L07

Recap

Symbiosis

- **Relationships of microorganisms with other microorganisms or with macroorganisms—prolonged and intimate relationships**
- **Symbiosis**, a word that means “living together”
- **Parasites** are microorganisms that benefit **at some expense to the host**
- **Pathogens** actually cause a **disease in the host**
- **Commensals** have **no discernible effect** on the host
- **Mutualists are beneficial to the host**
- **Mutualistic microorganisms** as intimate **evolutionary** partners that influence both the evolution and physiology of their hosts
- **Origins many millions of years ago** and have evolved to benefit the physiology of both partners, a process called coevolution —> **obligate symbiosis**
- Plants interact closely with microbes through their roots and leaf surfaces and even more intimately within their vascular tissue and cells

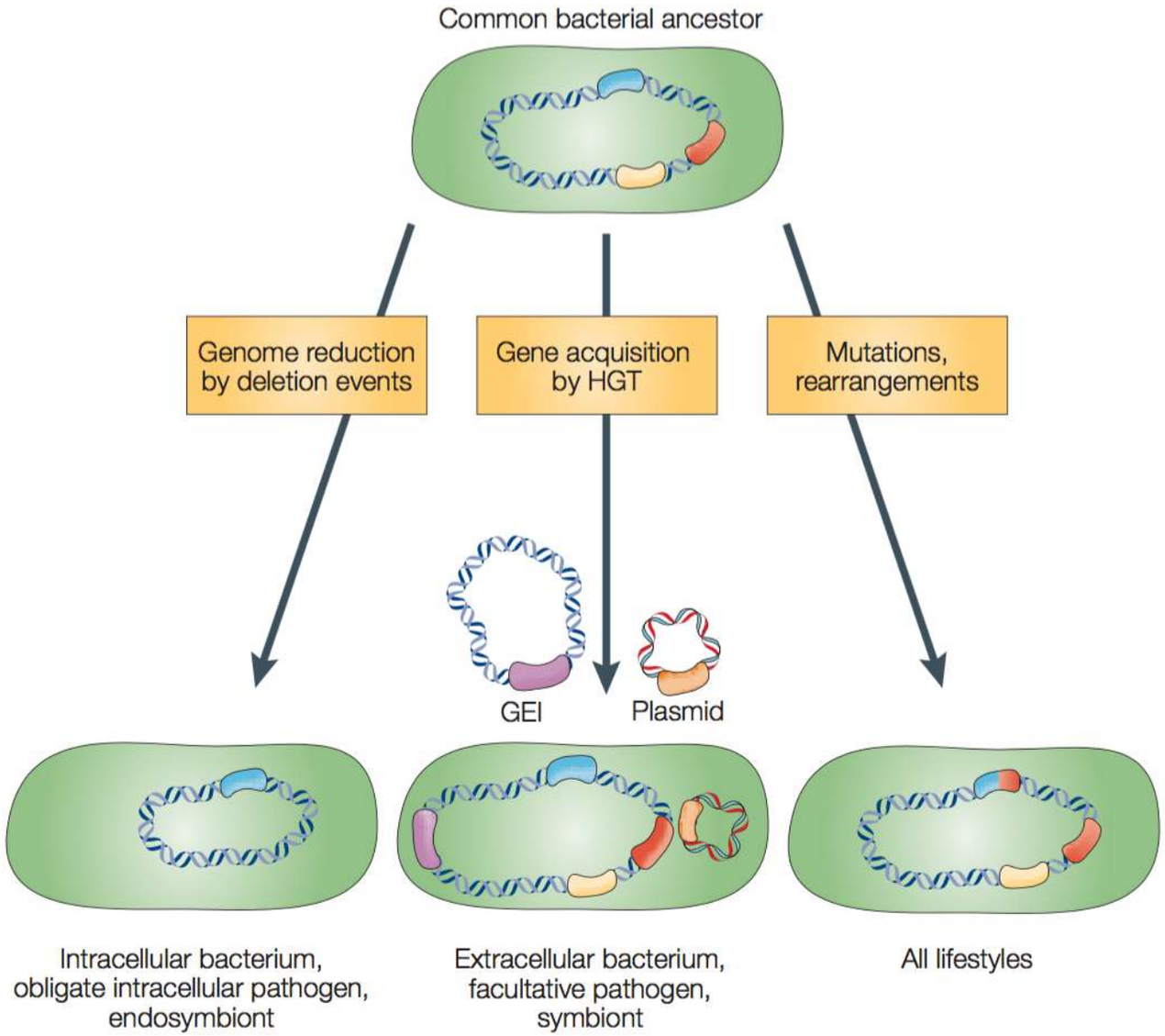
Evolution of bacterial variants by acquisition and loss of genetic information

Genome structure reflects bacterial lifestyle

Genome **reduction** is common in intracellular bacteria (obligate intracellular pathogens, endosymbionts) contributes to the evolution of strictly **host-dependent bacterial variants** —> bacteria rely on host cell to compensate for the gene functions that are lost

Gene acquisition by horizontal transfer between different species is common in extracellular bacteria (facultative pathogens, symbionts), which involves mobile genetic elements, such as plasmids, genomic islands (GEIs) and bacteriophages—> **increases versatility and adaptability** of the recipient —> allows bacteria **to adapt to a new or changing environment**

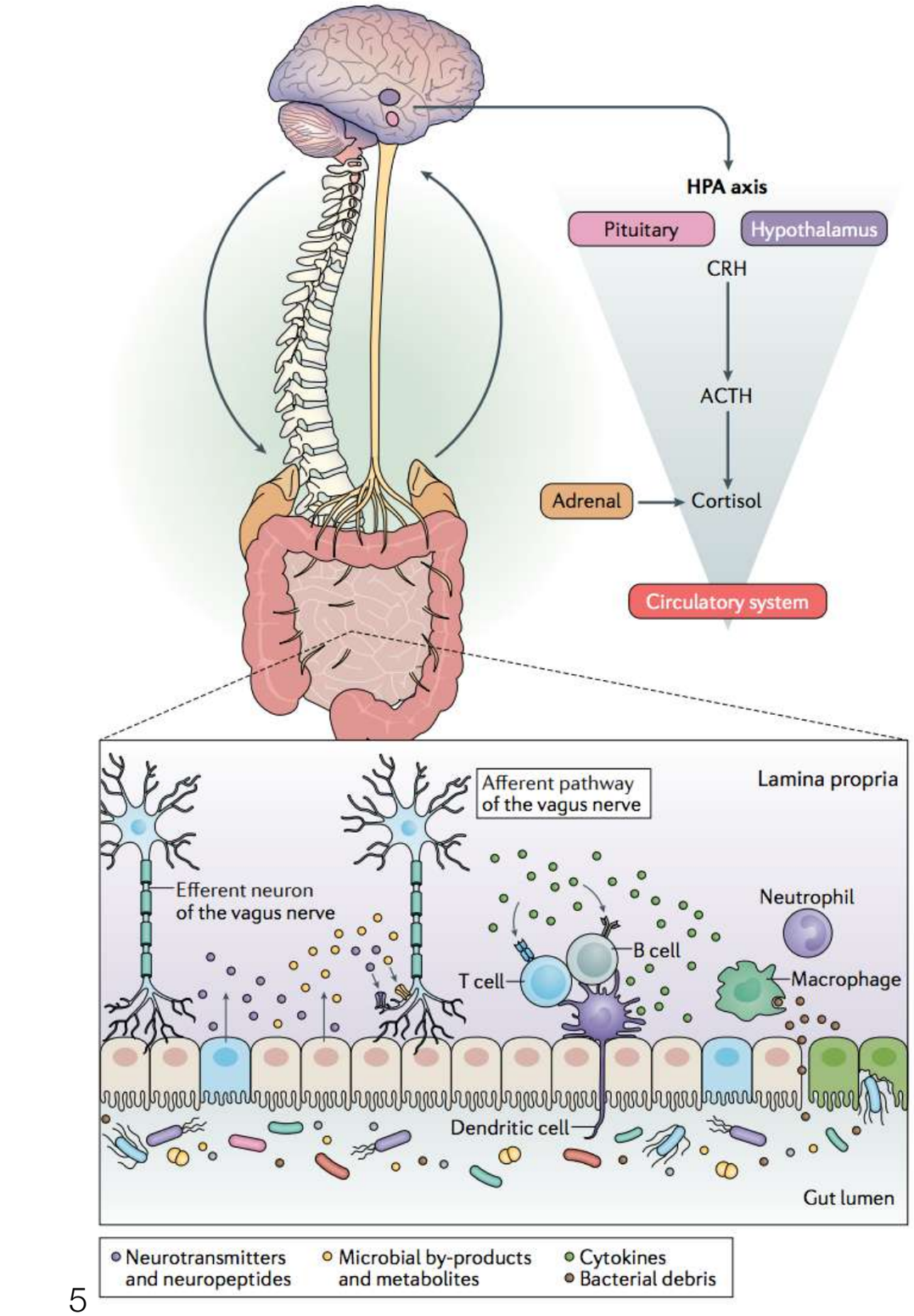
Point mutations and genetic rearrangements constantly contribute to evolution of new gene variants in all types of bacteria. HGT, horizontal gene transfer



