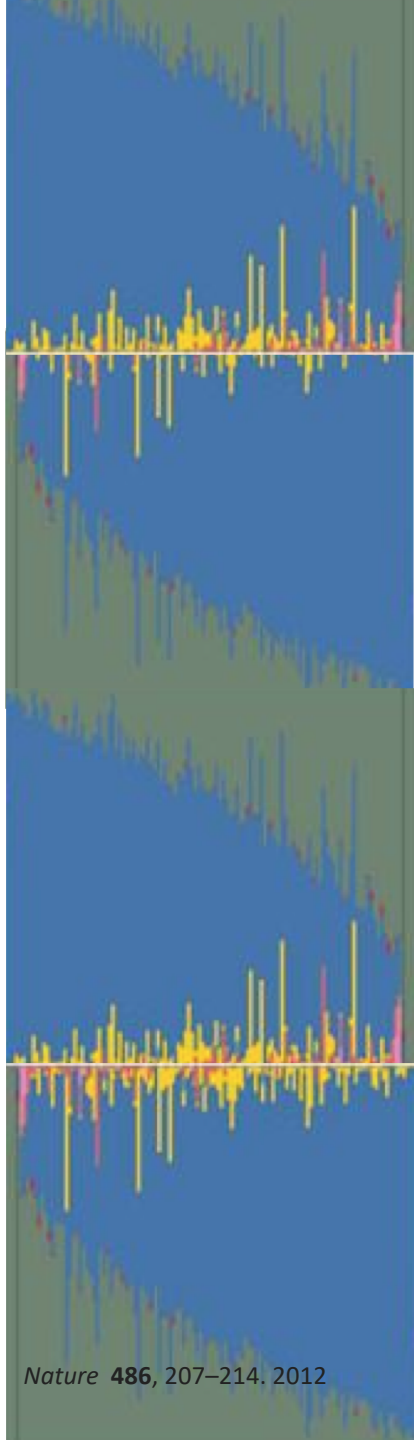
IID 209 Lecture #5:

Structure & biogeography of the gut microbiome, function, & basic disease associations

LEARNING OBJECTIVES

- Describe gut microbe and microbial processes
- Delineate properties and studies of the gut microbiome
- Identify health and disease associations related to the gut microbiota



Nature **486**, 207–214. 2012

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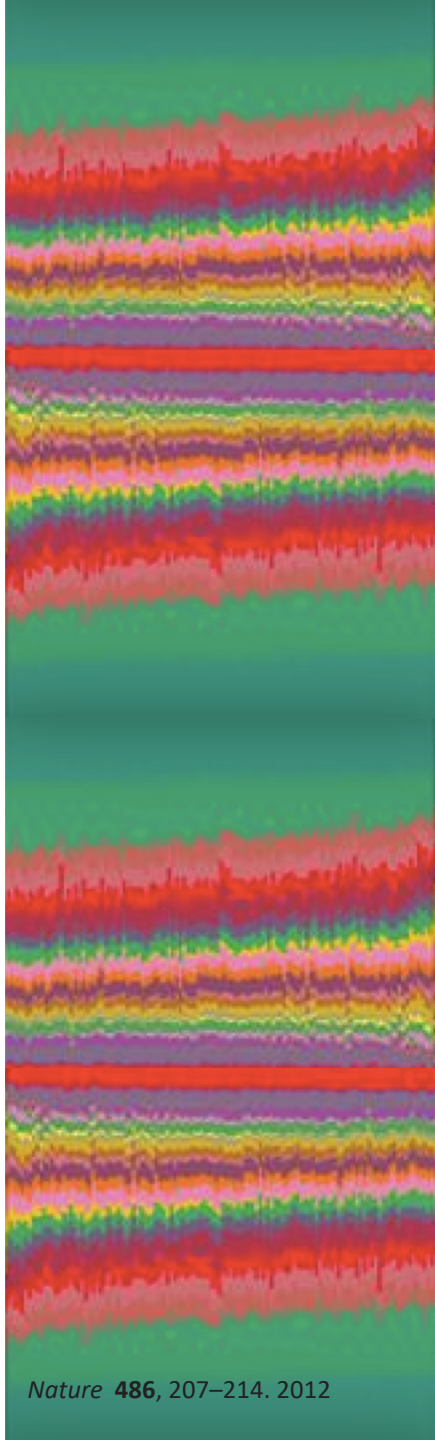
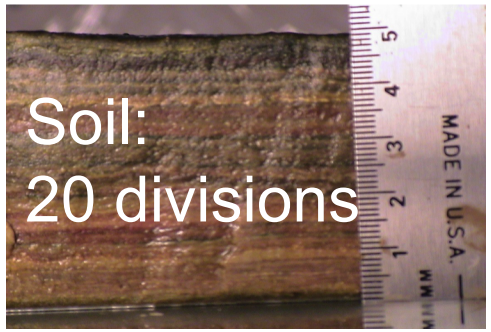
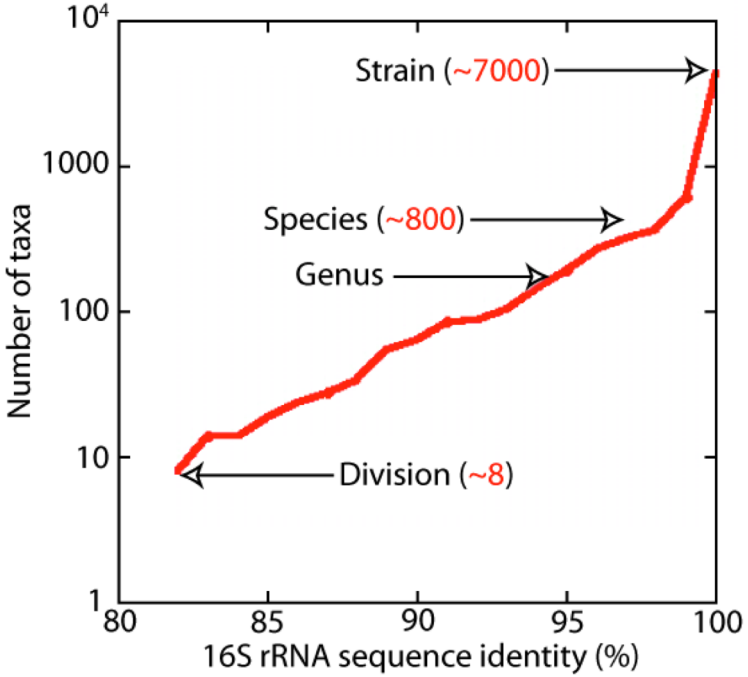
- Function of the gut microbiota
- Basic Disease Associations



Nature **486**, 207–214. 2012

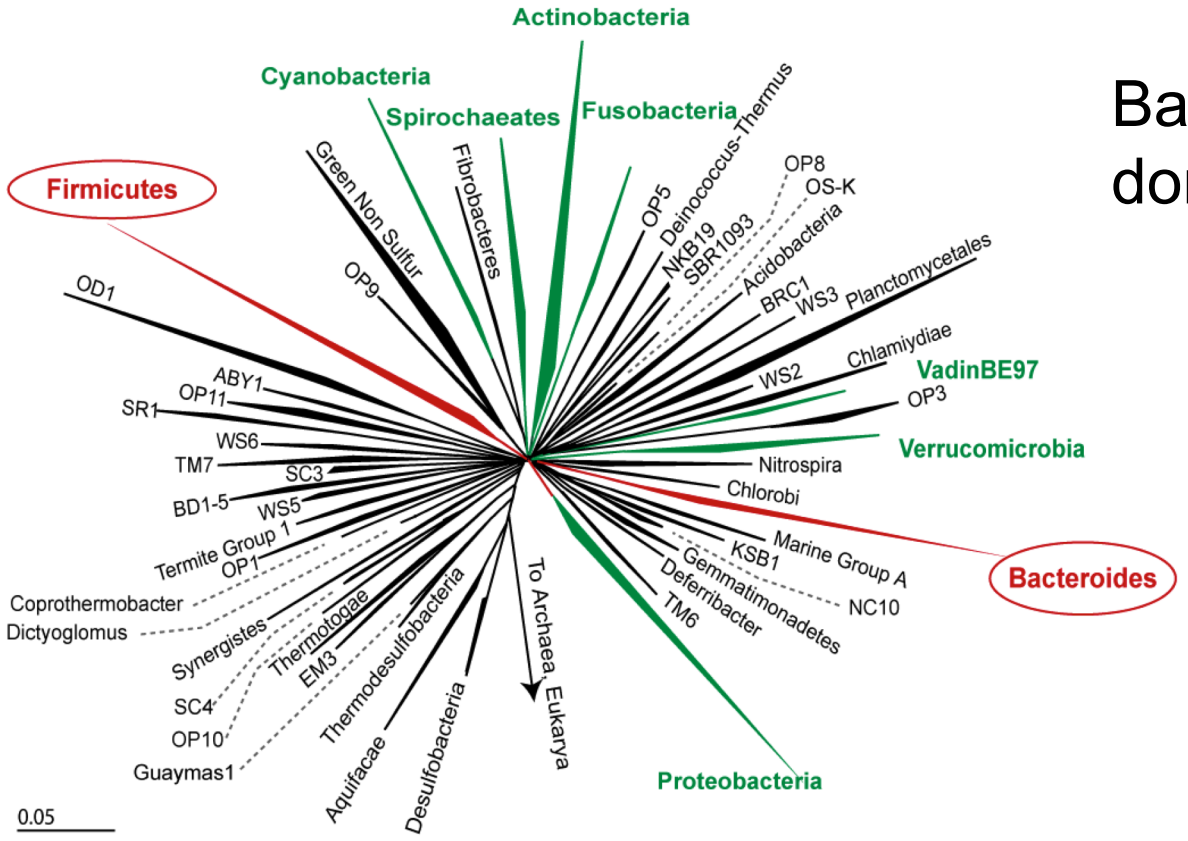
Our Gut Microbiota has Relatively Few Divisions but Tremendous Diversity at the Strain and Subspecies Level





Human gut: 9 divisions, 800 species, 7000 strains)

The Human Gut Contains 9 Bacterial Divisions



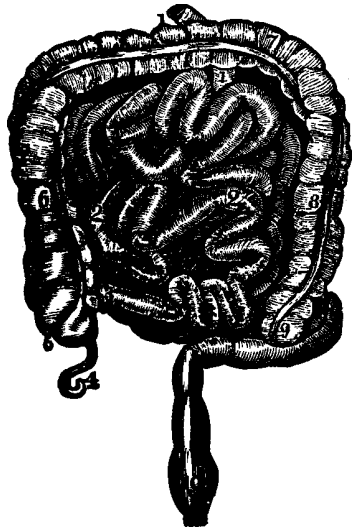
Bacteroidetes and Firmicutes dominate the distal gut

From J.I. Gordon 2008 (image generated by Ruth Ley)

THE BIG PICTURE

Gut microbiota provide a beneficial symbiotic relationship with most human hosts.

- Perform key functions in metabolism
  - Provide 10% of our daily calories via generation of short chain fatty acids
  - Vitamin production-- folate, Vitamin K
- Influence drug response
- Guide immune system development
- Protect from pathogenic microbes
- Far-ranging impact on health and quality of life.



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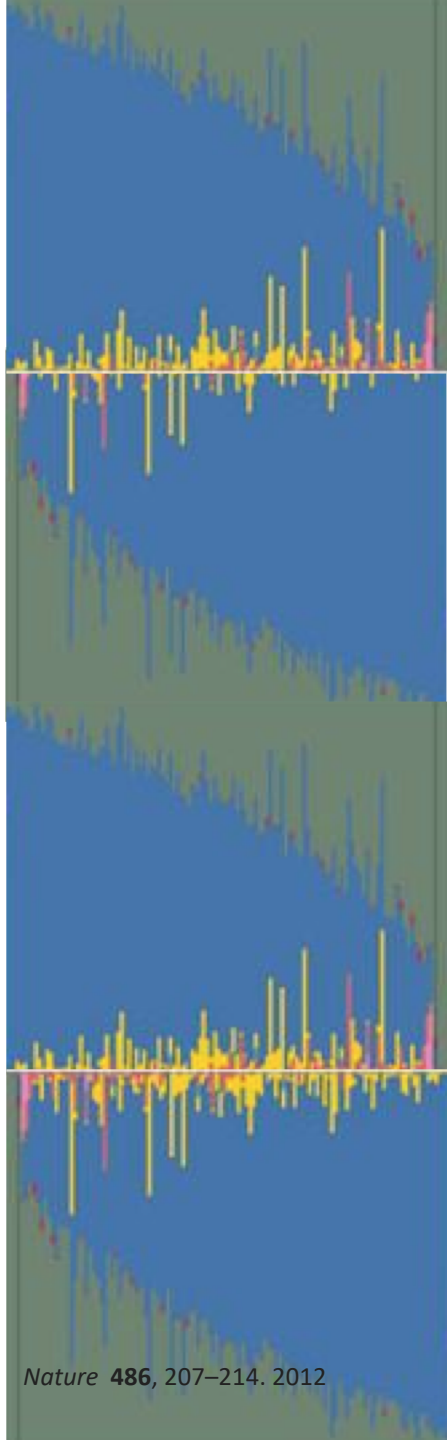
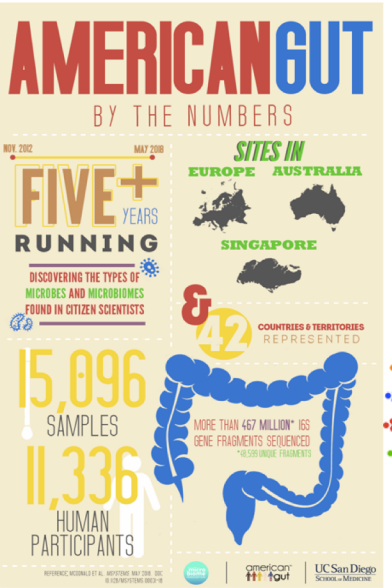


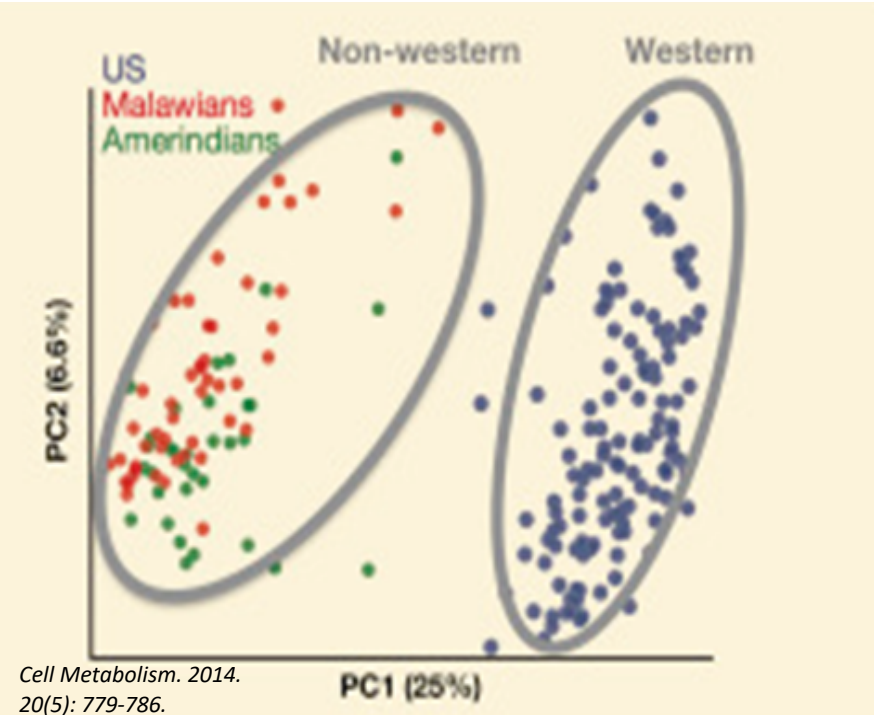
Nature **486**, 207–214. 2012

There are Many Ways to Consider Gut Microbiota Structure Peri- and Post-HMP and MetaHIT (population-scale initiatives)

