi:10.1128/mBio.02566-18


WAT
GPR109A
GPR41
GPR43
Lipolysis
Insulin-mediated fat accumulation
Brain
Satiety
Microglia
BBB permeability
Neurogenesis
Liver
Insulin sensitivity
Gluconeogenesis
AMPK activity
Lipid storage
Lung
HDAC9 inhibition
Treg
Asthma
IGN
GLP-1
Pancreas
Insulin secretion
GPR43
GPR41
GPR109A
SLC5A8
Bone marrow
Hematopoiesis of DC
Asthma
Acetate
Propionate
Butyrate
GPR43
FoxP3
HDAC
GPR41
GPR43
GPR43
GPR41
Neutrophil
Mast
Eosinophil
Naive T
GPR109A
IL10
Teff (Th17)
Immune cells
Inflammation
Tumorigenesis
Lamina propria
ENS
Gut motility
Secretory activity
Na+
GPR109A
GPR41
GPR43
Gi
Gi
Gs
Gi
Energy
HDAC
IL-1B
HDAC
PYY
GLP-1
Inflammation carcinogenesis
IGN
Intestinal transit




Karav S, Casaburi G, Frese SA. Reduced colonic mucin degradation in breastfed infants colonized by Bifidobacterium longum subsp. infantis EVC001. FEBS Open Bio. 2018;8(10):1649–1657. Published 2018 Sep 17


Fiber-rich (FR) diet
Fiber-free (FF) diet
FR/FF diet
(no commensal microbiota)
Mature mucus layer:
intact barrier function
Microbiota eroded mucus
layer: barrier dysfunction
Immature barrier function
Fiber-degrading
microbiota
Mucus-degrading
microbiota
Mucosal pathogen
Bacterial dietary-
fiber degradation
Bacterial host-secreted
mucus degradation




**Precarious Symbiosis Between Host and Microbiome in Cardiovascular Health, Volume: 73, Issue: 5, Pages: 926-935, DOI: (10.1161/HYPERTENSIONAHA.119.11786)**

# Top β-Mannan Content of Plants

**Chickpeas**

- Associated with higher levels of health and better nutritional status (O'neil et al. J Nutr Food Science 2014)
- When thoroughly cooked and/or fermented lectins are denatured but mannan content persists
- Studies demonstrate a unique ability to feed most beneficial microbes

**Coconut**

- Consumed by many of the World's healthiest populations daily
- A high fat food associated with favorable microbiome diversity indexes in multiple species
- Coconut fiber has no anti-nutrient effects

**La Rosa SL, Leth ML, Michalak L, et al. The human gut Firmicute Roseburia intestinalis is a primary degrader of dietary β-mannans. Nat Commun. 2019;10(1):905. Published 2019 Feb 22. doi:10.1038/s41467-019-08812-y**

Graf D, Di Cagno R, Fåk F, et al. Contribution of diet to the composition of the human gut microbiota. Microb Ecol Health Dis. 2015;26:26164. Published 2015 Feb 4. doi:10.3402/mehd.v26.26164

Nielson T. Baxter, Alexander W. Schmidt, Arvind Venkataraman, Kwi S. Kim, Clive Waldron, Thomas M. Schmidt.
Dynamics of Human Gut Microbiota and Short-Chain Fatty Acids in Response to Dietary Interventions with Three Fermentable Fibers
mBio Jan 2019, 10 (1) e02566-18; DOI: 10.1128/mBio.02566-18