Dobrindt et al., 2004

TRANS-KINDOM SYMBIOSIS

- **Trans-kingdom symbiosis, gut bacteria cooperate with their animal hosts**
- **Regulation the development and function of the immune, metabolic and nervous systems**
- **Dynamic bidirectional communication along the ‘gut–brain axis’**



Morais et al., 2020

Ab initio

Prior 1983, knowledge based on culturable gut bacteria only and gut was considered as pretty axenic place

- Major questions:
- Do individuals share a core human microbiome?
- Is there a correlation between the composition of microbiota colonizing a body site and host genotype?
- Do differences in human microbiome correlate with human health?
- Are differences in the relative abundance of specific bacterial populations important to either health or disease?

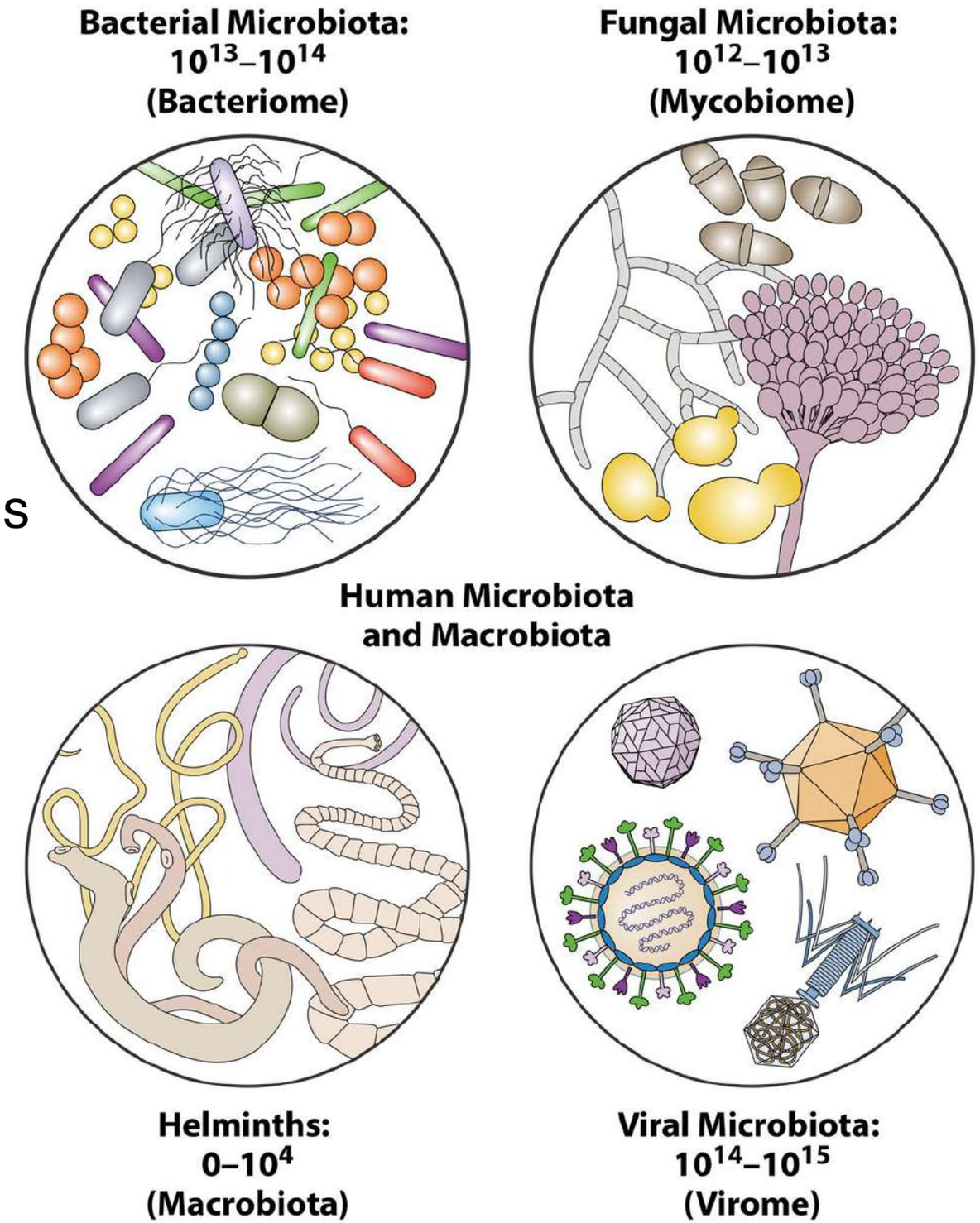
Healthy westernized humans

Obbligate symbionts

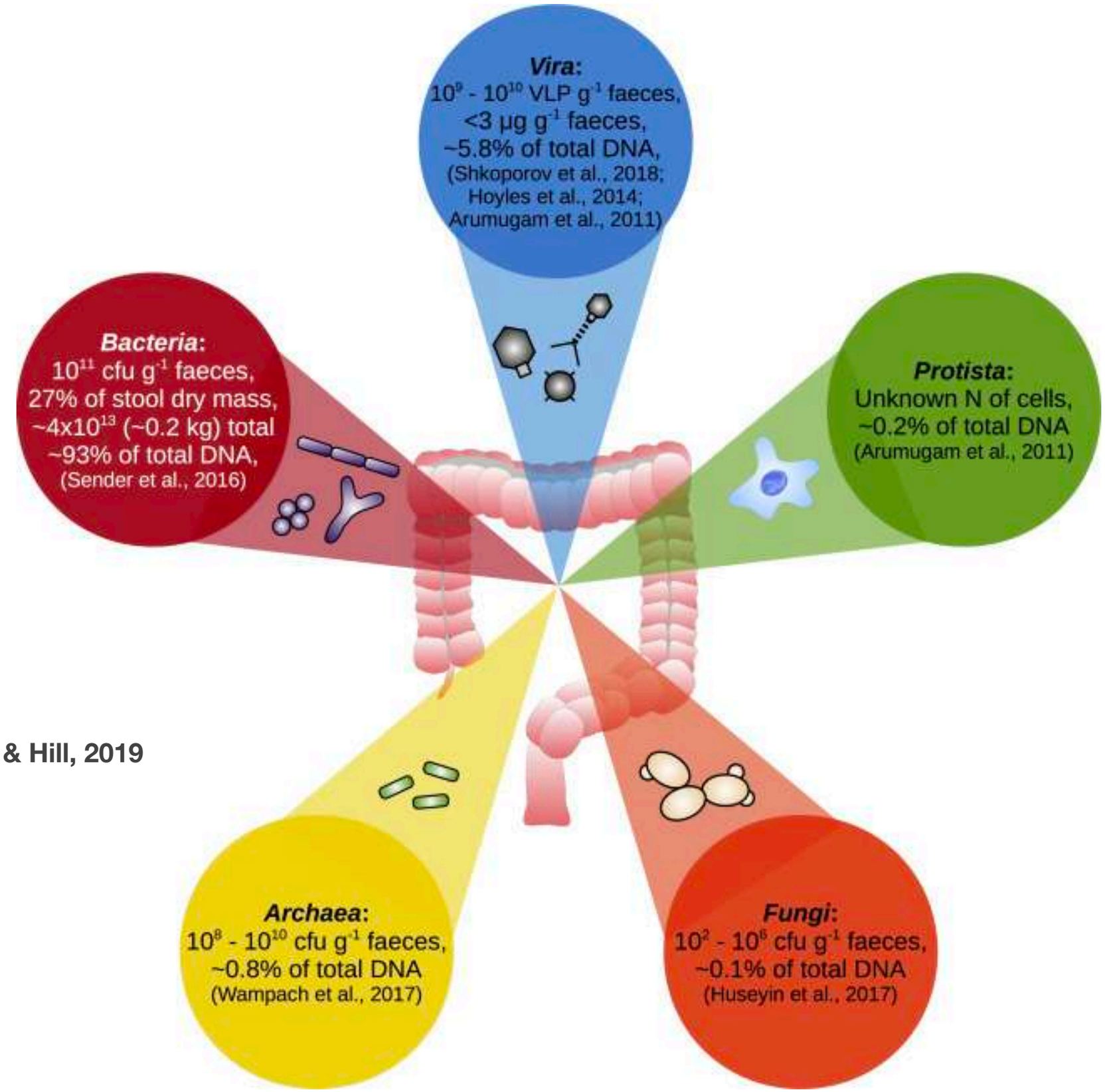
- Streamlined genomes: retain only genes required for host fitness and essential molecular processes, such as translation, replication, and transcription
- Genome reduction implies that the symbionts are reliant on the host for many functions no longer encoded in the symbiont genome