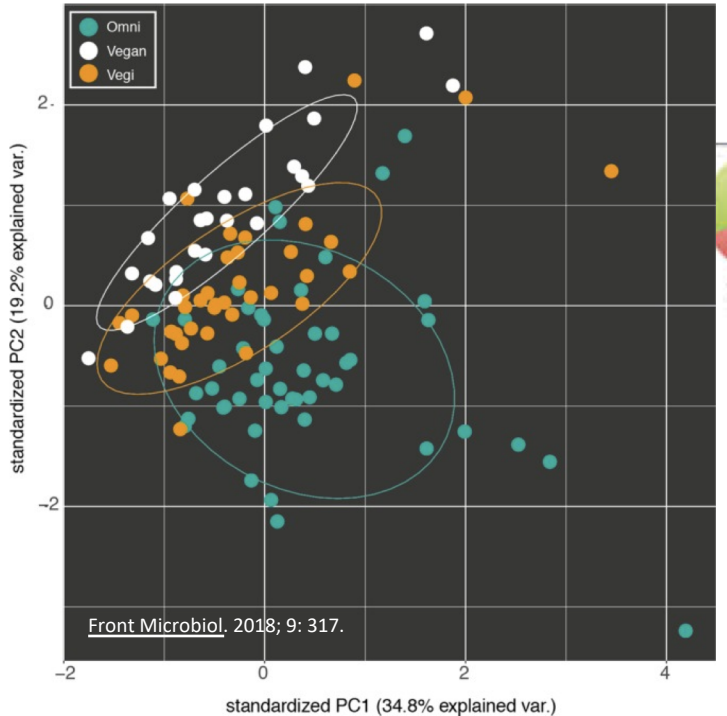
- THE AMERICAN GUT PROJECT, ‘crowd-sourced’
- BIOM-Mass and The Harvard Chan Center for the Microbiome in Public Health
- CAS-CMI (Chinese Academy of Sciences Initiative of Microbiome)
- Eldermet
- International Human Microbiome Consortium



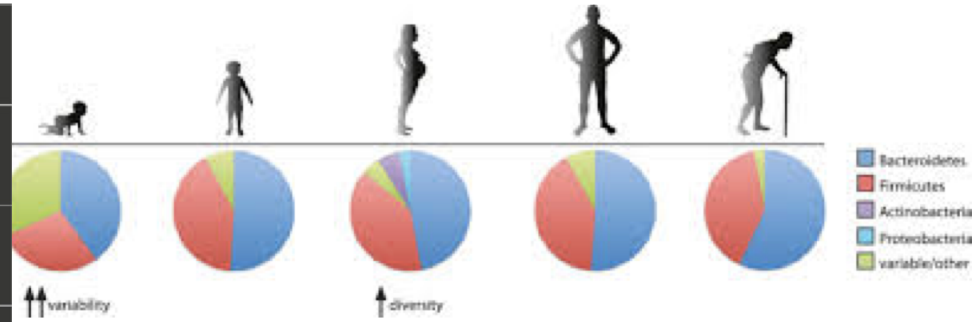
There are Many Gut Microbiota Structures to Consider
(healthy global populations and populations across lifespan)



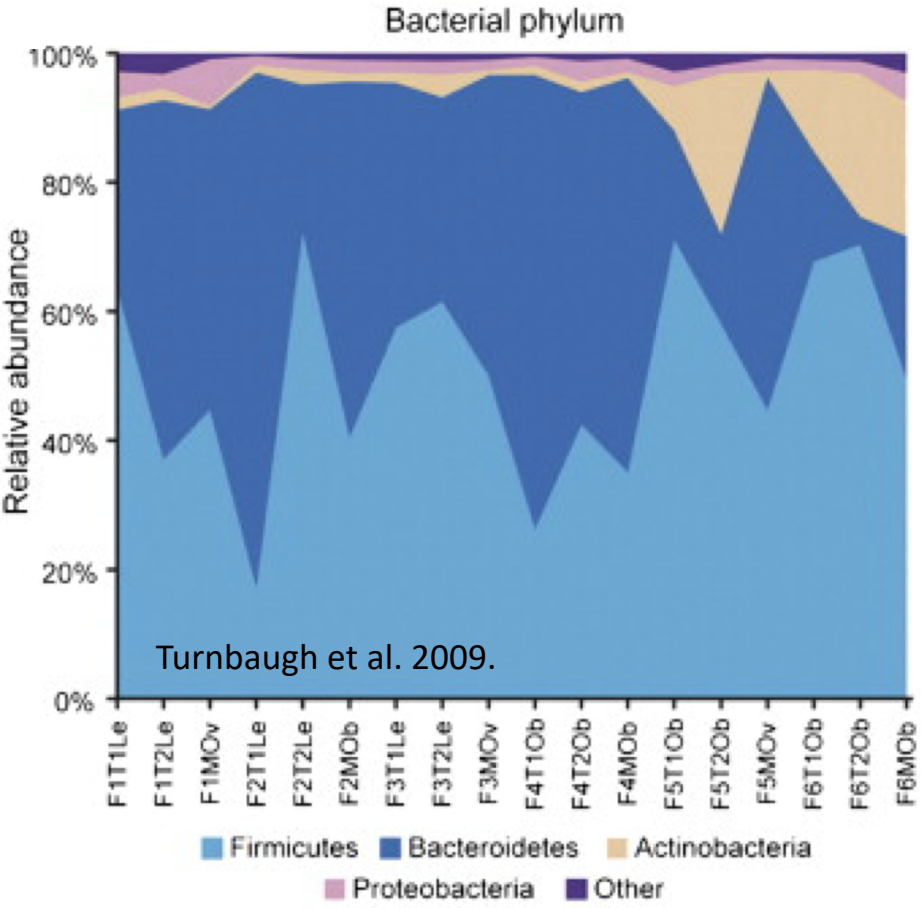
Cell Metabolism. 2014. 20(5): 779-786.



Front Microbiol. 2018; 9: 317.



Gut Microbiota Structure: Who Is There…



Turnbaugh et al. 2009.

What is a healthy gut microbiome?

- One that is stable or resists change in response to stress and returns to homeostasis in response to perturbation (eco-perspective)
  - Resistance and Resilience

Is there an ideal community of microbes?

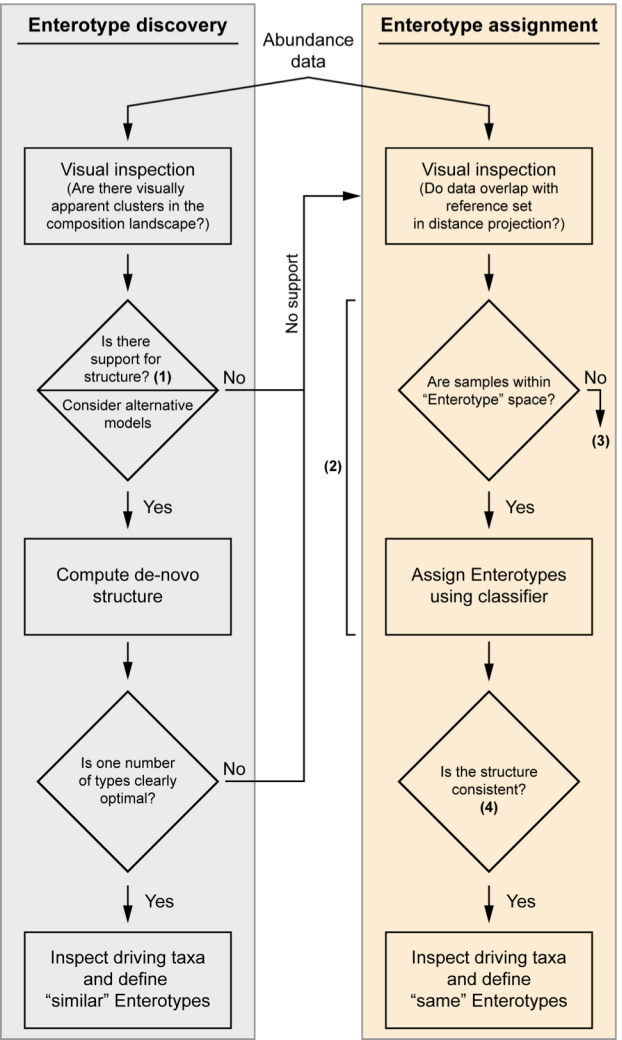
- No, rather a healthy set of metabolic functions

What properties define a healthy gut microbiome?

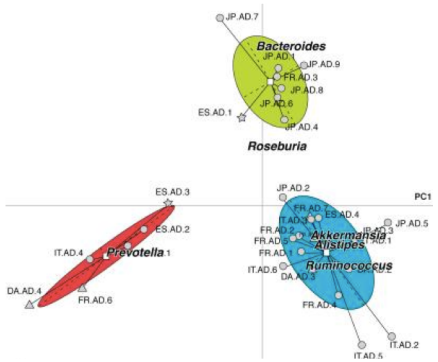
- Diversity

Concept of Core Microbiome & Enterotype…

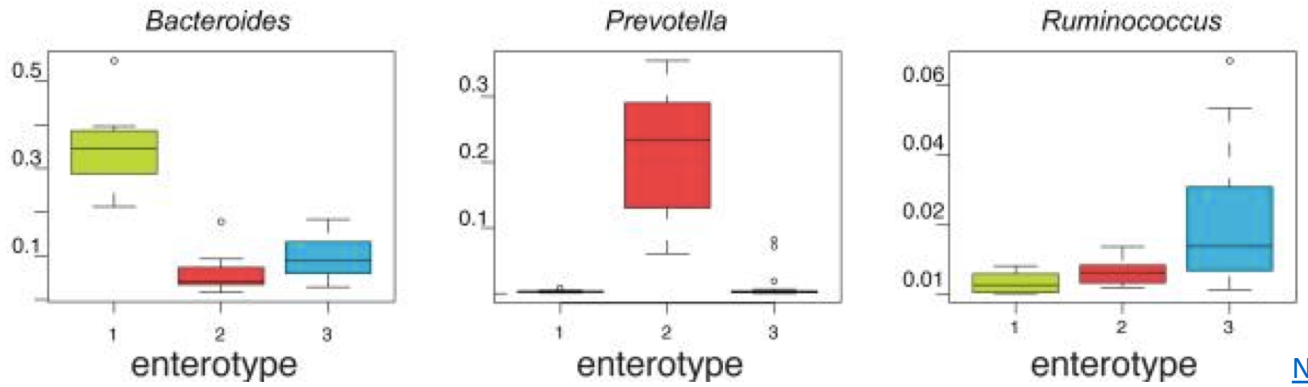
An Enterotype Classifier Model: a goal to simplify microbiome structure and then some controversy



- Finding patterns in data– what we all strive for
- Caveats in 'over-fitting' and 'over-simplifying'– what we are all mindful of
- Dangers in losing control of how your data are communicated– what we all fear



Popular Press Version: "You've likely heard of **blood types** and may even know your own. Someday, you may also know your gut type or enterotype. ~~ENTEROTYPE = BLOOD TYPE"~~



"entero-gradients"

Nature. 2011 May 12; 473(7346): 174–180.

What are some of the factors that influence gut microbiota structure?

Factor	Evidence from	Selected References
Mode of fetus delivery	Humans	Dominguez-Bello et al. (2010), Palmer et al. (2007)
Geographic origin	Humans	De Filippo et al. (2010)
Host genotype	Humans	Spor et al. (2011) and references therein; Li et al. (2012)
	Mice	Kovacs et al. (2011), Ley et al. (2005), Benson et al. (2010)
Diet	Humans	Walker et al. (2011), Wu et al. (2011)
	Animals	Turnbaugh et al. (2008), Hildebrandt et al. (2009), Turnbaugh et al. (2009)
Antibiotics	Humans	Willing et al. (2011a), Jernberg et al. (2007), Dethlefsen and Relman (2011)
	Mice	Yap et al. (2008), Cani et al. (2008)
Probiotics	Humans	Rauch and Lynch (2012) and references therein
	Animals	Garcia-Mazcorro et al. (2011)
Age	Humans	Tiihonen et al. (2010), Biagi et al. (2010)
Stress	Humans	Konturek et al. (2011) and references therein

https://doi.org/10.1016/j.chom.2012.10.012

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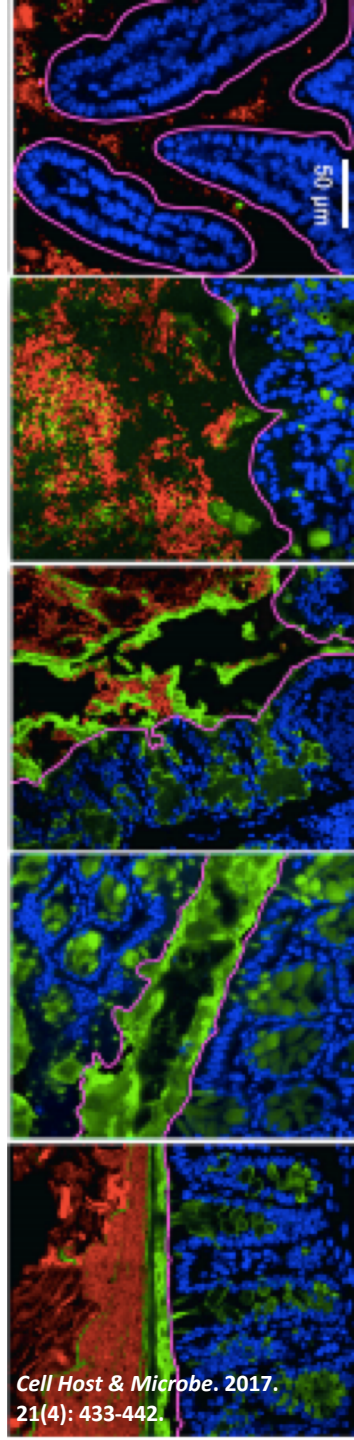
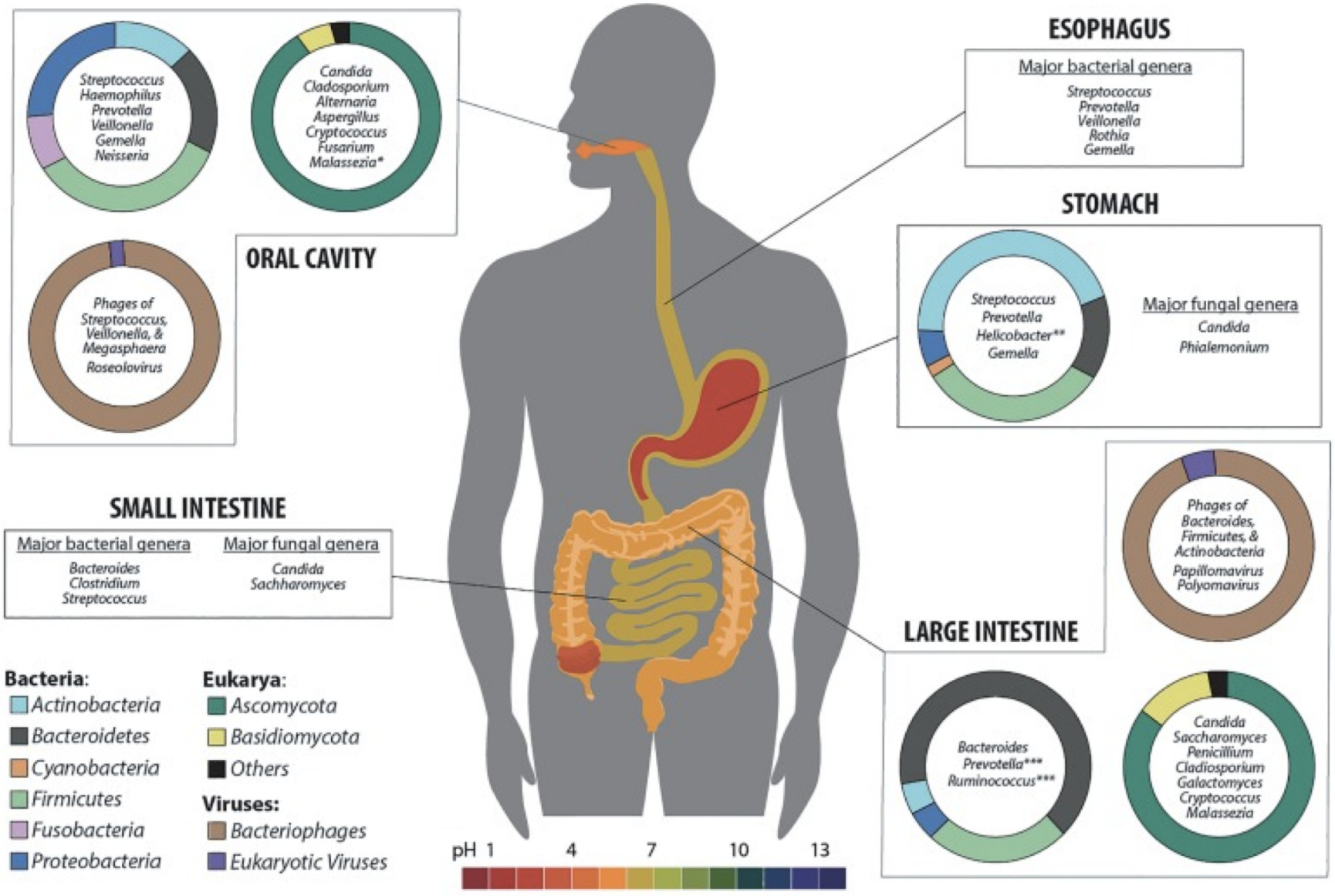


Cell Host & Microbe. 2017. 21(4): 433-442.