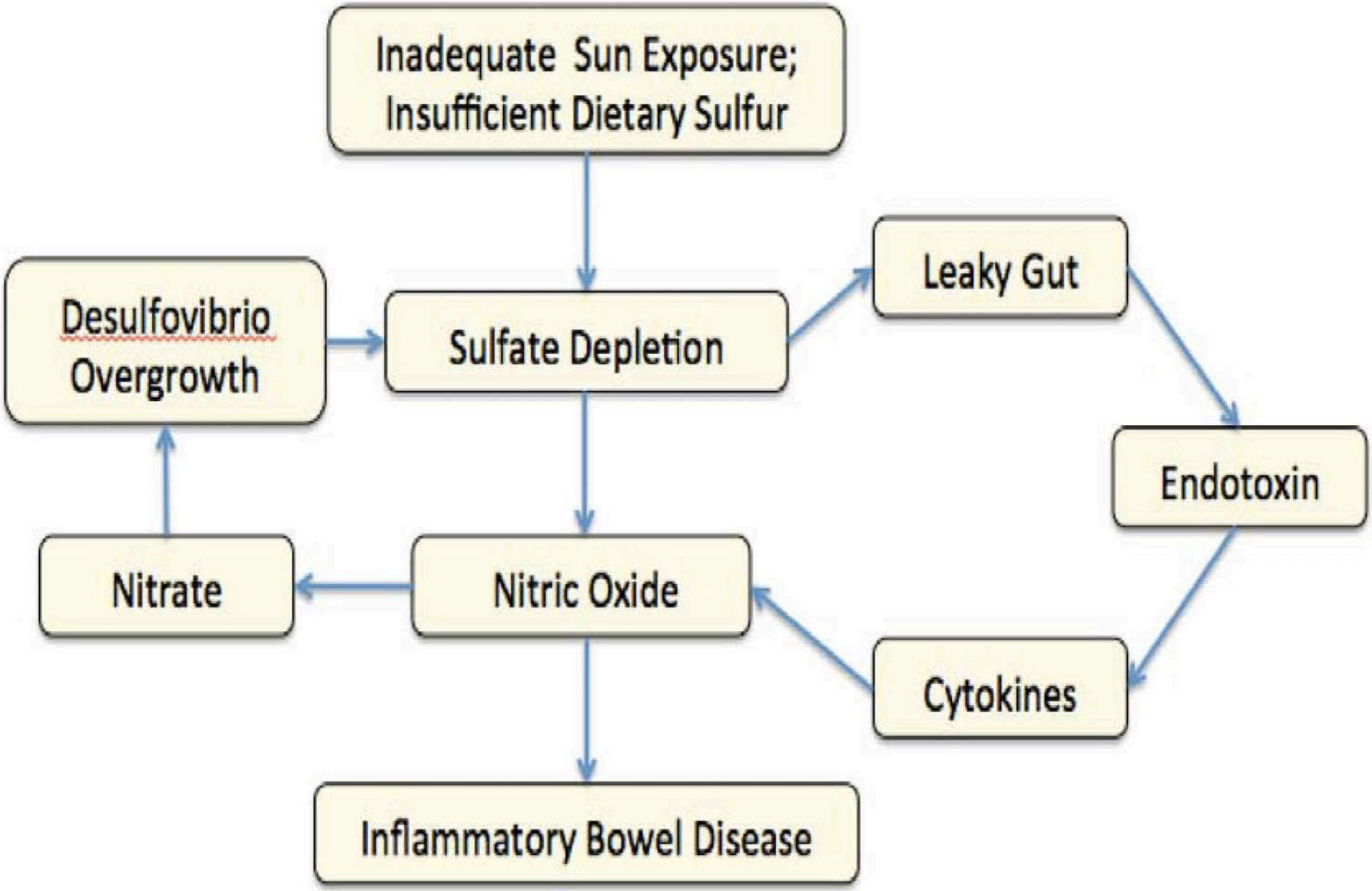
# Common Microbial Overgrowth Patterns and Chronic Disease

- Desulfovibrio – mood and psychiatric disorders
- Veilonella-most chronic/inflammatory disease
- Fusobacterium spp-colon inflammation, cancer, and compromised immune response
- Klebsiella spp-autoimmune disease Crohn's, ulcerative colitis