- Primary symbionts vs. disease-causing bacteria (pathogens): **primary symbionts** tend to **lose genes** encoding proteins required in **catabolic pathways**, **pathogenic bacteria typically retain these**, but **lose** genes for **anabolic** pathways
- Differing relationships with their hosts; the insect symbiont provides the host with essential biosynthetic nutrients while the pathogen obtains important biosynthetic nutrients from the host

What is a human being?

- Complex ecosystem
- Cross-Domain and Viral Interactions



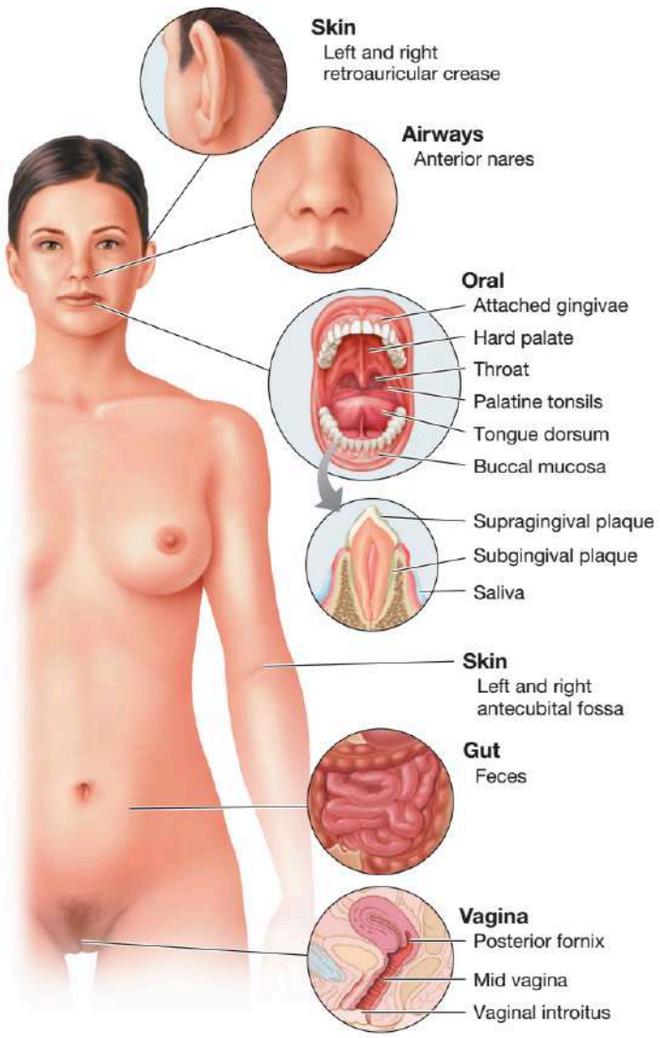
Rowan-Nash et al., 2019



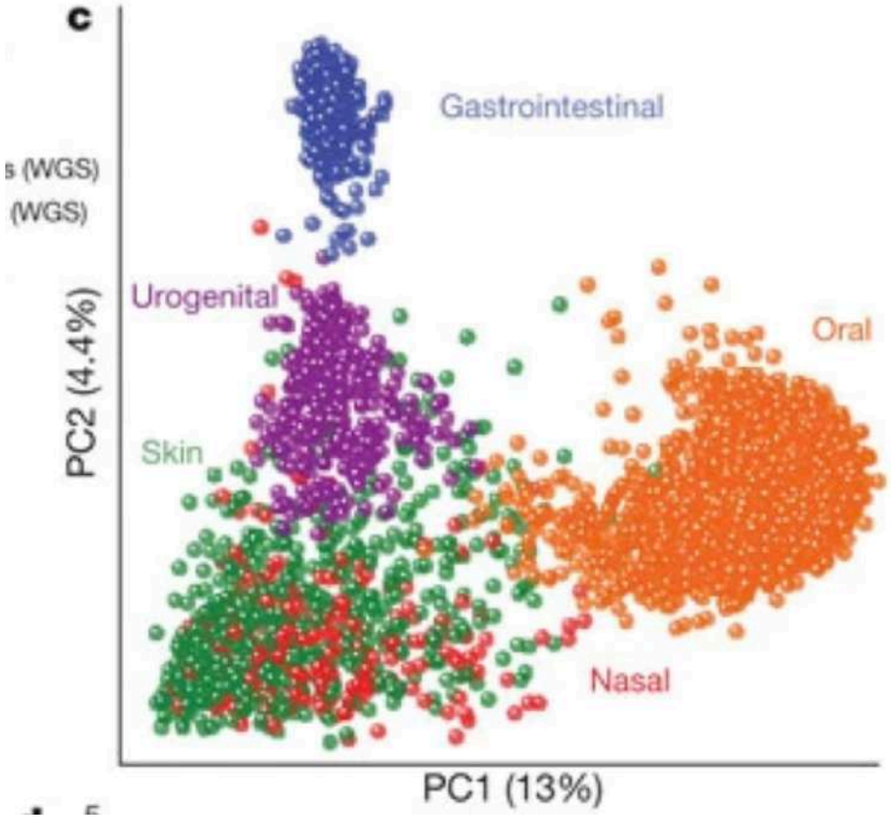
Shkoporov & Hill, 2019

Human-microbes association

- Microbiome: functional collection of different microbes in a particular environmental system
- Human microbiome formed by different microbiota (i.e. organisms living in a specific environment)
- Human holobiont and found an approximate ratio of only 1:1 of bacterial to human cells (Senders et al., 2016)
- Total number of gut bacteria of today's human population is between 3×10^{23} and 5×10^{23}, dental plaque: 8×10^{21} cells, skin:1×10^{21} cells