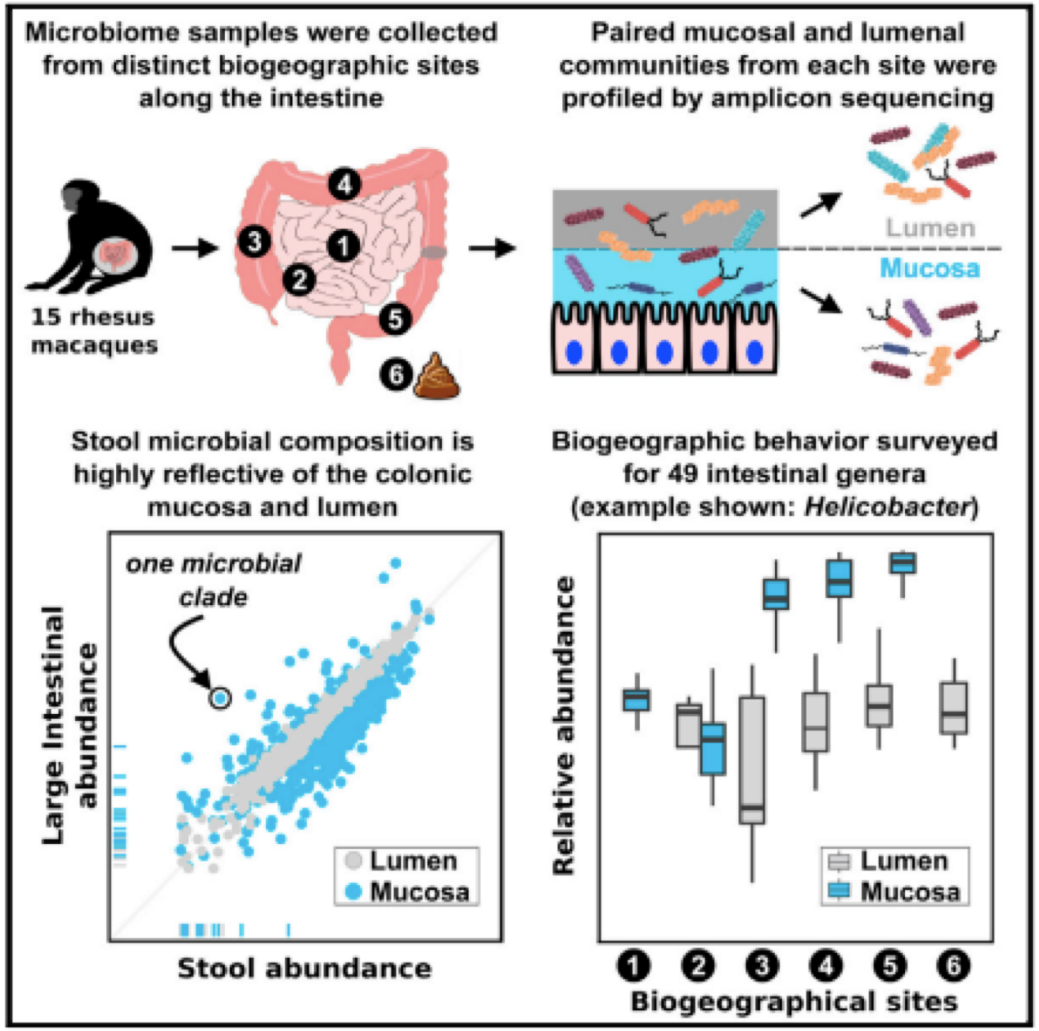
The GI tract offers distinct microhabitats for the microbiota



- **Chemical gradients (e.g., pH, oxygen levels, bile)**
- **Nutrient availability (lumen, mucins, & transit time)**
- **Physical characteristics of surface (epithelial type, mucus, etc.)**
- **Immune effectors**

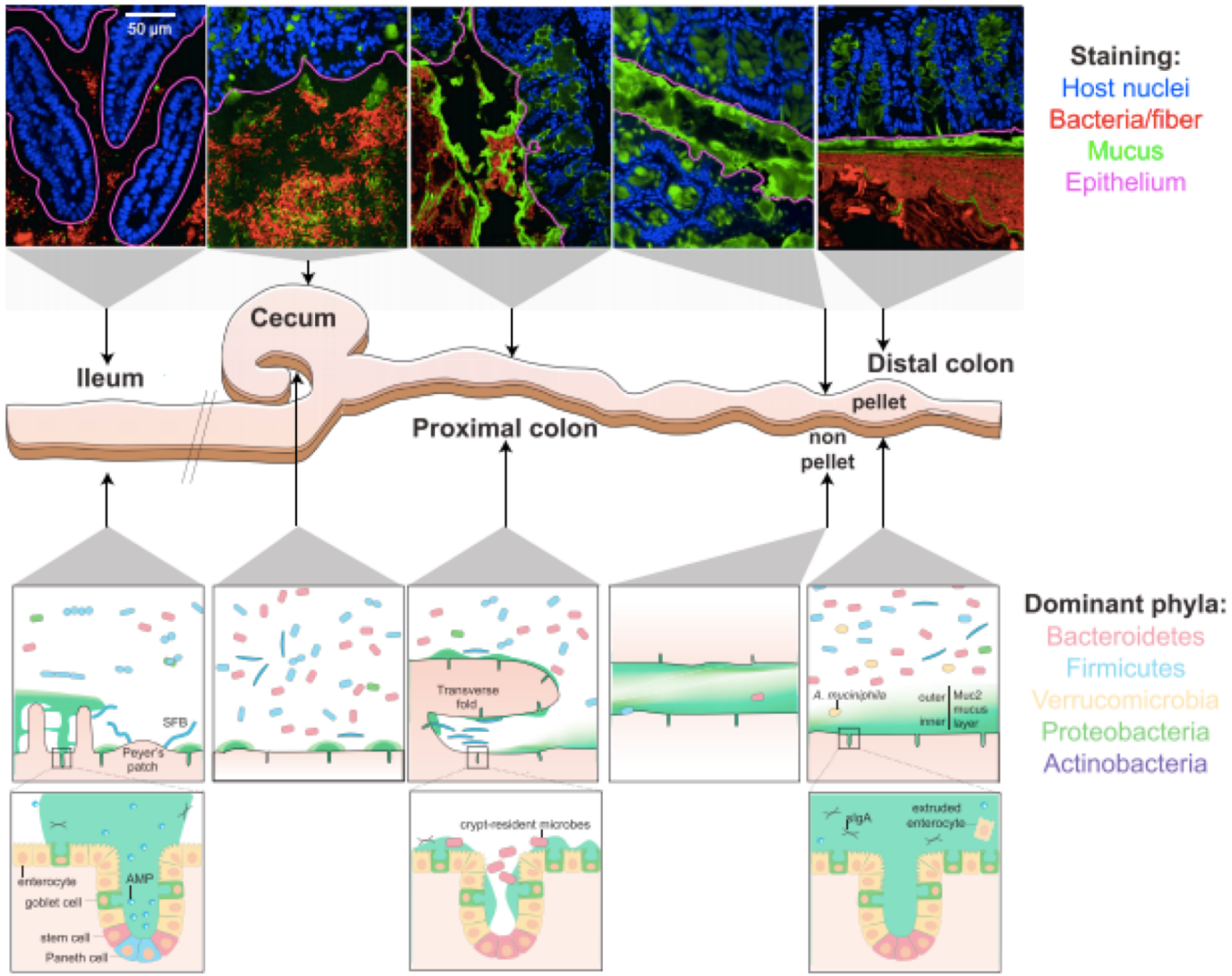
Microbes Environ. 2017 Dec; 32(4): 300–313.

Biogeography of the lumenal and mucosal gut microbiome from a non-human primate



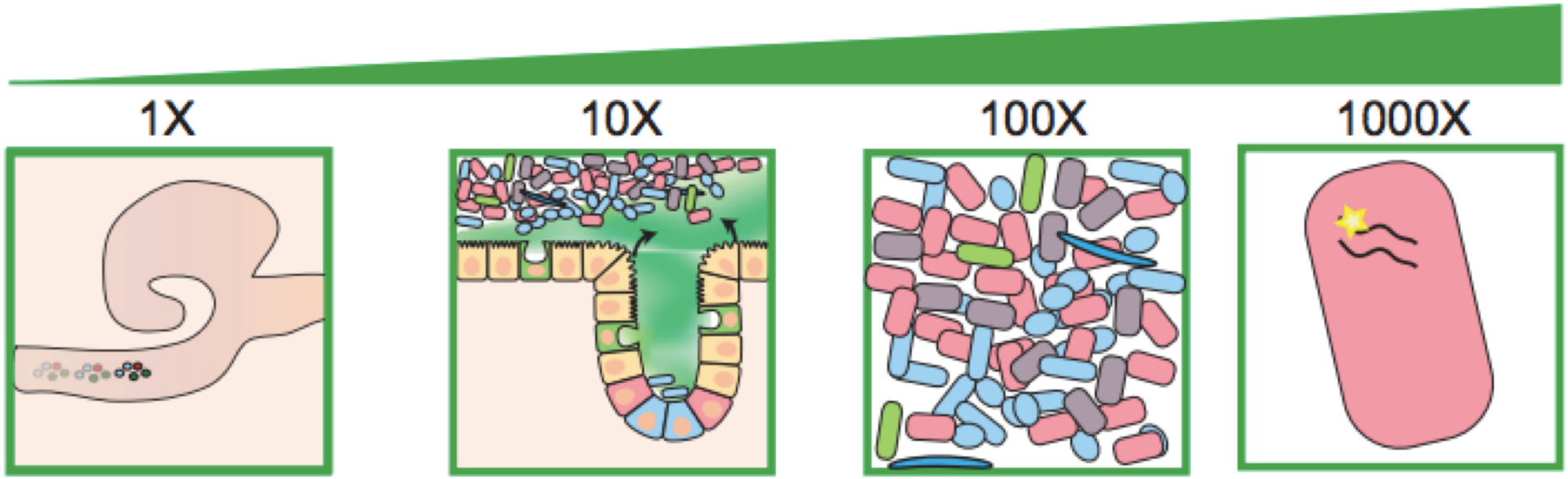
http://dx.doi.org/10.1016/j.chom.2015.01.015

Biogeography of the mouse gut microbiota



http://dx.doi.org/10.1016/j.chom.2017.03.010

Model systems such as mice are providing opportunities to innovate and refine biogeography and functional studies



http://dx.doi.org/10.1016/j.chom.2017.03.010

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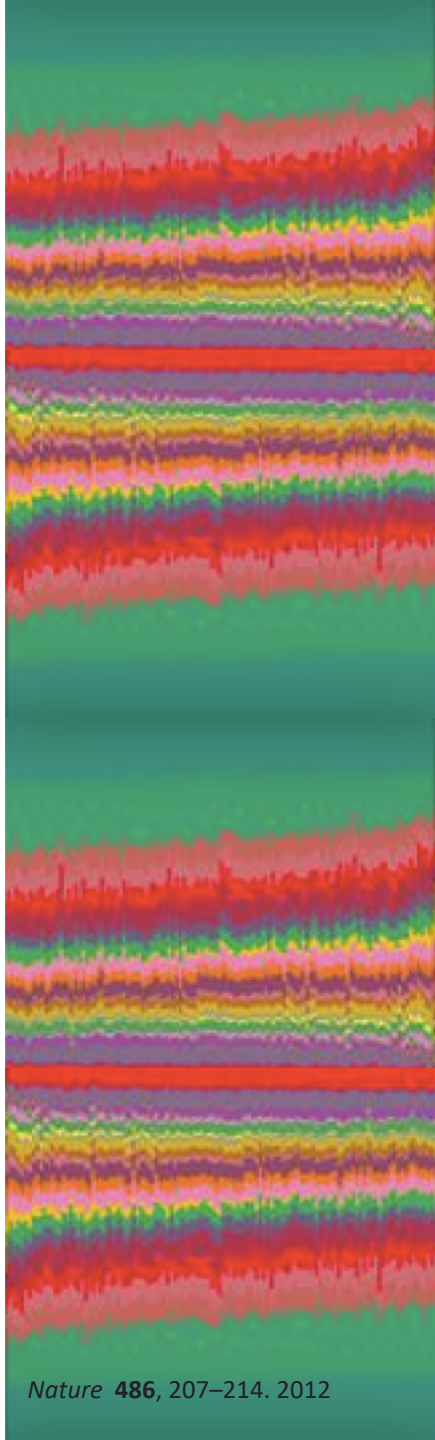
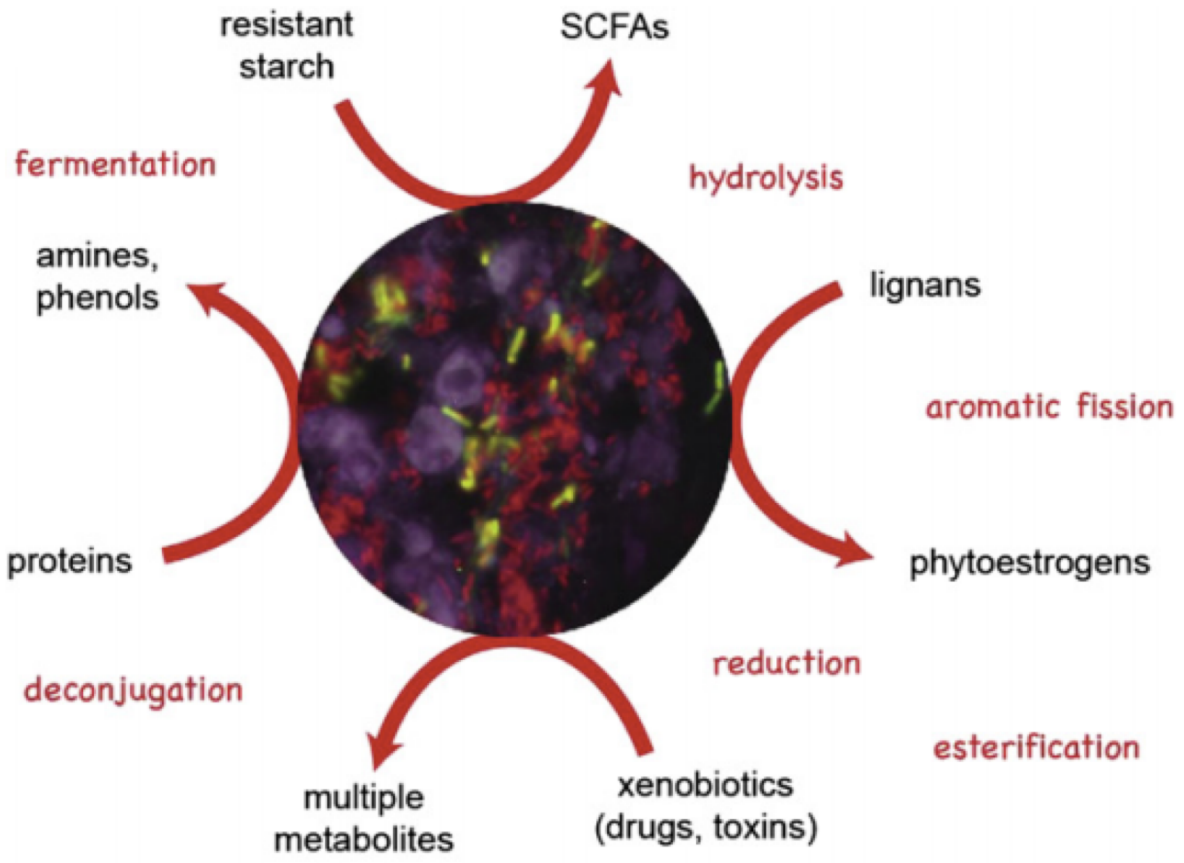