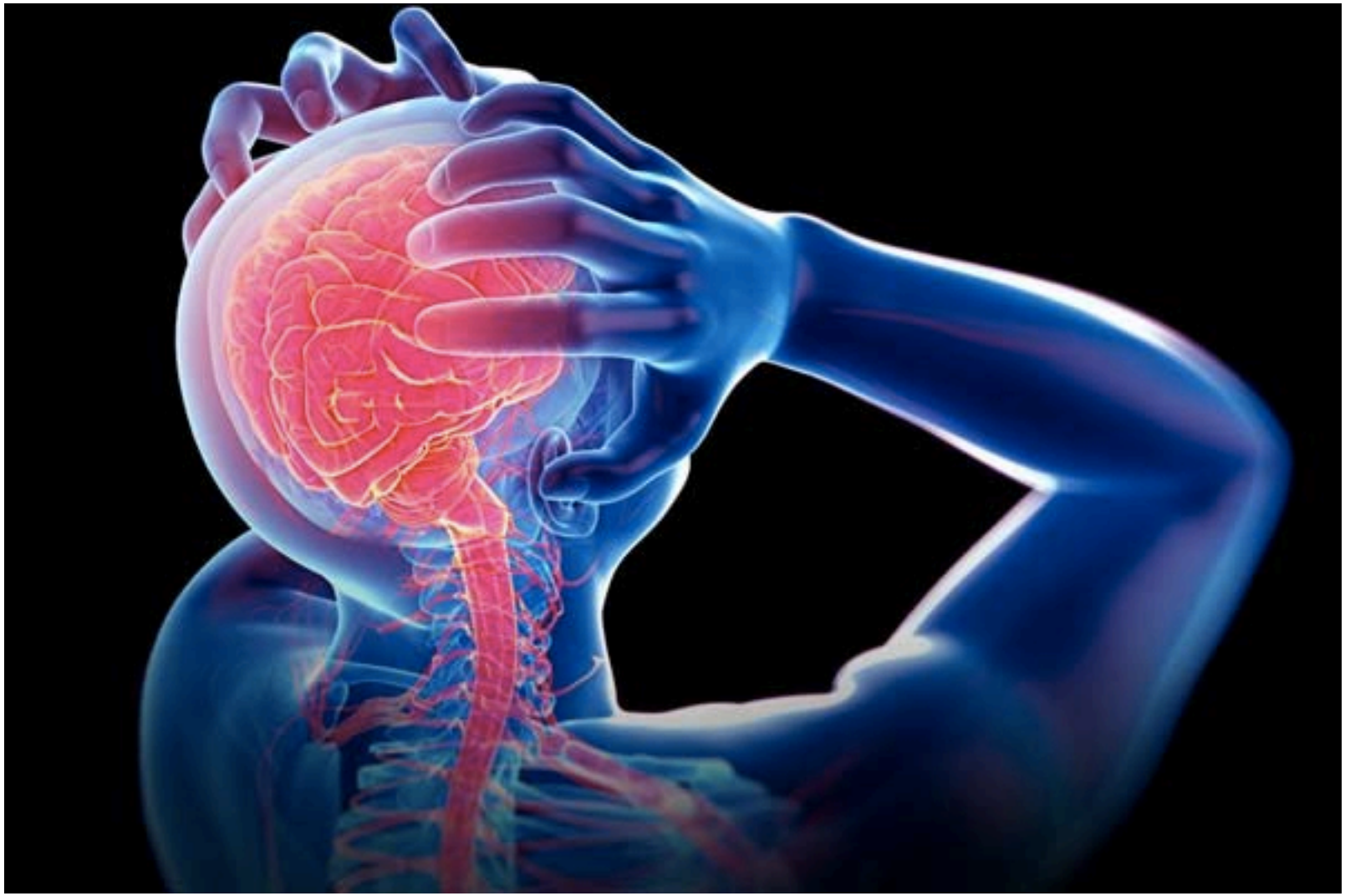
# Fusobacterium Species Growth Factors

- High energy density drinks
- Low intake of polyphenols
- Low intake of brightly colored vegetables
- Refined grain products/flours
- Foods containing added sugars
- Carbohydrate-dense foods