Madigan et al. 2018

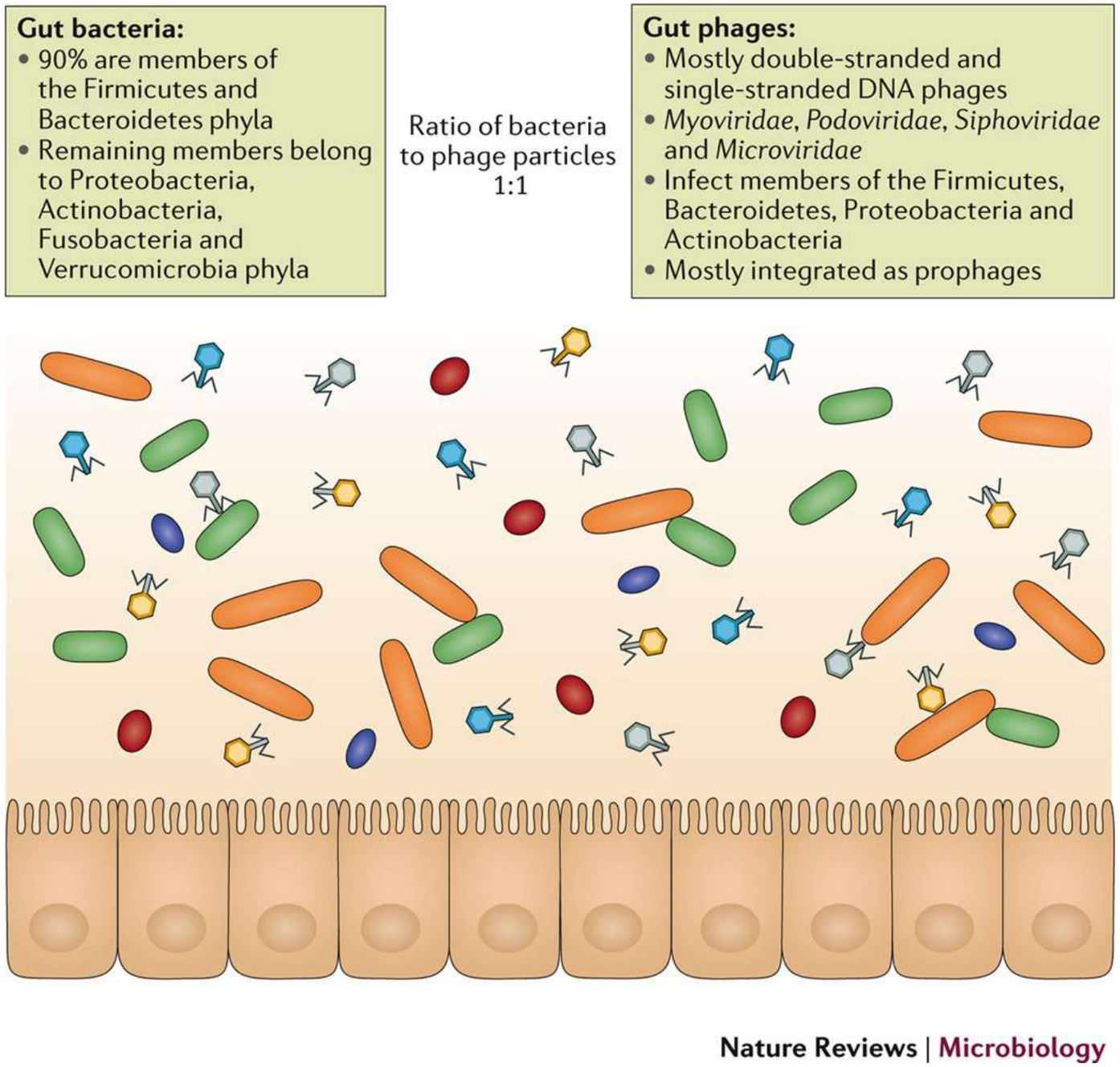


The Human Microbiome Project Consortium, 2012

What about viruses?

Human Virome

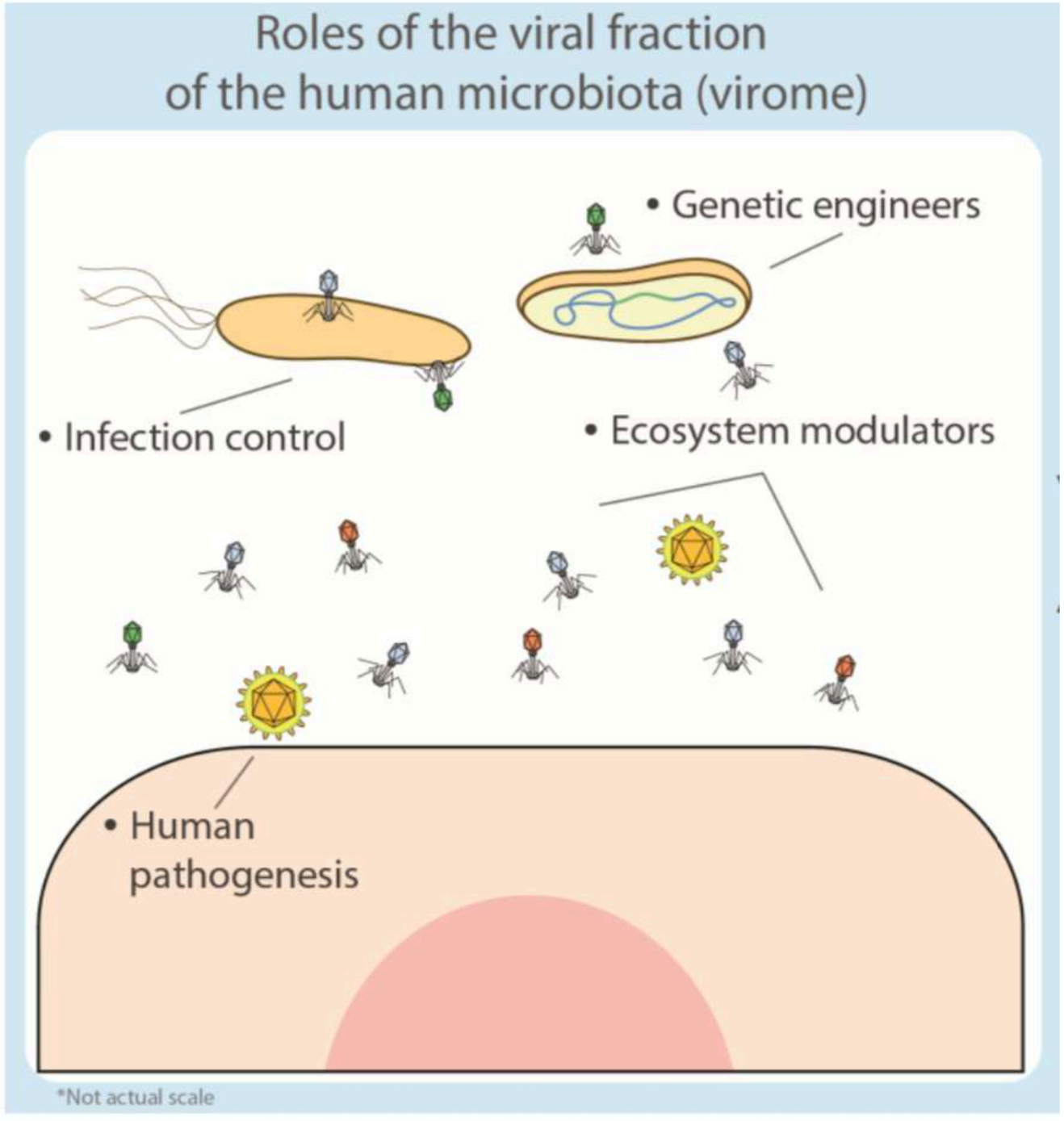
- The human gut is home to dense bacterial and phage populations that are involved in regulating human health
- Phages regulate bacterial abundance, diversity and metabolism in numerous ecosystems, but their effects in the human gut remain largely unexplored
- Despite high bacterial abundance and metabolism, the majority of described phages in the gut are integrated within their bacterial hosts, which suggests dynamic interactions that are specific to this system