Nature **486**, 207–214. 2012

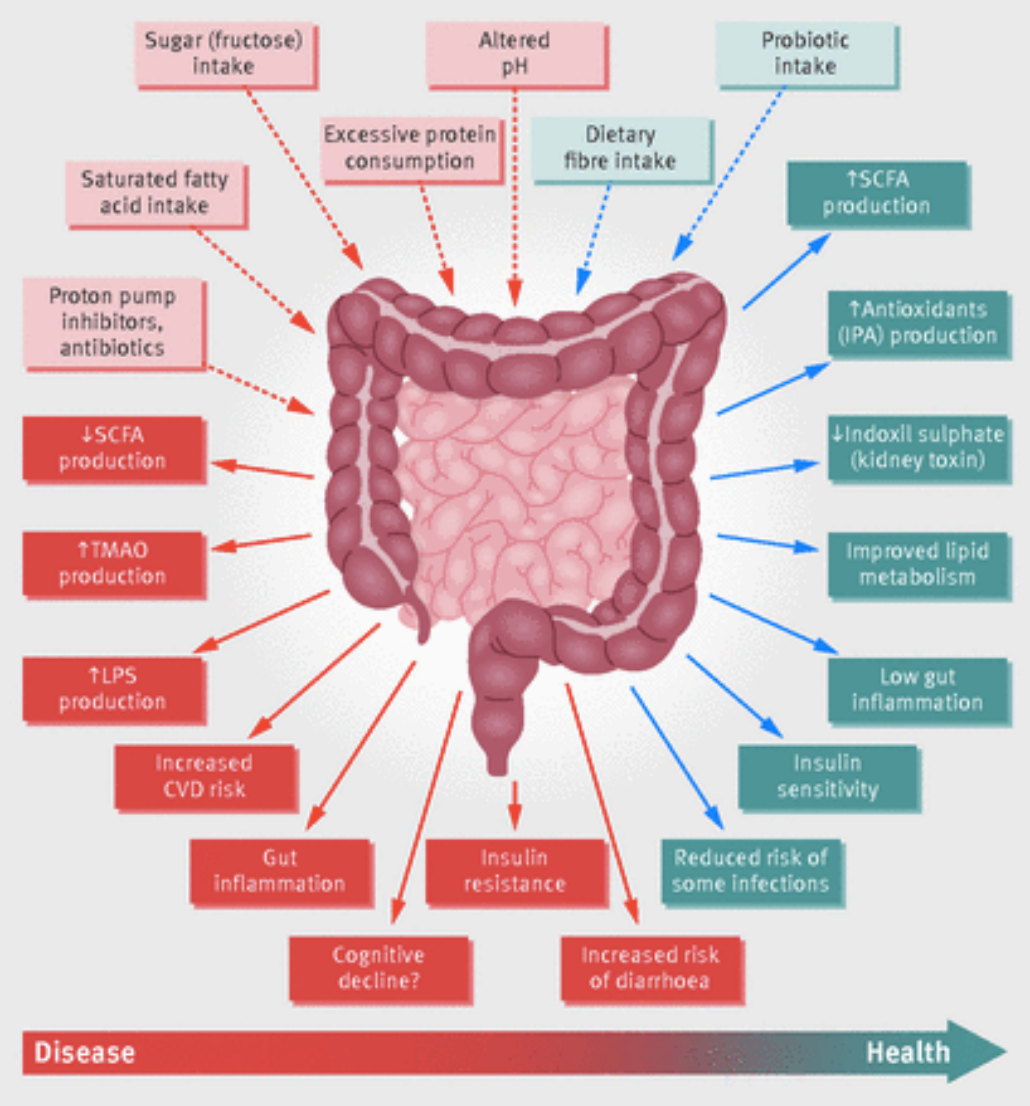
Gut microbiota function
metabolic

Function = metabolic activities and end products that result from microbial activity



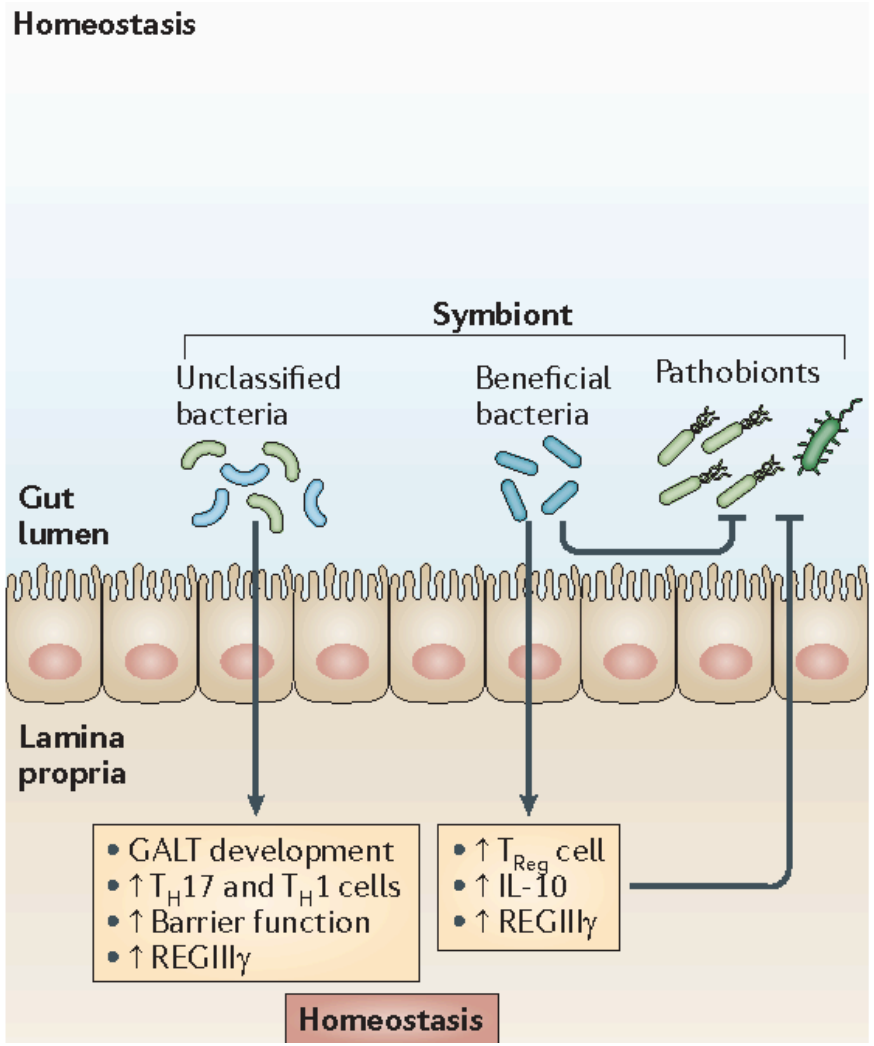
https://doi.org/10.1016/j.chom.2012.10.012

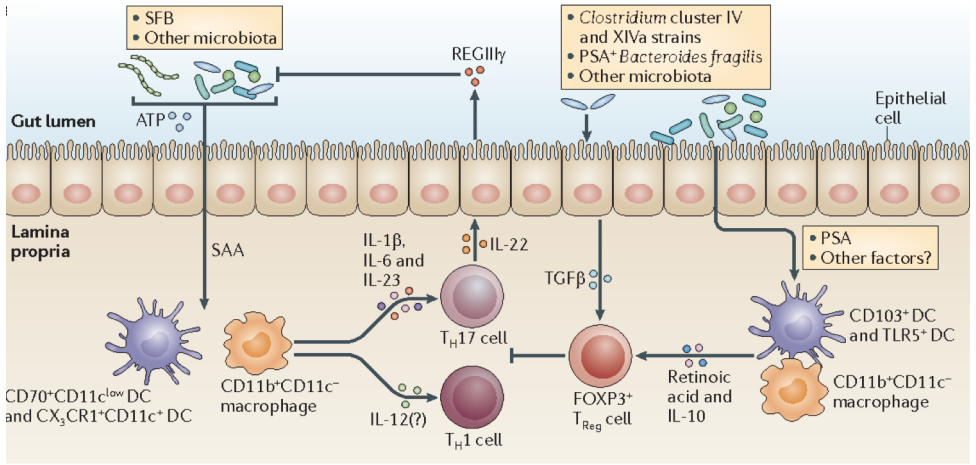
Gut microbiota function meting out health and disease

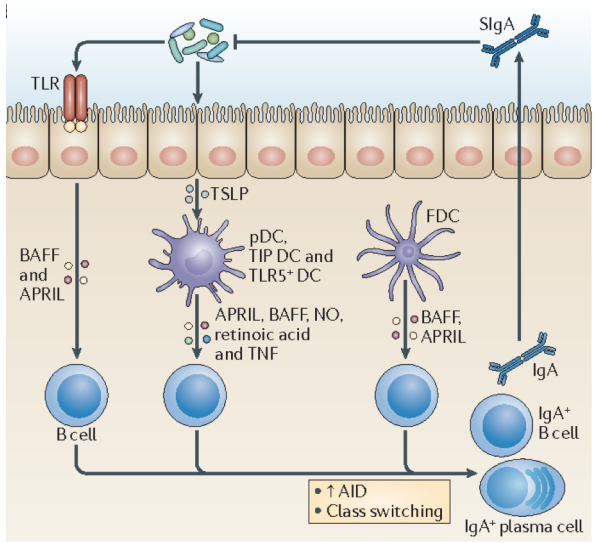


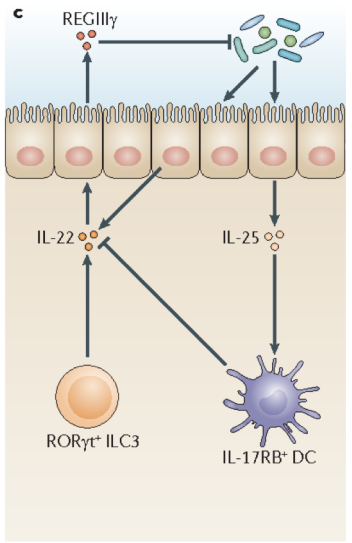
https://www.bmj.com/content/361/bmj.k2179

Gut microbiota and the Immune system

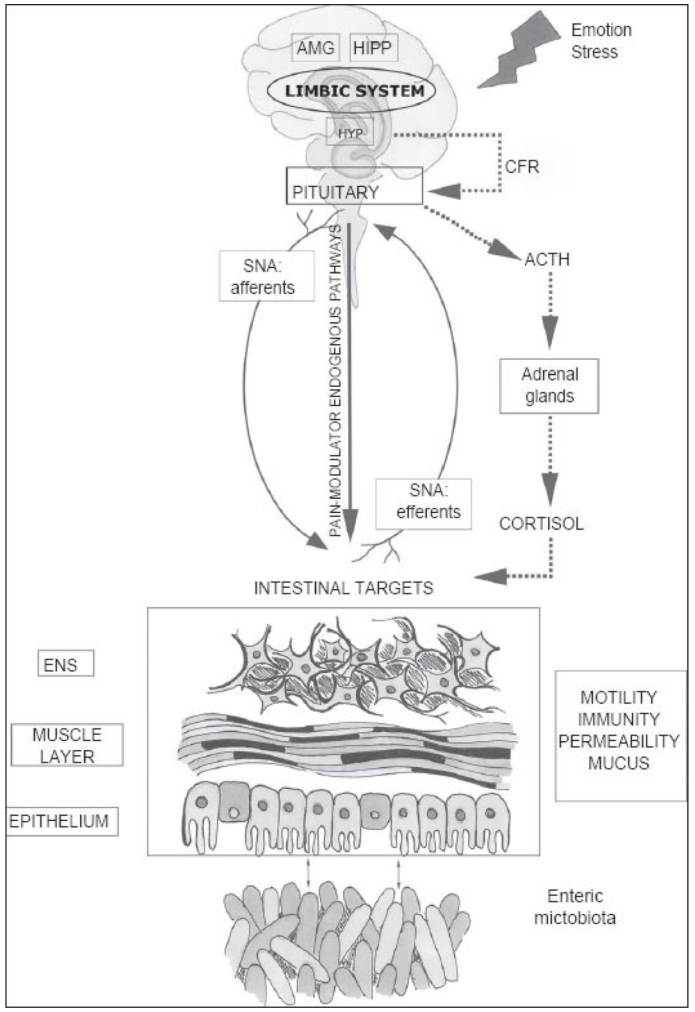








The Gut Brain Axis



The microbiota, interacts not only locally with intestinal cells and the enteric nervous system, but also directly with CNS through neuroendocrine and metabolic pathways.

From gut microbiota to brain:

- Production, expression and turnover of neurotrasmitters (i.e. serotonin, GABA) and neurotrophic factor (BDNF)
- Protection of intestinal barrier and tight junction integrity
- Modulation of enteric sensory afferents
- Bacterial metabolites
- Mucosal immune regulation

From brain to gut microbiota:

- Alteration in mucus and biofilm production
- Alteration in motility
- Alteration of intestinal permeability
- Alteration in immune function

Ann Gastroenterol. 2015 Apr-Jun; 28(2): 203–209.