**Afra K, Laupland K, Leal J, Lloyd T, Gregson D. Incidence, risk factors, and outcomes of Fusobacterium species bacteremia. BMC Infect Dis. 2013;13:264. Published 2013 Jun 5. doi:10.1186/1471-2334-13-264**



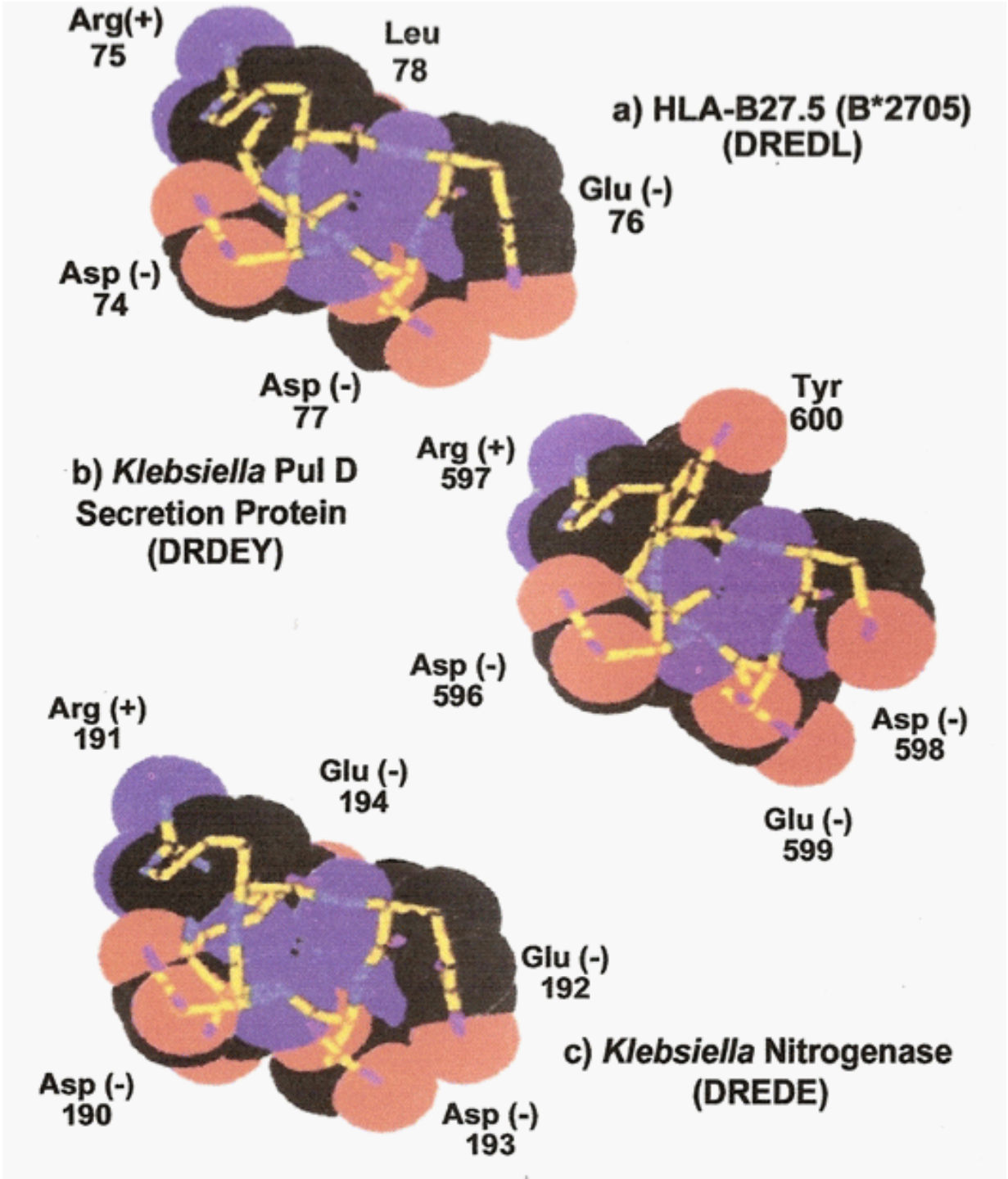

Goldstein EJ, Citron DM, Peraino VA, Cross SA. Desulfovibrio desulfuricans bacteremia and review of human Desulfovibrio infections. J Clin Microbiol. 2003;41(6):2752–2754. doi:10.1128/jcm.41.6.2752-2754.2003



**Bruce-Keller AJ, Salbaum JM, Luo M, et al. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. Biol Psychiatry. 2015;77(7):607–615. doi:10.1016/j.biopsych.2014.07.012**

# Klebsiella

- A major, most significant risk factor, for development of autoimmune diseases of the GI and skeletomuscular system
- Crohn's, Ulcerative Colitis, Ankylosing spondylitis, Rheumatoid arthritis
- Produces a digestive enzyme in metabolic response to dietary starch
- Pullanase enzyme drives innate immune response and attack on self tissue


Arg(+)
75
Leu
78
a) HLA-B27.5 (B*2705)
(DREDL)
Glu (-)
76
Asp (-)
74
Asp (-)
77
b) Klebsiella Pul D
Secretion Protein
(DRDEY)
Tyr
600
Arg (+)
597
Asp (-)
596
Asp (-)
598
Glu (-)
599
Arg (+)
191
Glu (-)
194
Glu (-)
192
c) Klebsiella Nitrogenase
(DREDE)
Asp (-)
190
Asp (-)
193

# Research with Enteral Patient Microbiome Changes

- Whole foods, plant-based formula supports greater diversity and higher lebvels of commensal/beneficial species

- Majority of commercial enteral formulas cause loss of keystone species in relatively short periods of time