Khan Mirzaei & Maurice, 2017

Virome role

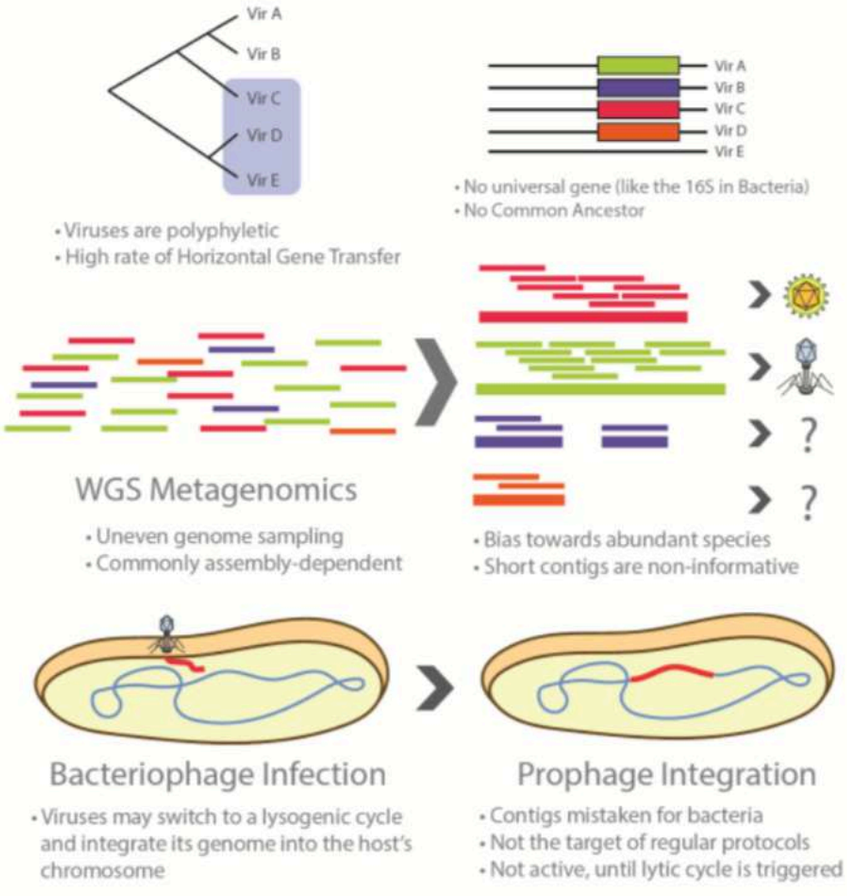
- Different bacteria–phage interactions occur depending on the health status and development stage of the human host
- The approximately 10^{15} phages that inhabit the human intestine are predominantly dsDNA viruses in the *Myoviridae*, *Podoviridae*, and *Siphoviridae* families of the order *Caudovirales* and ssDNA viruses of the family *Microviridae*, constituting an estimated 1,200 viral genotypes



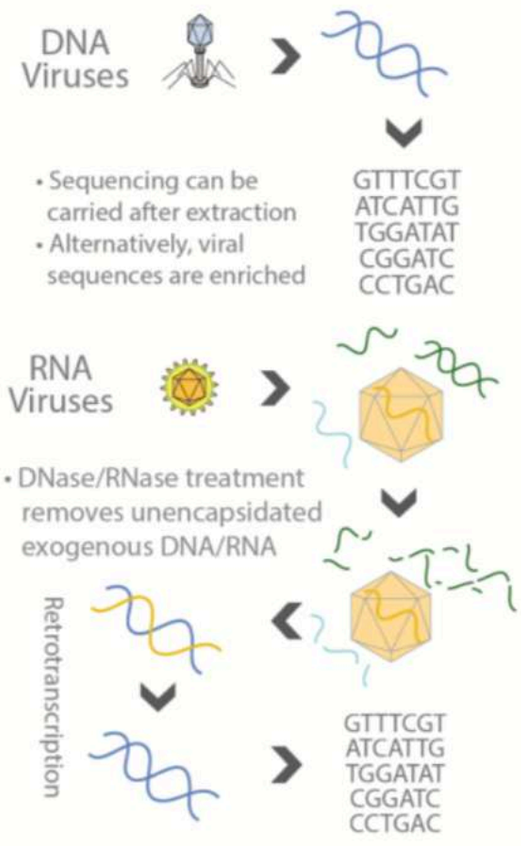
- Lopez et al. 2019

Virome challenges

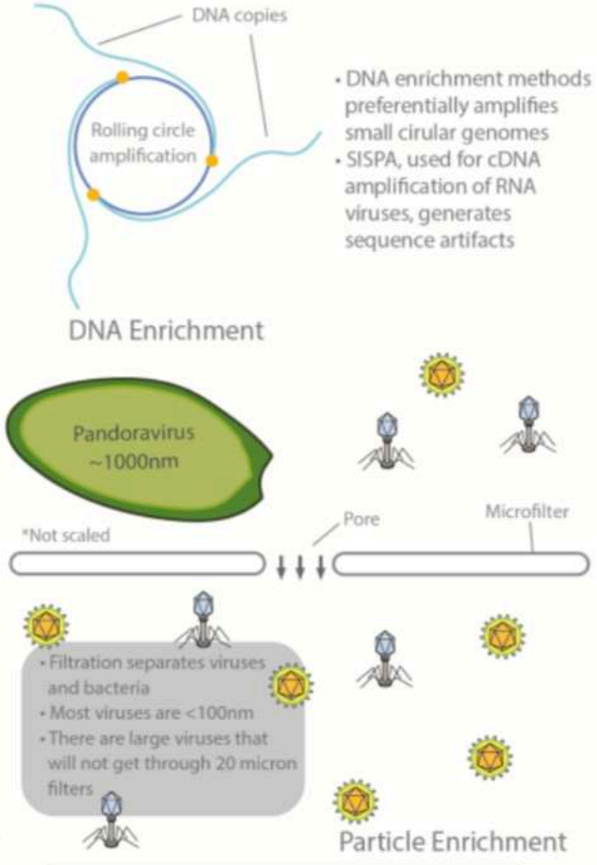
1) No universal gene exists, WGS required