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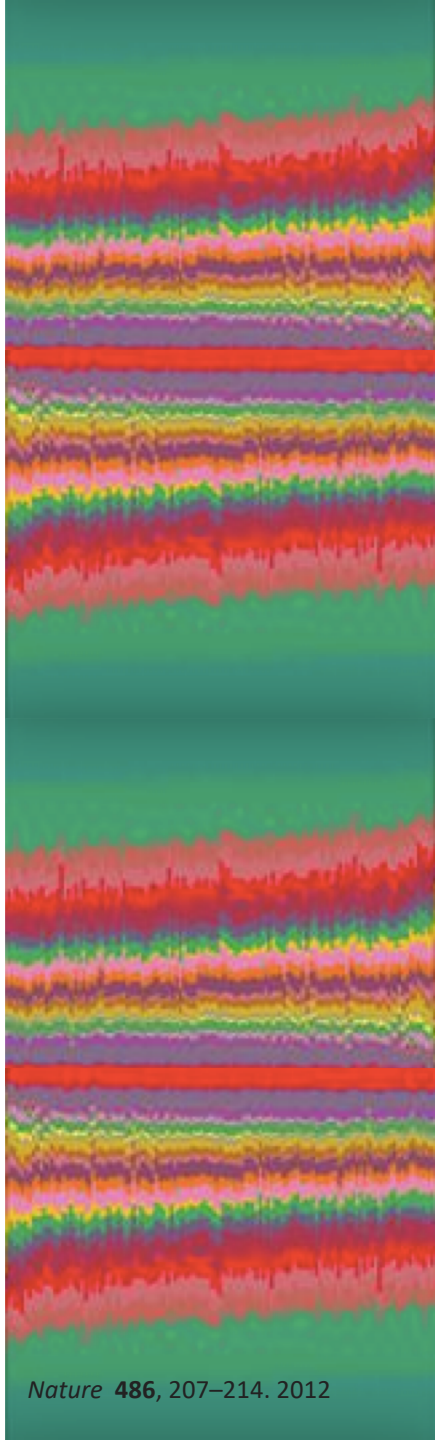
- **Basic Disease Associations-Dysbiosis Associated Diseases**



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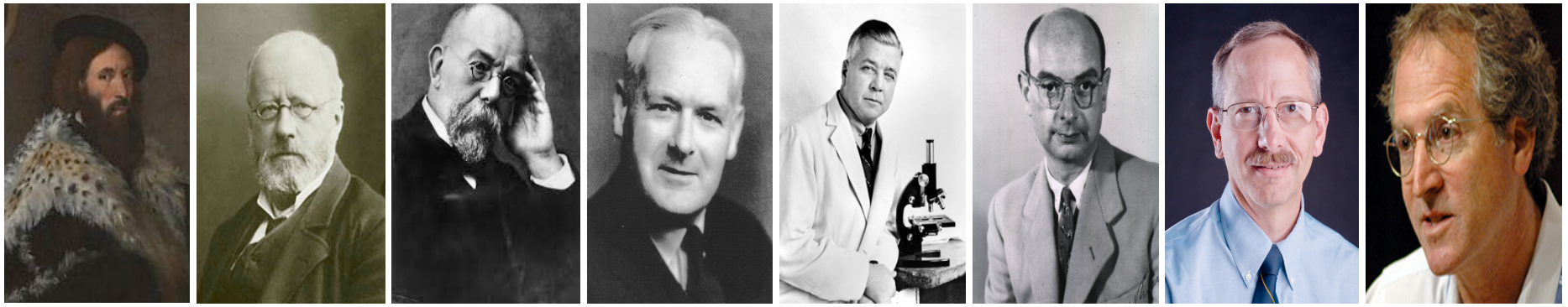
The Microbiome in Health & Disease

Aging
Allergy and Atopic Diseases
Asthma
Autism Spectrum Disorders
Cancer
Celiac Disease
Colitis and Crohn's Disease
Diabetes, type 1 and 2
Fecundity & Fertility
HIV and AIDS
Heart Disease
Human Health
Infectious Diseases

Malaria Transmission
Malnutrition
Metabolism
Mood & Psychiatric Disorders
Multiple Sclerosis
Neurodegenerative Diseases
Non-alcoholic fatty liver disease
Obesity
One Health
Osteoporosis
Pre-term Labor
Rheumatoid Arthritis
Zoonoses

"Understanding the microbiome will transform our understanding of how healthy bodies become diseased, how aging leads to infirmity, and especially how we might alter our internal ecosystems to prevent and treat a vast range of conditions."

Causality theory from miasma to the microbiome



Fracastoro Klebs Koch Bradford Rivers Evans Fredericks Relman

From Koch's four postulates to a framework

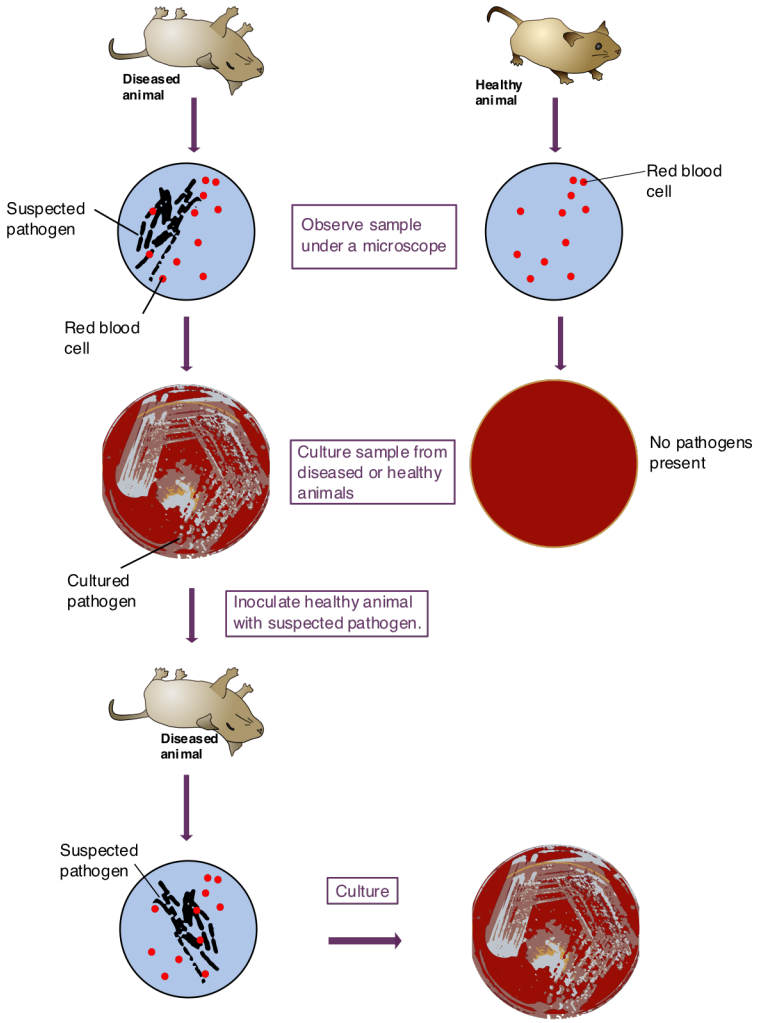
Koch's Postulates:

① The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.

② The microorganism must be isolated from a diseased organism and grown in pure culture.

③ The cultured microorganism should cause disease when introduced into a healthy organism.

④ The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.



wikipedia

Epidemiology

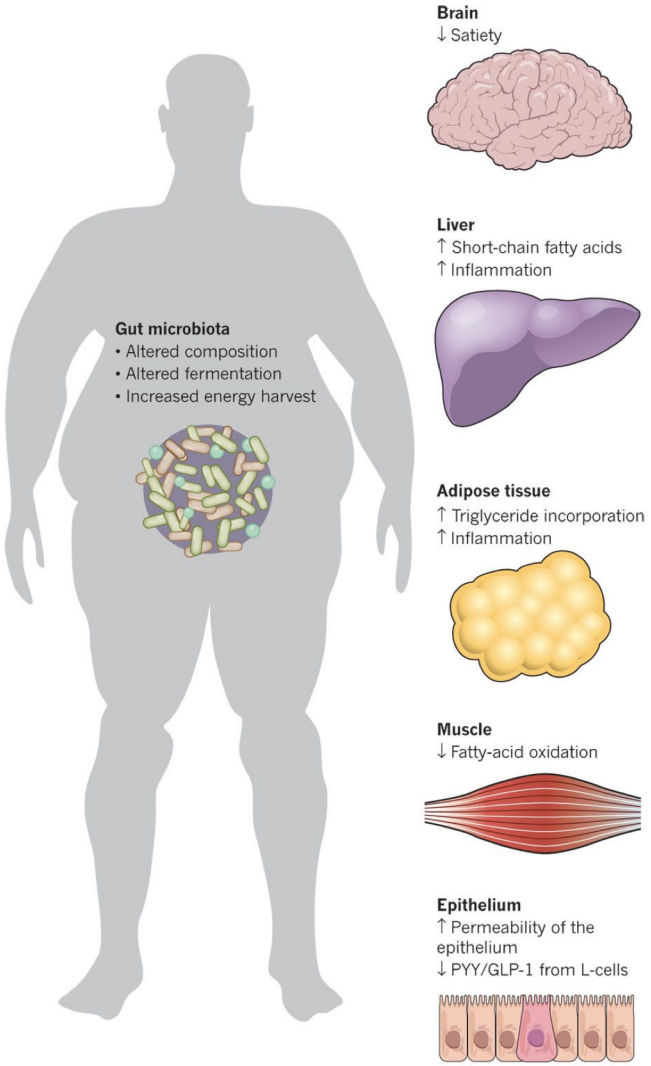
Immunological Response

Experimental Disease Reproduction

Biological Plausibility

Elimination or modification or addition of agent

Overnutrition(obesity) & the gut microbiota

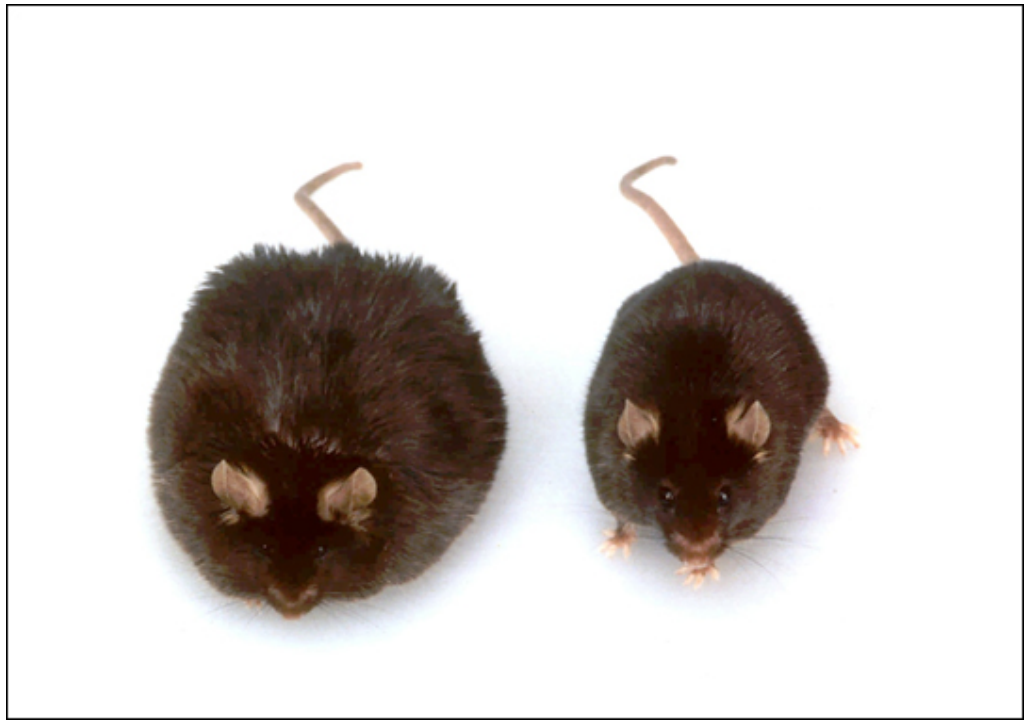


- Obesity is an abnormal or excessive fat accumulation that presents a risk to health.
- A crude population measure of obesity is the body mass index (BMI), a person's weight (in kilograms) divided by the square of his or her height (in meters). A person with a BMI of 30 or more is generally considered obese.
- A person with a BMI equal to or more than 25 is considered overweight.
- Overweight and obesity are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer.
- Once considered a problem only in high income countries, overweight and obesity are now dramatically on the rise in low- and middle-income countries, particularly in urban settings.

-**World Health Organization**

https://www.slideshare.net/mongithyousif/gut-microbiota-in-health-and-disease-76411624

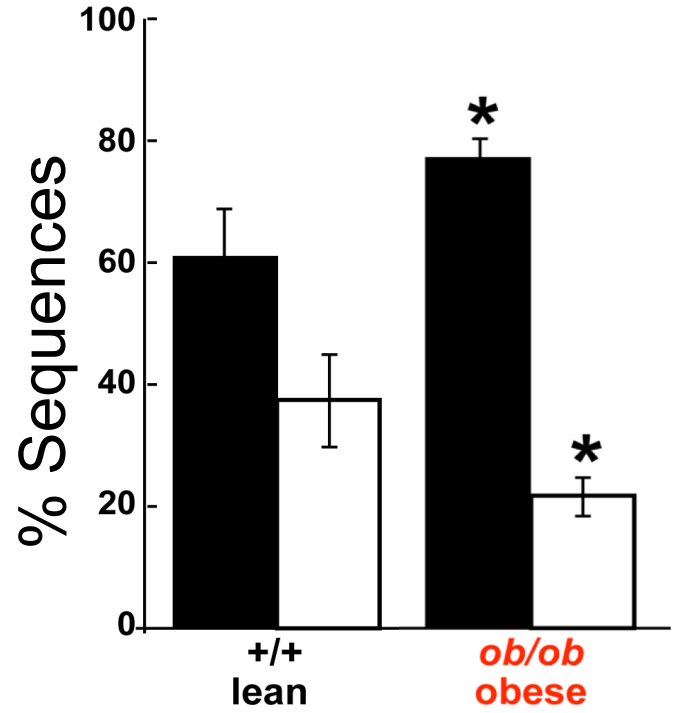
Since the Gut Microbiota is a Metabolic Organ, Can it Affect the Risk for Obesity?