**McClanahan, D., Yeh, A.S., Firek, B.A., Zettle, S., Rogers, M.S., Cheek, R., Nguyen, M.V., Gayer, C.P., Wendell, S.G., Mullett, S.J., & Morowitz, M.J. (2019). Pilot Study of the Effect of Plant-Based Enteral Nutrition on the Gut Microbiota in Chronically Ill Tube-Fed Children. JPEN. Journal of parenteral and enteral nutrition.**

**Gallagher, K. , Flint, A. , Mouzaki, M. , Carpenter, A. , Haliburton, B. , Bannister, L. , Norgrove, H. , Hoffman, L. , Mack, D. , Stintzi, A. and Marcon, M. (2018), Blenderized Enteral Nutrition Diet Study: Feasibility, Clinical, and Microbiome Outcomes of Providing Blenderized Feeds Through a Gastric Tube in a Medically Complex Pediatric Population. Journal of Parenteral and Enteral Nutrition, 42: 1046-1060. doi:10.1002/jpen.1049**

# Summary of Most Influential Lifestyle and Dietary Characteristics

- Limit use of antibiotics and reduce exposure to antibiotic residues (choose organic)
- Avoid chemical additives, artificial sweeteners, and emulsifiers
- Choose fiber-rich vegetables at most meals
- Select foods rich in polyphenols every day
- Get aerobic exercise
- Limit window of time to eat, less snacking
- Avoid concentrated, high sugar and energy-based foods and formulas

CMBM

Webinar Series

This webinar has been recorded. The presentation and the slides will be available within 24 hours at CMBM.org/webinar.

# MIND, MOOD & FOOD

## Optimal nutrition for body & brain

September 20-25, 2020

The Esalen Institute, Big Sur, CA

cmbm.org/mmf

The Center for Mind-Body Medicine

Esalen