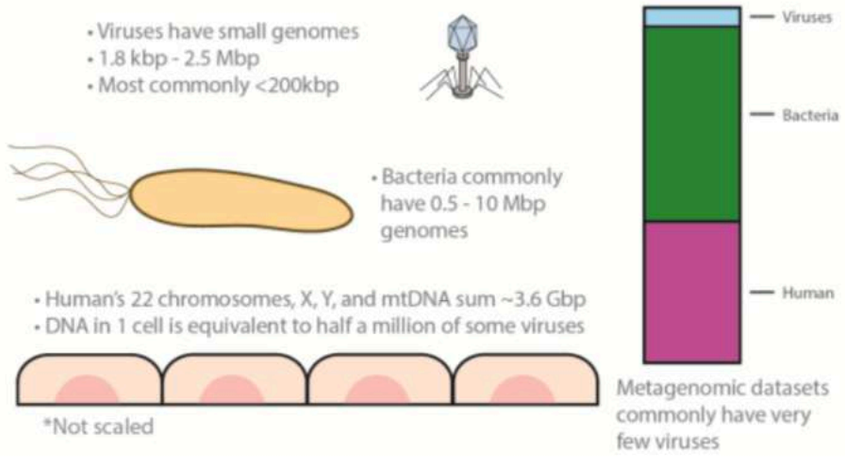
2) Viromics require DNA+RNA protocols



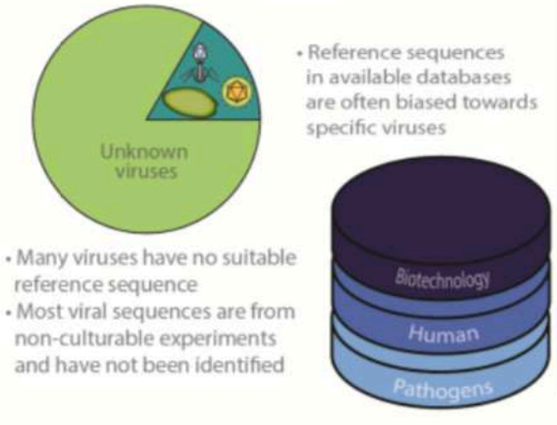
3) Experimental bias of enrichment methods



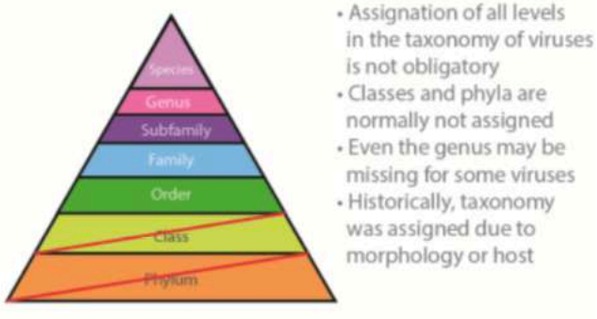
4) RNA/DNA from the host and bacteria



5) Uncharacterized viruses



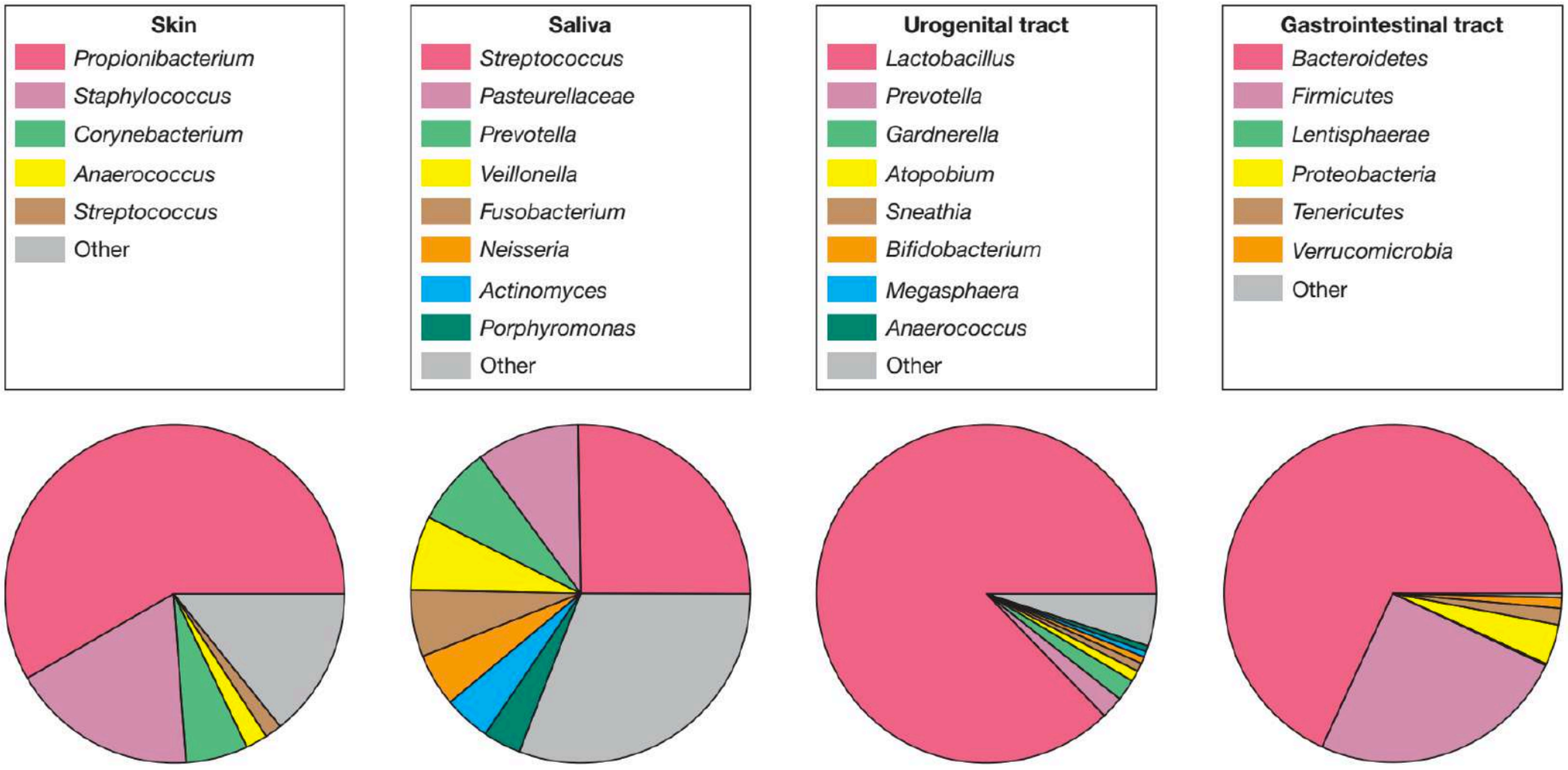
6) Complex Taxonomy



Lopez et al. 2019

Human-microbes an ecosystem within ecosystems

- Microbial population based on cultured-dependent methods differ from culture-independent methods