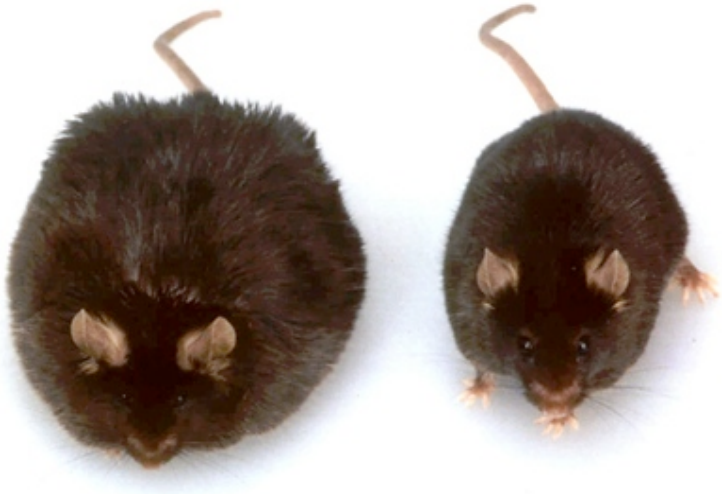


- Epidemiology
- Immunological Response
- Experimental Disease Reproduction
- Biological Plausibility
- Elimination or modification or addition of agent

https://envlit.educ.msu.edu/publicsite/files/.../KBS_Human%20Microbiome.ppt

Different gut microbial community structure in obese mice



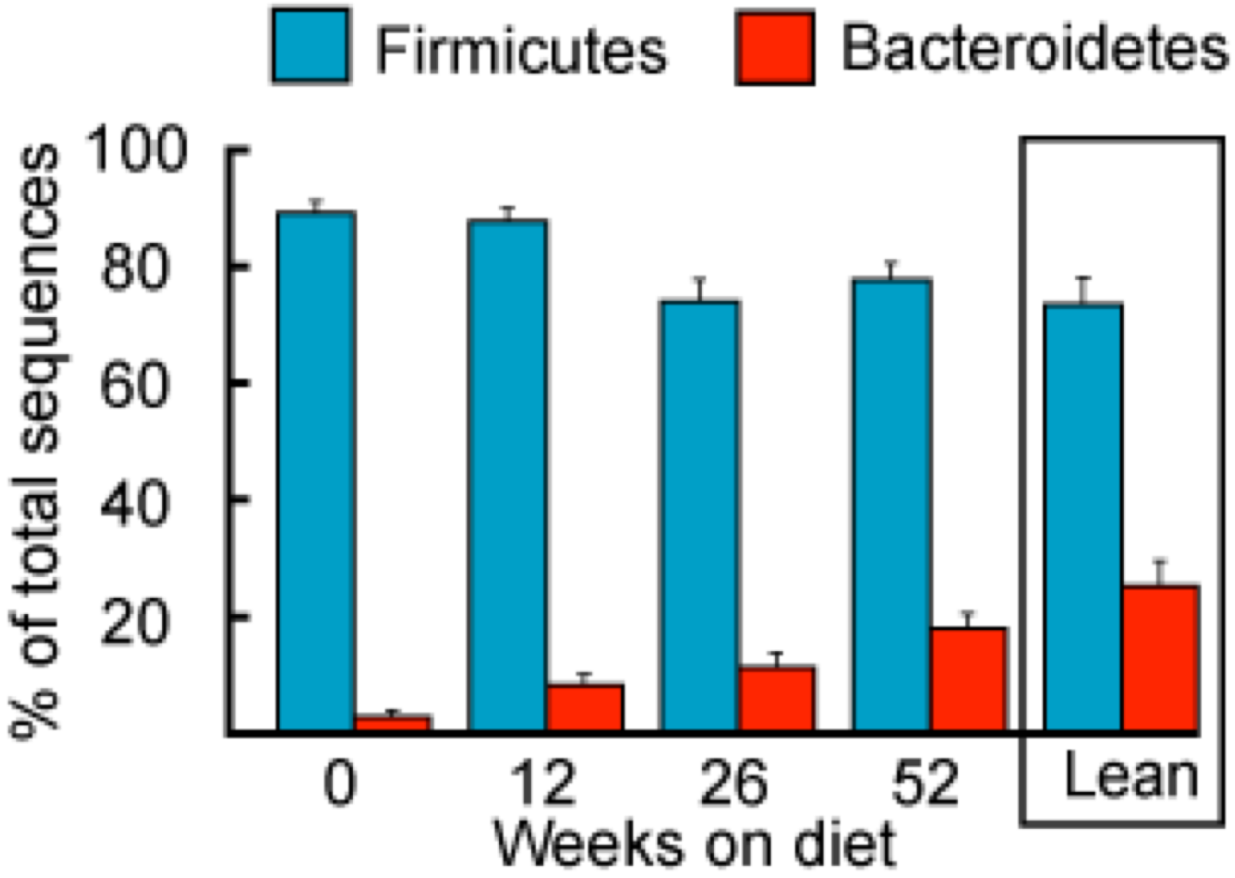


Firmicutes

Bacteroidetes

Ley *et al.*, PNAS 102: 11070-5 (2006)

Effects of dieting

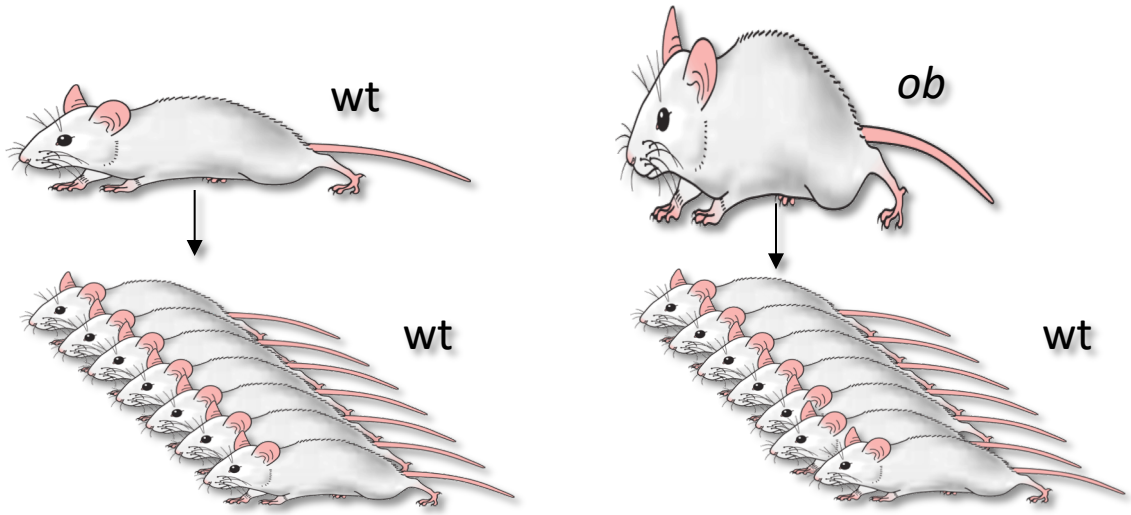


Ley *et al*. Nature 444: 1022 (2006)

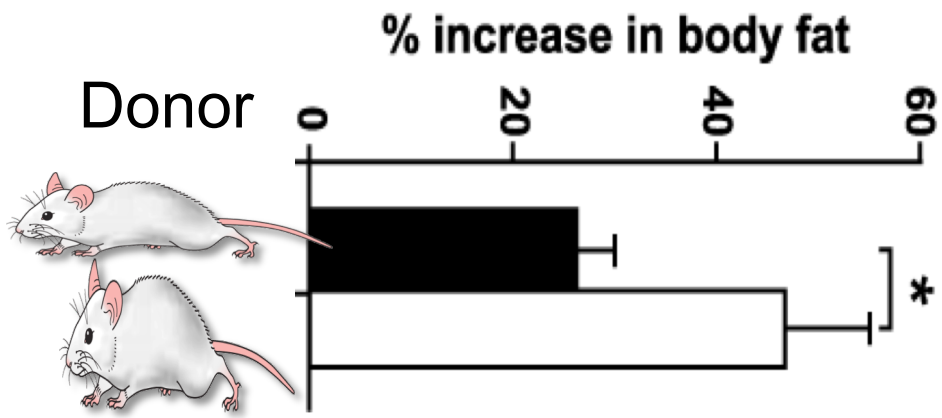
Microbiota fecal transplantation

Conventionally raised donors

Germ-free Wild type recipients

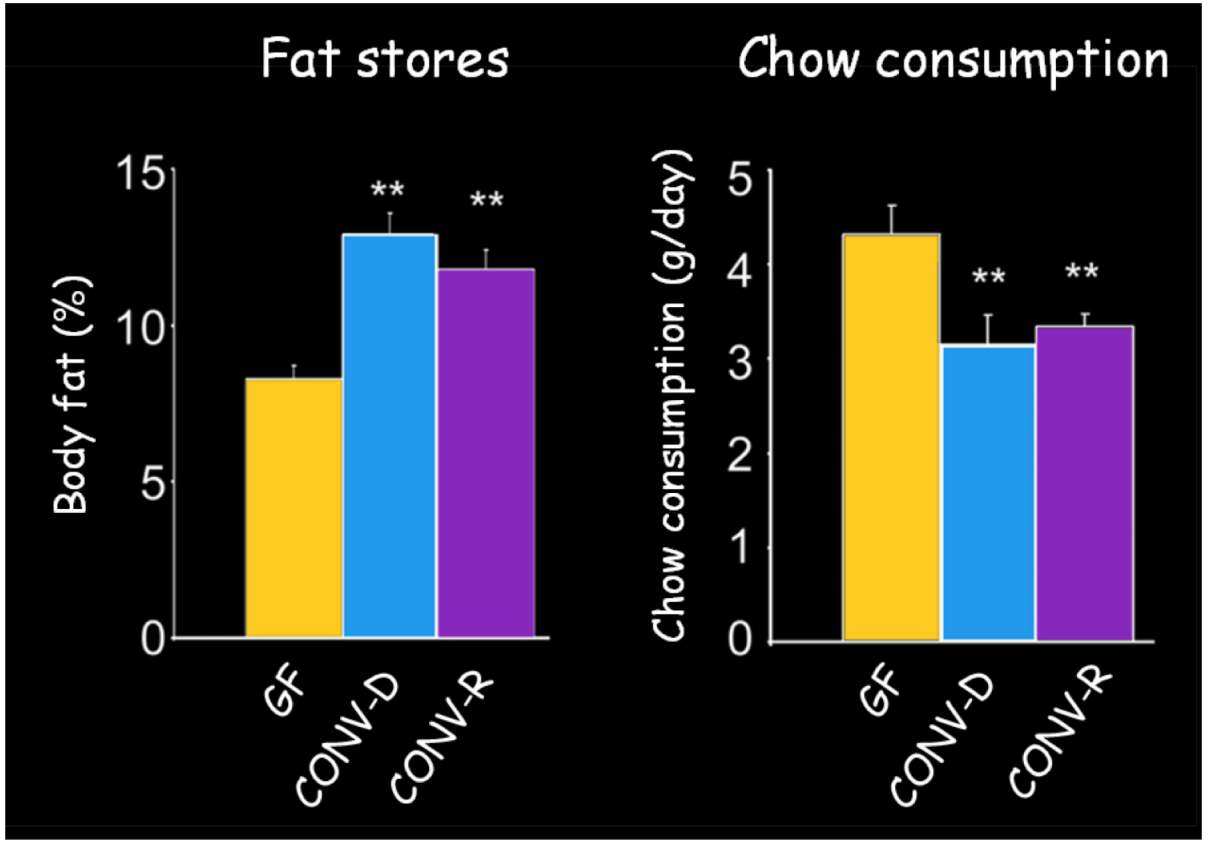


Donor

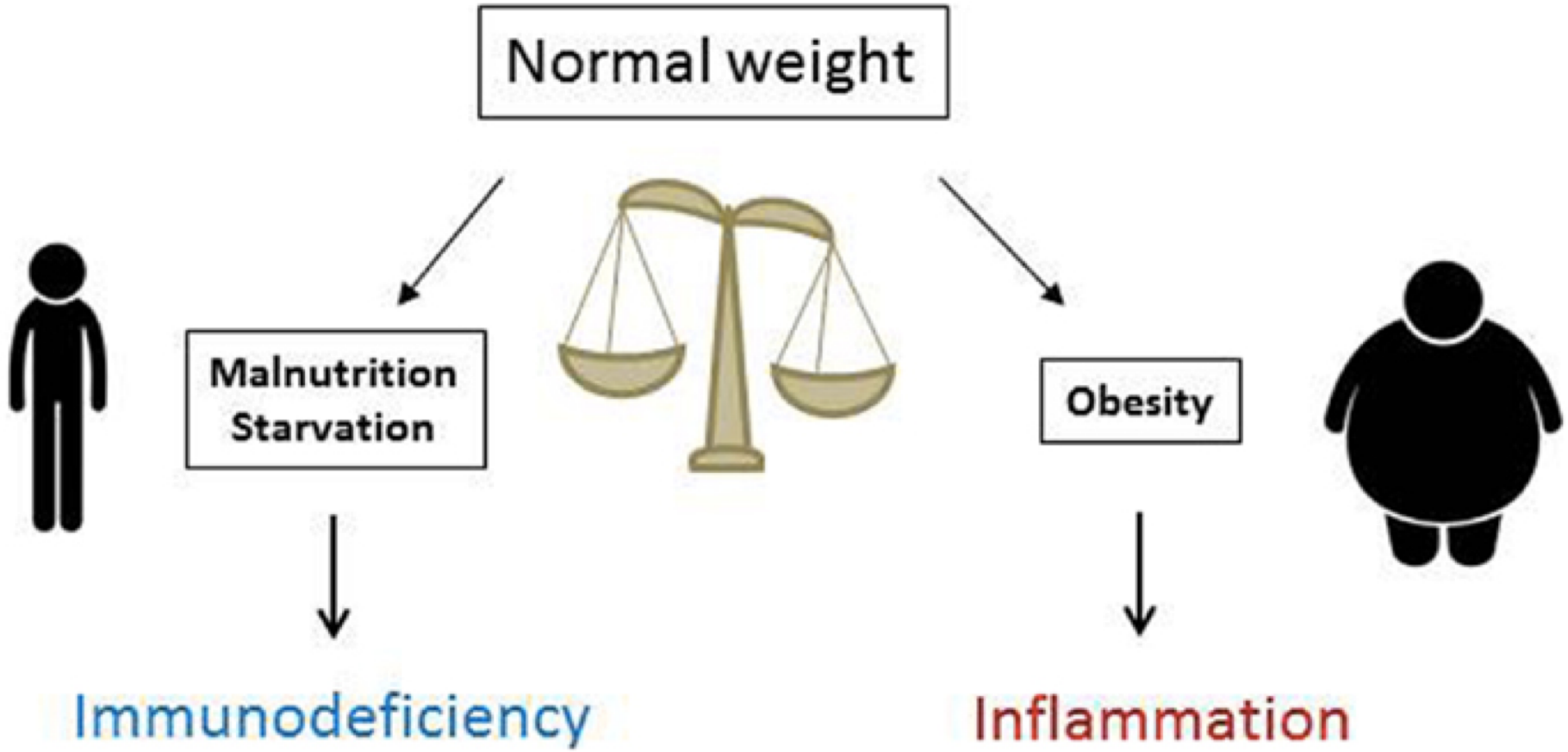


Turnbaugh *et al.*, Nature 444: 1027-1031

Mice that receive a fecal transplant from obese donors not only become obese, but do so while eating less food…



Conventionalized mice (CONV-D) are formerly germ-free (GF) recipients of a gut microbiota transplant from conventionally-raised (CONV-R) donors



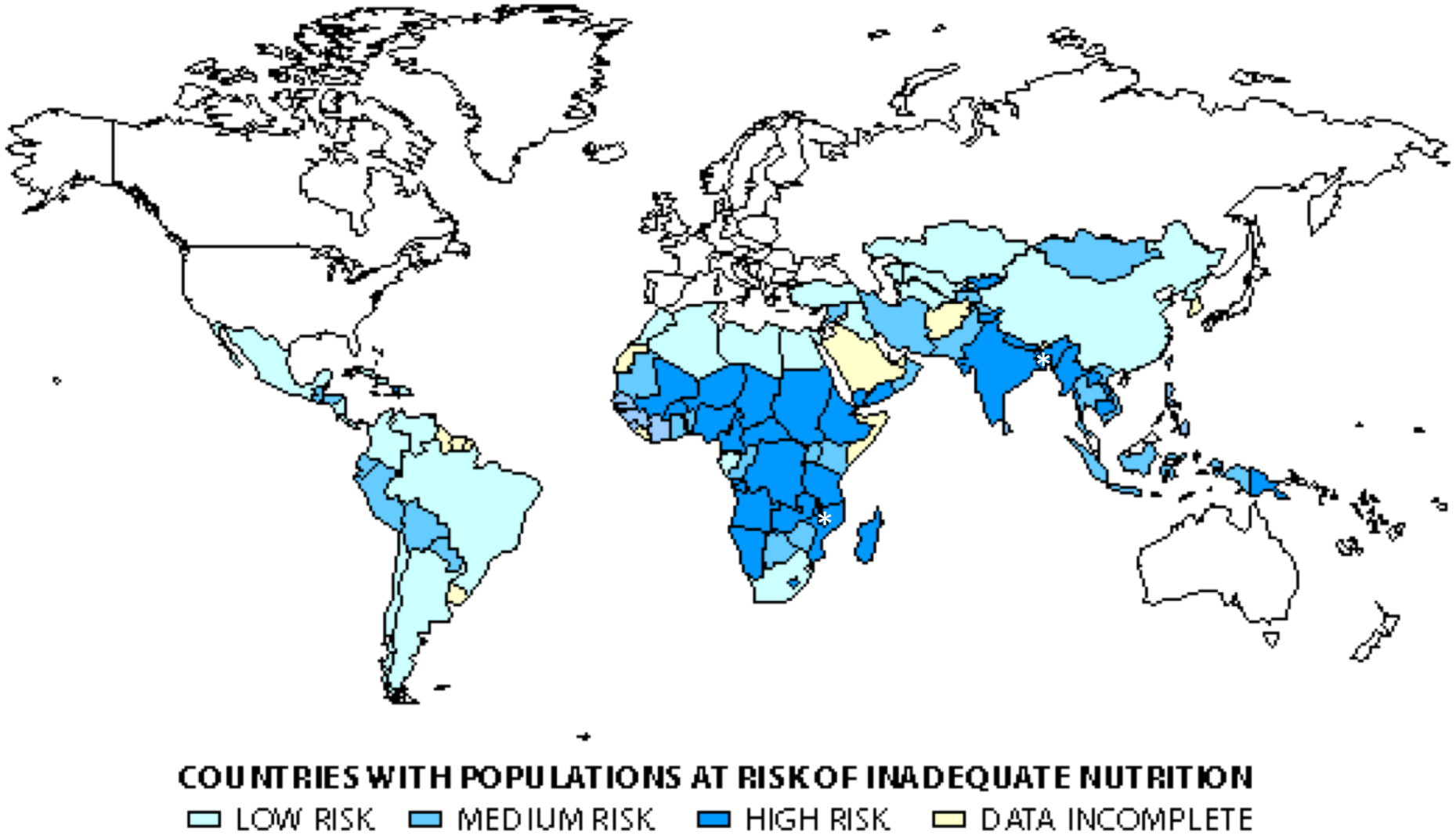
https://www.frontiersin.org/articles/10.3389/fimmu.2014.00379/full