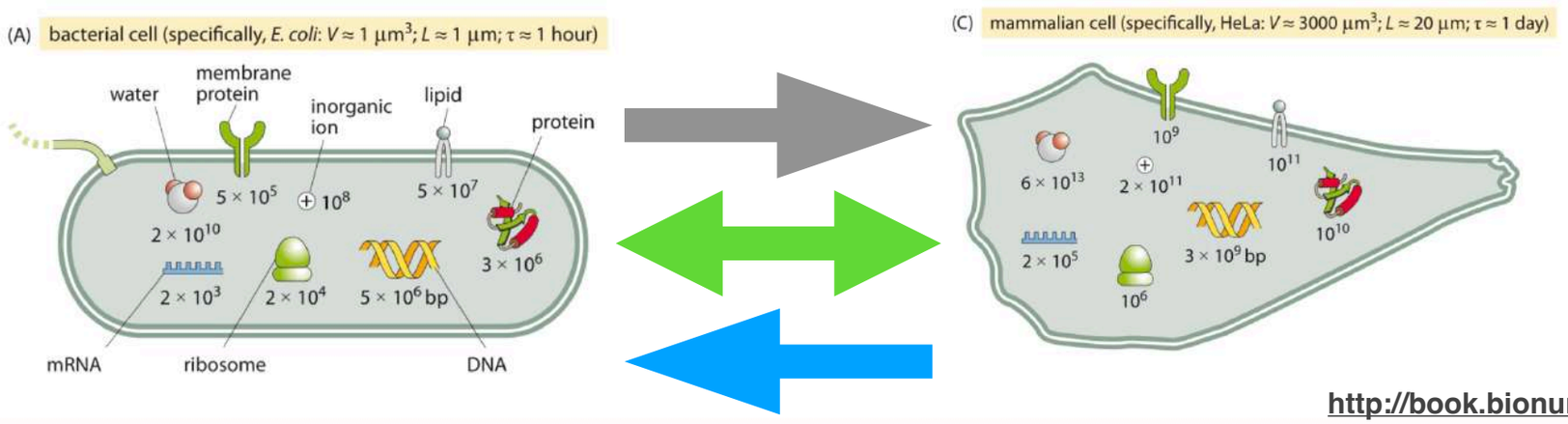


- 16S rRNA gene: species cluster with > 97% sequence similarity, culture-independent method

Madigan et al. 2018

Human-microbes interactions

- Many programs to study Prok-Euk interaction in the human ecosystems



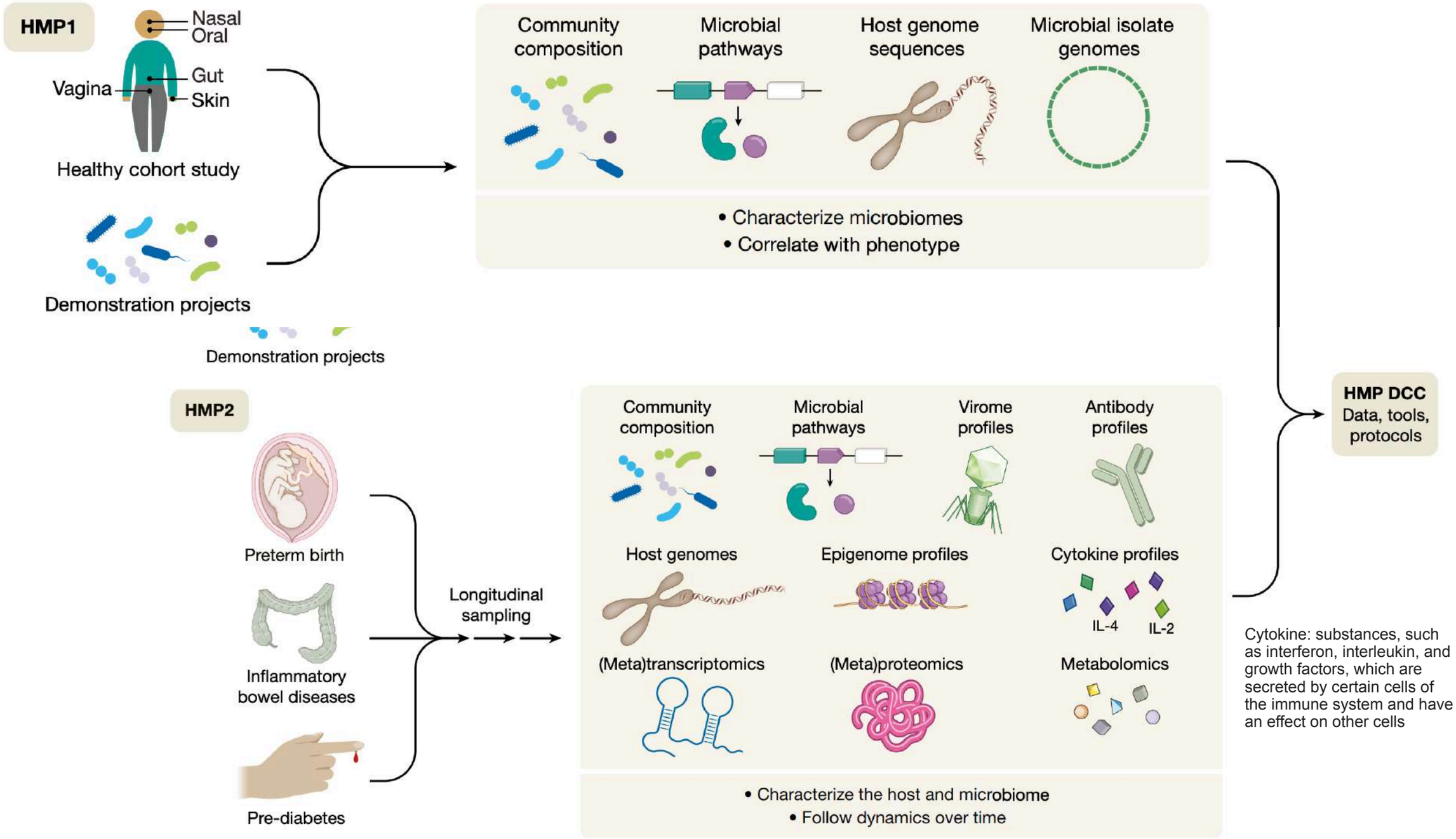
http://book.bionumbers.org/

TABLE 24.1 Major human microbiome research programs

Research program	*Participating countries*	*Programmatic objectives*
MetaGenoPolis	France	Demonstrate the impact of the human gut microbiota on health and disease using metagenomics technology
International Human Microbiome Standards	European Commission	Optimize methods for the assessment of the effects of the gut microbiome on human health through the standardization of procedures and protocols
Korean Twin Cohort Project	Korea	Characterize microbiota associated with epithelial tissue in a twin cohort study group, with the goal of identifying targets for early disease diagnosis and prevention
NIH Human Microbiome Project (HMP)	USA	Characterize the microbes that live in and on the human body, and assess the ability to demonstrate correlations of changes of the human microbiome with health
Canadian Human Microbiome Initiative	Canada	Characterize the microorganisms colonizing the human body. Evaluate their relationship to health and examine compositional changes associated with chronic disease
NIH Jumpstart Program	USA	Generate the complete genome sequences of 200 bacterial strains isolated from the human body; recruit donors for securing samples from five body regions, and perform 16S rRNA and metagenomic sequence analysis of the sampled body regions
Integrative Human Microbiome Project	USA	Crowdsourcing model to secure fecal samples for 16S rRNA sequence analysis