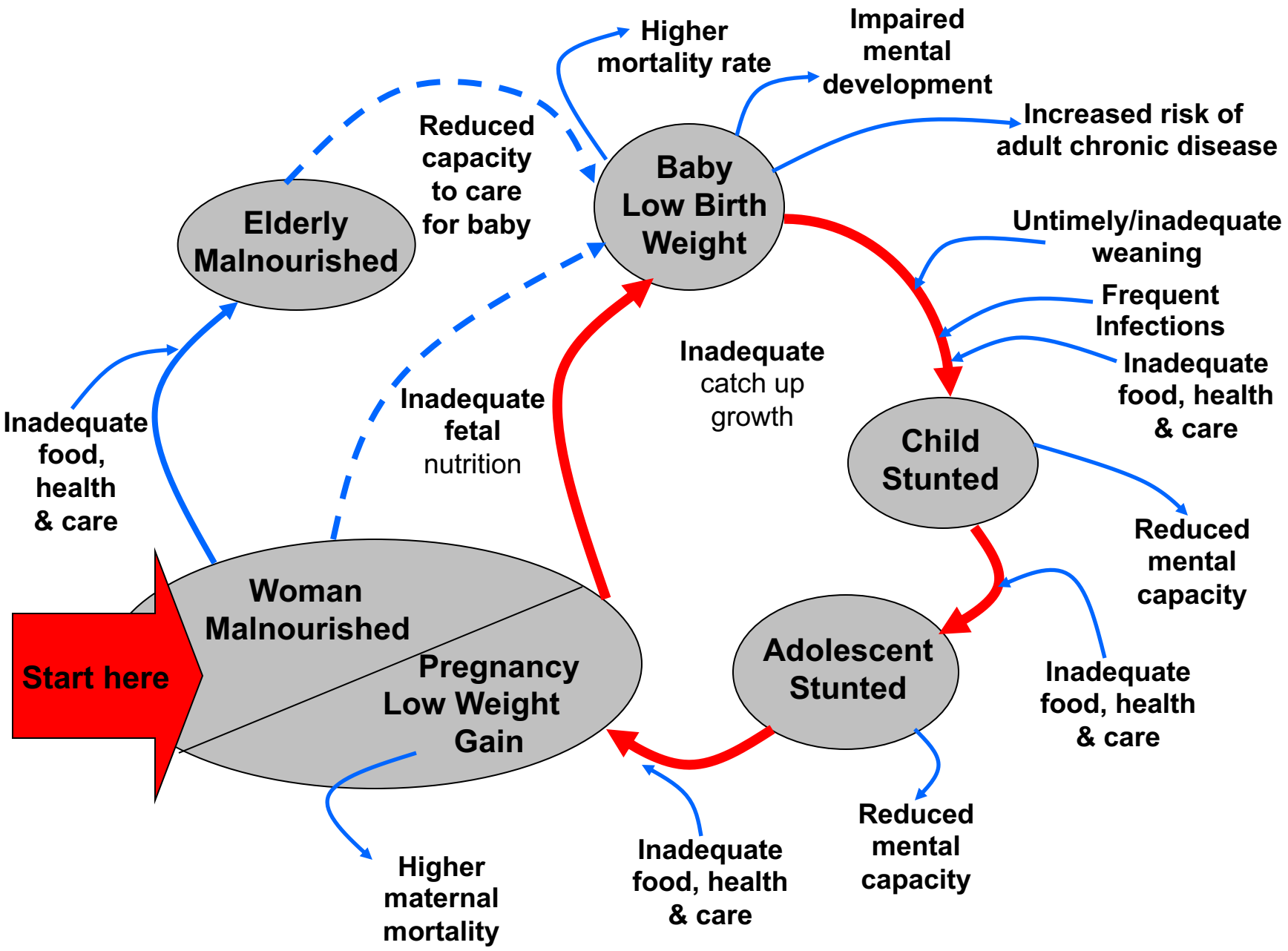
What is malnutrition?

World Health Organization definition:

The term is used to refer to a number of diseases, each with a specific cause related to one or more nutrients (for example, protein, iodine or iron) and each characterized by cellular imbalance between the supply of nutrients and energy on the one hand, and the body's demand for them to ensure growth, maintenance, and specific functions, on the other.

Countries at risk of malnutrition

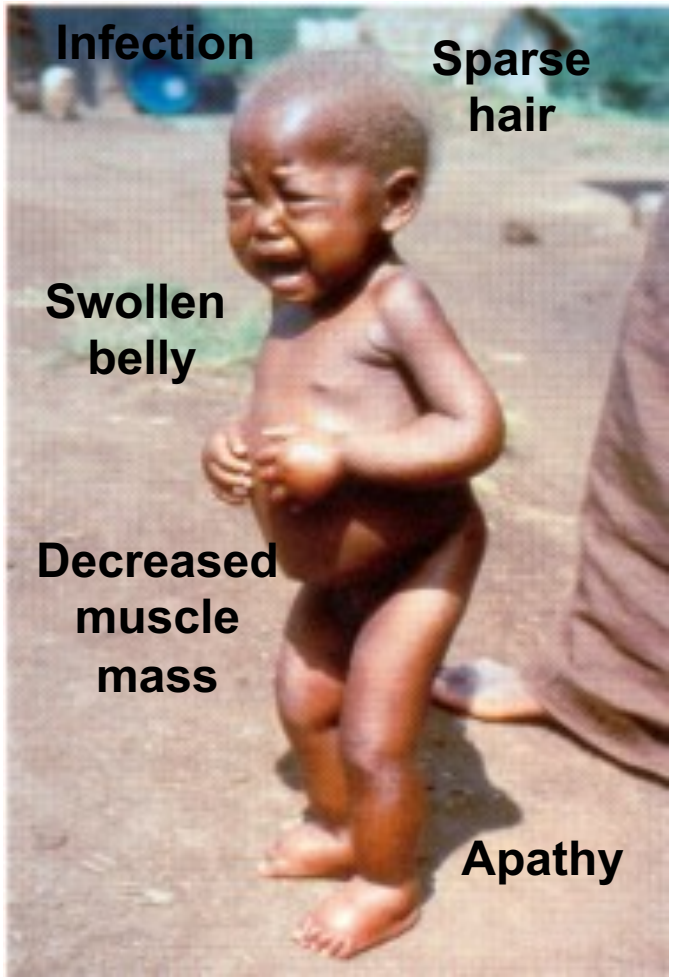



Higher mortality rate
Impaired mental development
Increased risk of adult chronic disease
Reduced capacity to care for baby
Elderly Malnourished
Baby Low Birth Weight
Untimely/inadequate weaning
Frequent Infections
Inadequate food, health & care
Inadequate catch up growth
Inadequate fetal nutrition
Inadequate food, health & care
Child Stunted
Reduced mental capacity
Start here
Woman Malnourished
Pregnancy Low Weight Gain
Adolescent Stunted
Inadequate food, health & care
Higher maternal mortality
Inadequate food, health & care
Reduced mental capacity

Lia Fernald


So how does the microbiome fit in?

Kwashiorkor

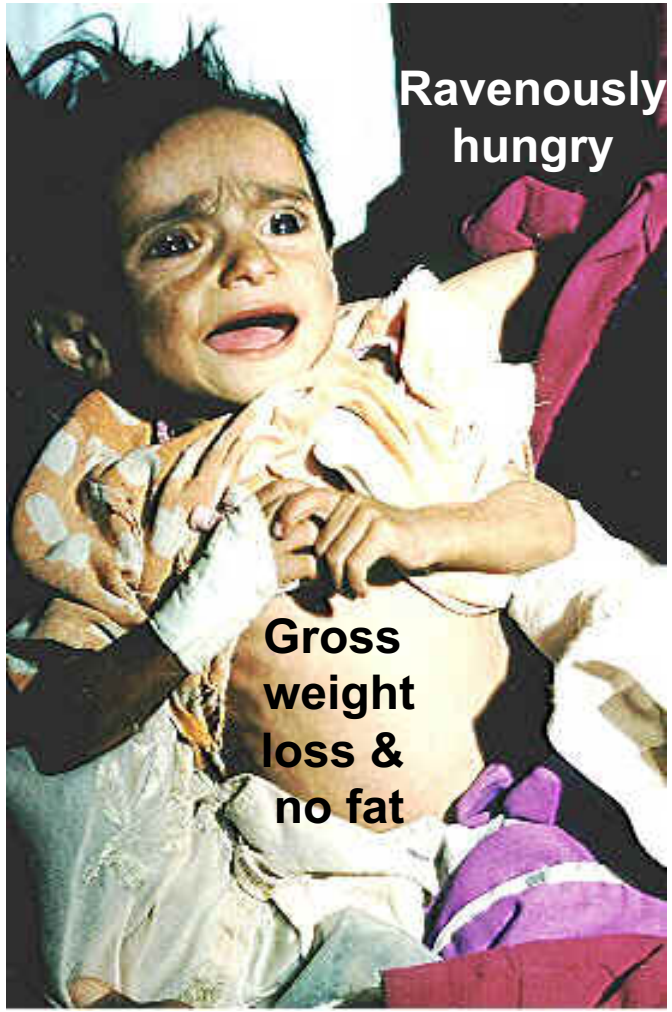


Kwashiorkor (low protein)

- **Decreased muscle mass** (failure to gain weight and of linear growth)
- **Swollen belly** (edema and lipid build-up around the liver)
- **Changes in skin pigment** may lose pigment where the skin has peeled away (desquamated) and the skin may darken where it has been irritated or traumatized
- **Hair lightens** and thins, or becomes reddish and brittle.
- **Increased infections** and increased severity of normally mild infection, diarrhea
- **Apathy**, lethargy, irritability

Death does not occur from actual starvation but from infection

Marasmus (low calories)



Marasmus

- Deficit in calories – “marasmus” comes from Greek origin of word “to waste”
- Gross weight loss
- Hyper-alert and ravenously hungry
- Children have no subcutaneous fat or muscle

➔ eventually starve to death (immediate cause often is pneumonia)

Marasmus – mechanism

- Energy intake is insufficient for body's requirements – body must draw on own stores
- Liver glycogen exhausted in a few hours – skeletal muscle protein used via gluconeogenesis to maintain adequate plasma glucose
- When near starvation is prolonged, fatty acids are incompletely oxidized to ketone bodies, which can be used by brain and other organs for energy
- High cortisol and growth hormone levels

Severe Malnutrition: Consequences

Mental development

- Lower IQ levels
- Poorer school performance

Behaviors of recovered severely malnourished children

- shy, isolated, withdrawn
- decreased attention span
- immature, emotionally unstable
- fewer peer relationships/reduced social skills
- played less/stayed nearer to mothers

Summary: Severe malnutrition

- Severe malnutrition is defined as > 3 s.d. away from median reference standards
- 66M children under the age of 5 are severely malnourished (64M of these in developing countries)
- Key types of severe malnutrition are kwashiorkor (low protein) and marasmus (low calories);
- Severe malnutrition results in severe deficits for children

RUTF

Plumpy'Nut, a ready-to-use therapeutic food (RUTF)

Nutritional value per 92 g

Energy 2,100 kJ (500 kcal)

Ingredients: peanut paste, vegetable oil, powdered milk, powdered sugar, vitamins, minerals

Culturally Sensitive and Sustainable Nutritional Rescue

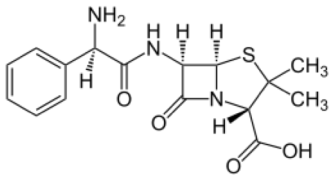
Kichuri Ingredients

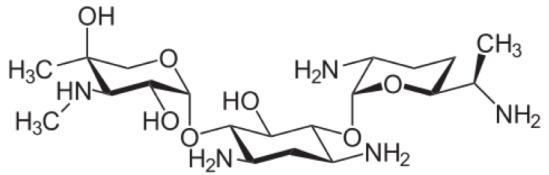
prepared from rice, lentils (dal), green leafy vegetables, and soybean oil

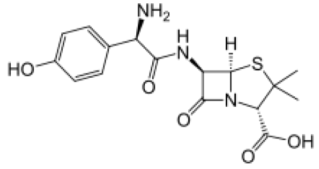
Halwa Ingredients

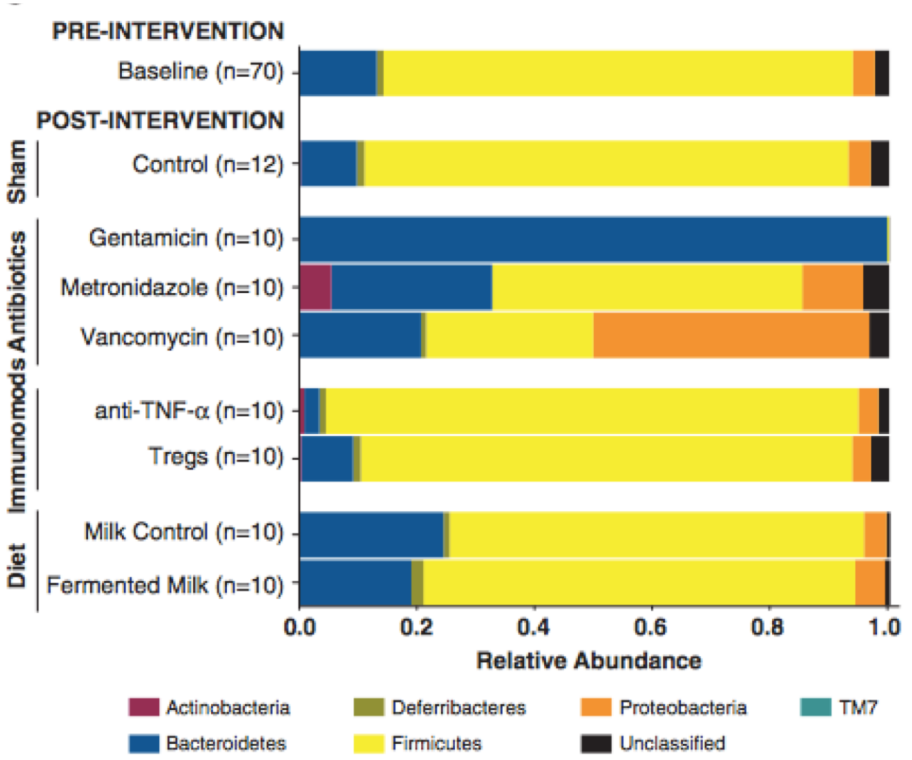
prepared from wheat-flour, lentils, molasses, and soybean oil.

Ampicillin, Gentamicin, Amoxicillin



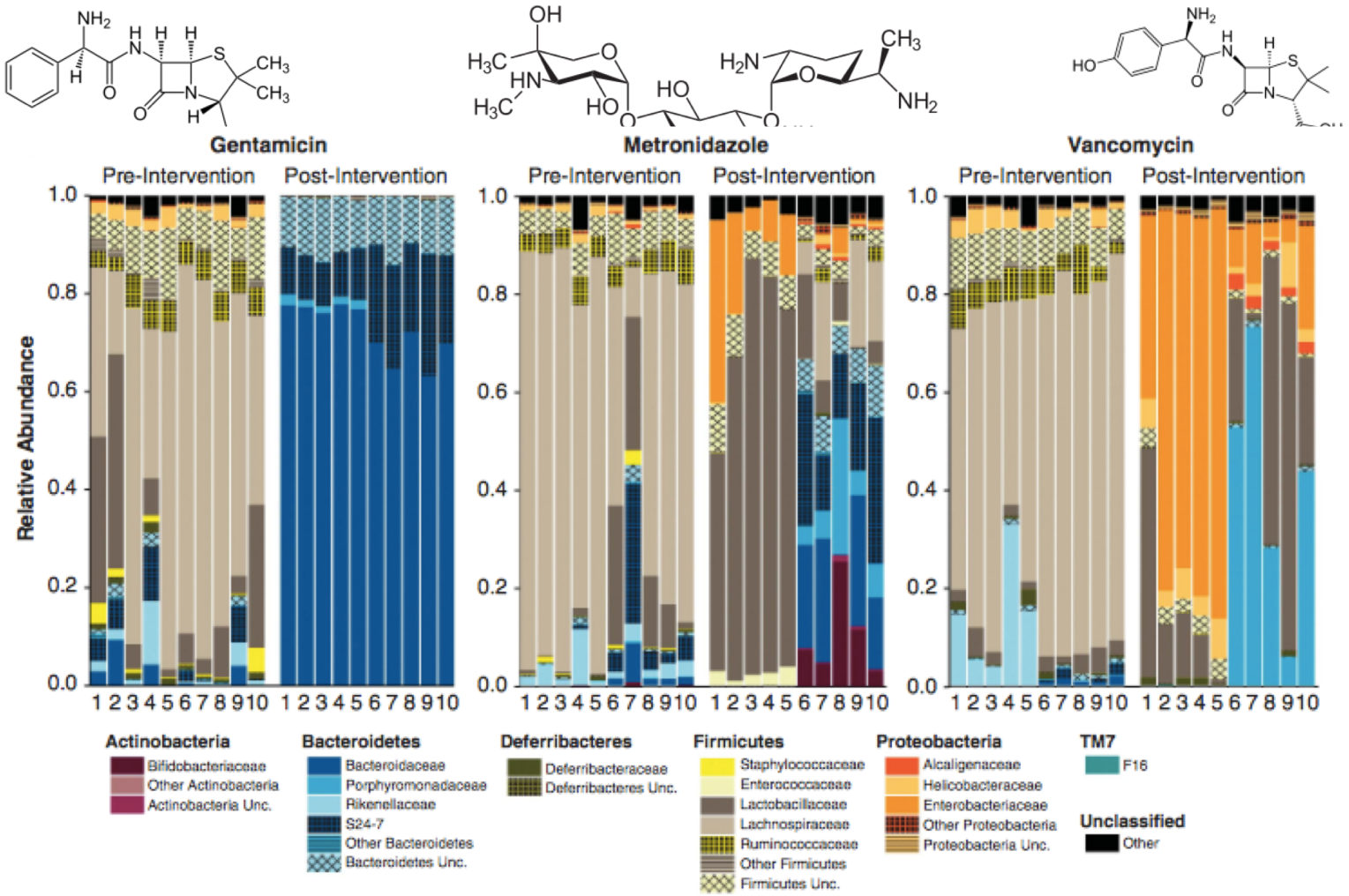






Bottom Line: Abx disrupt colon gut microbial ecology

Ampicillin, Gentamicin, Amoxicillin



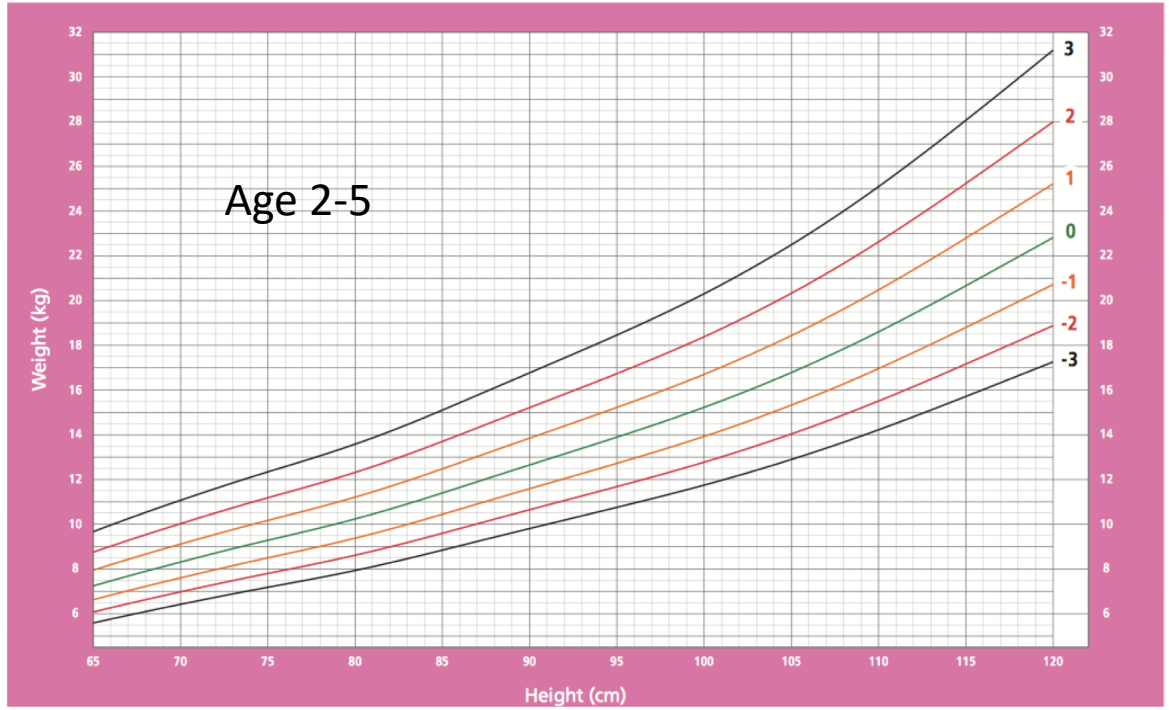
Bottom Line: Abx disrupt colon gut microbial ecology

Z-score
WHZ, WAZ, HAZ, **M**AZ

- Statistical measurement of a **score's** relationship to the mean in a group of **scores**.
- A **Z-score** of 0 means the **score** is the same as the mean.
- A **Z-score** can also be positive or negative, indicating whether it is above or below the mean and by how many standard deviations.

SAM and MAM

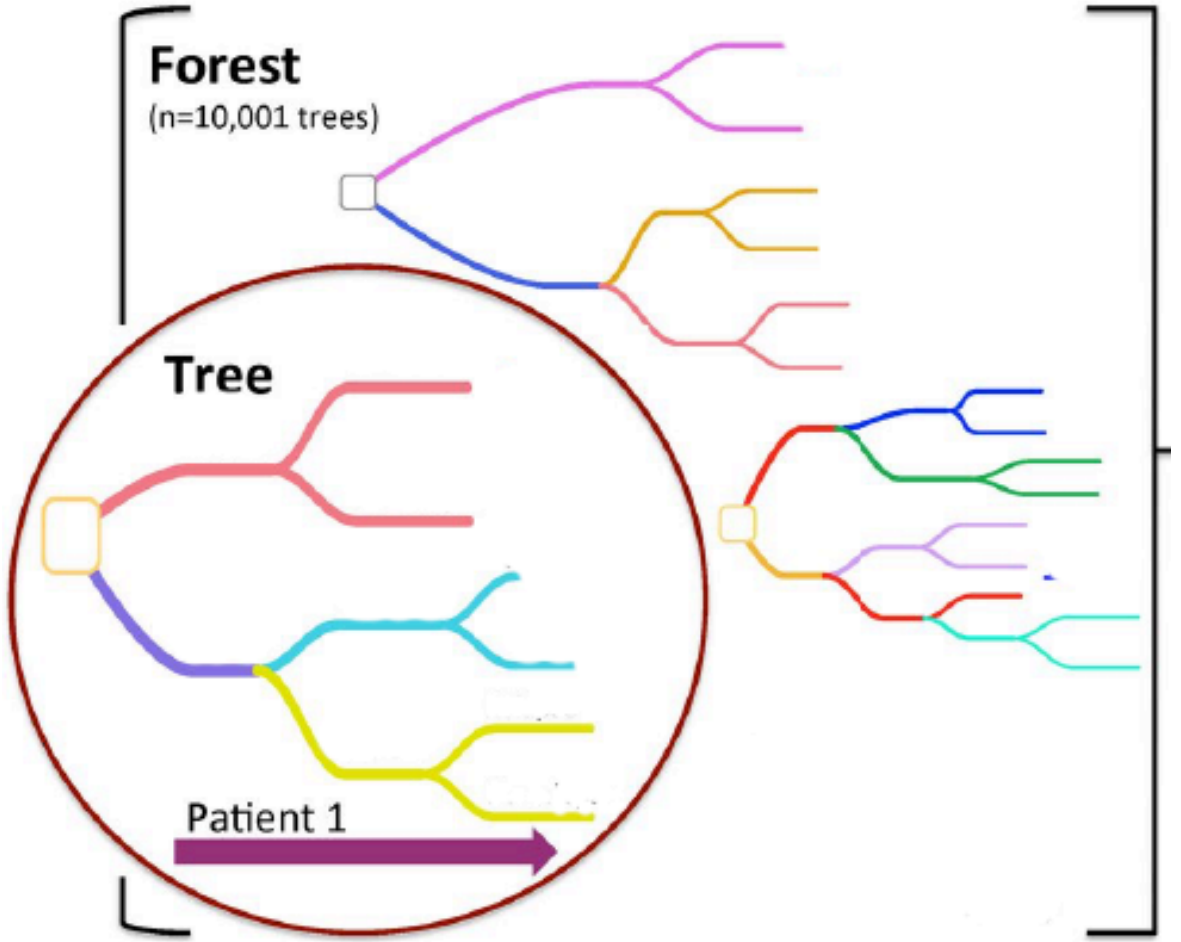
- SAM: WHZ <= -3
- MAM:WHZ <-2 but > -3



Spearman’s Rho

A non-parametric test used to measure the strength of association between two variables, where the value r = 1 means a perfect positive correlation and the value r = -1 means a perfect negative correlation.

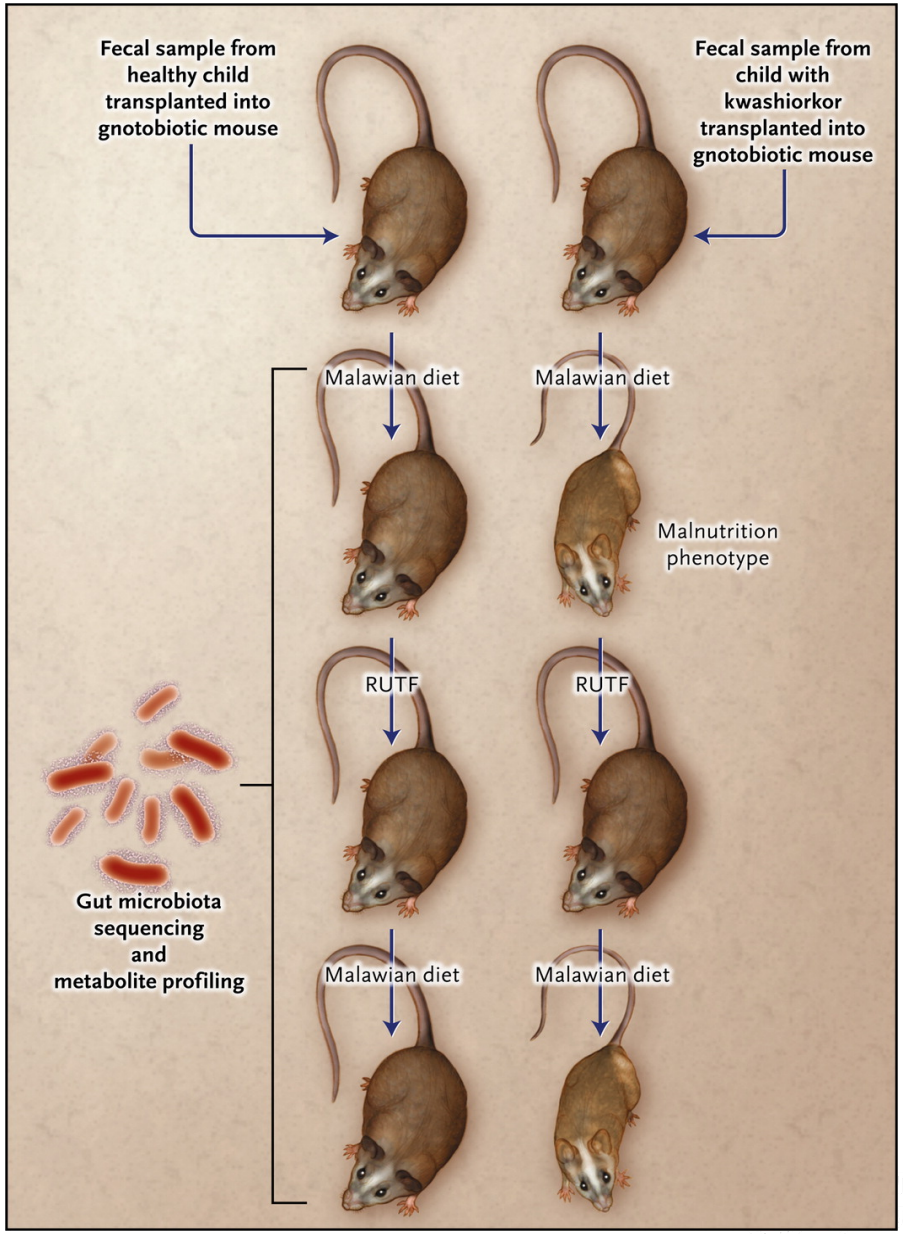
Random Forests machine learning algorithm



Microbiota maturity indices provide a microbial measure of human postnatal development, a way of classifying malnourished states, and a parameter for judging therapeutic efficacy

Subramanian et al. *Nature 2014*
https://www.nature.com/articles/nature13421

Gut Microbiota in Children with Kwashiorkor



Garrett WS. N Engl J Med 2013;368:1746-1747.

Microbial Ecology of Malnutrition: an ideal system for study & intervention?

What would YOU do?

- **As a data scientist?**
- **As a pediatrician trained in public health or MPH-trained implementation scientist?**
- **As a basic, wet bench scientist?**

PERMISSION SLIPS FOR GNOTOBIOTICS FIELD TRIP