Madigan et al. 2018

HMP 1 & HMP 2

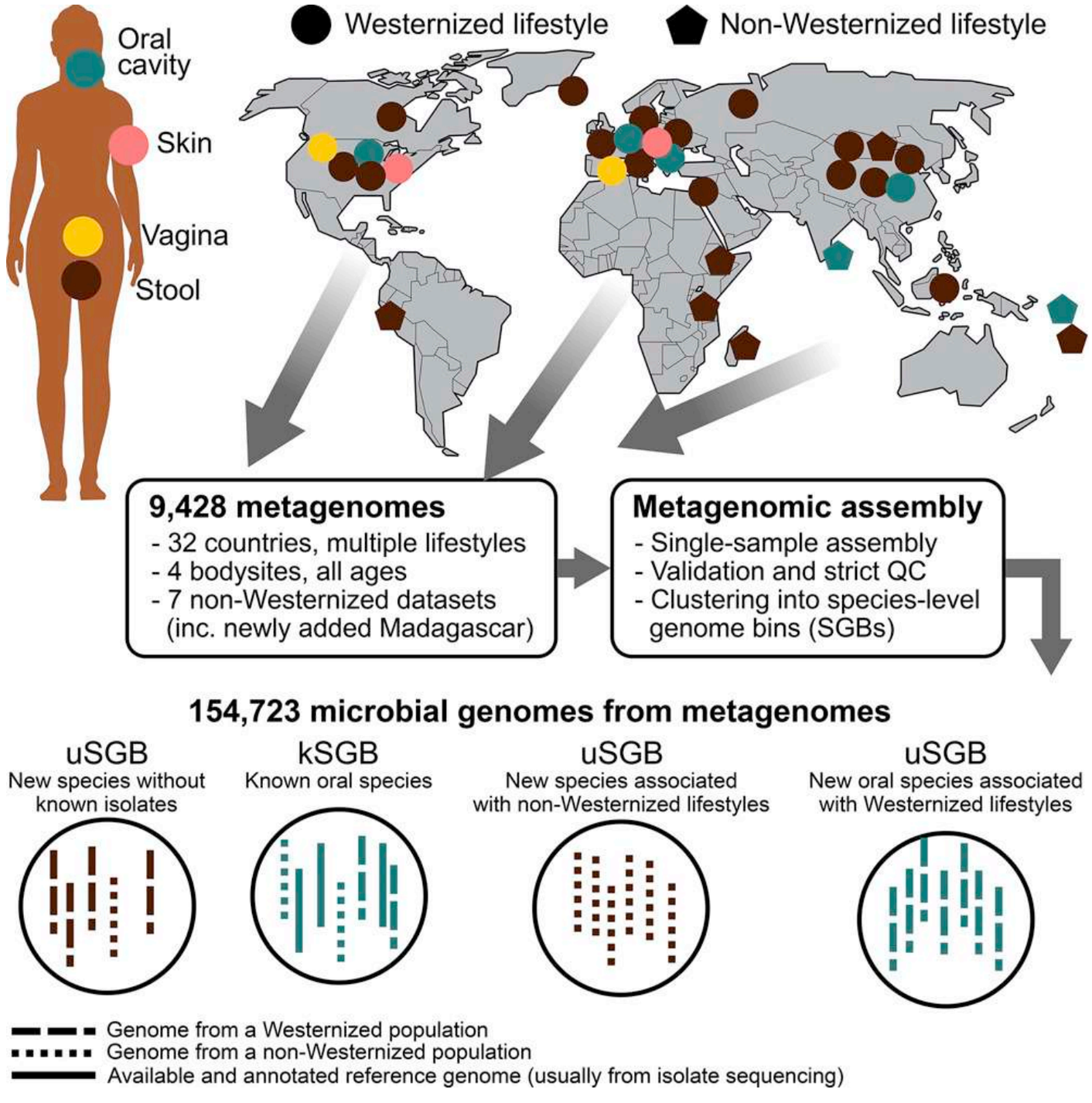


Cytokine: substances, such as interferon, interleukin, and growth factors, which are secreted by certain cells of the immune system and have an effect on other cells

iHMP, 2019

Exploring international microbiomes

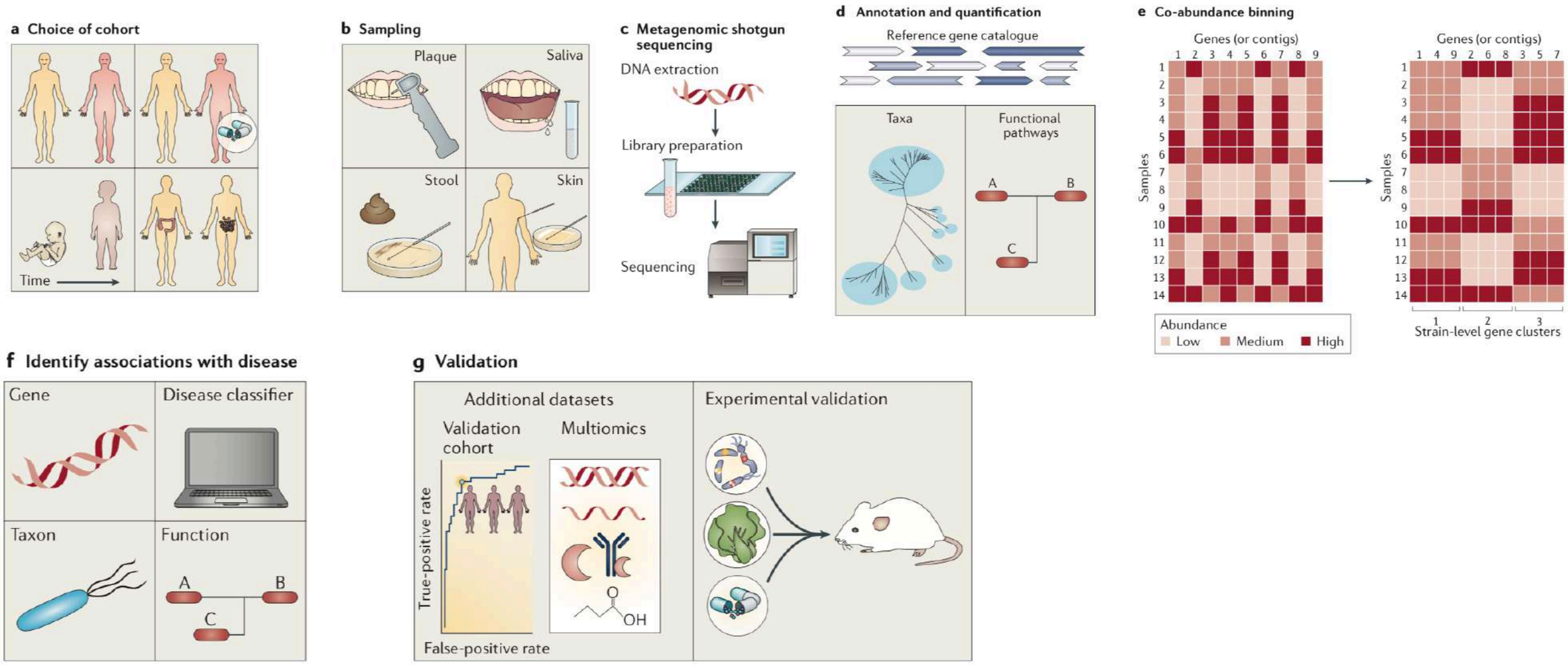
- The body-wide human microbiome plays a role in **health**, but its full diversity remains **uncharacterized**, particularly outside of the gut and in **international population**
- Most characterization of these ecosystems is still focused on microbes that are easily **cultivable**, particularly when those with sequenced isolate genomes are considered
- **Culture-independent** genomic approaches that are scalable to large cohorts have facilitated access to an expanded set of **isolation-recalcitrant members** of the microbiome, but they also suggested the presence of a **large fraction of still unexplored diversity**
- **Non-Westernized populations** harbor a large fraction of the newly discovered species



Pasolli et al., 2019

Metagenome-wide association studies

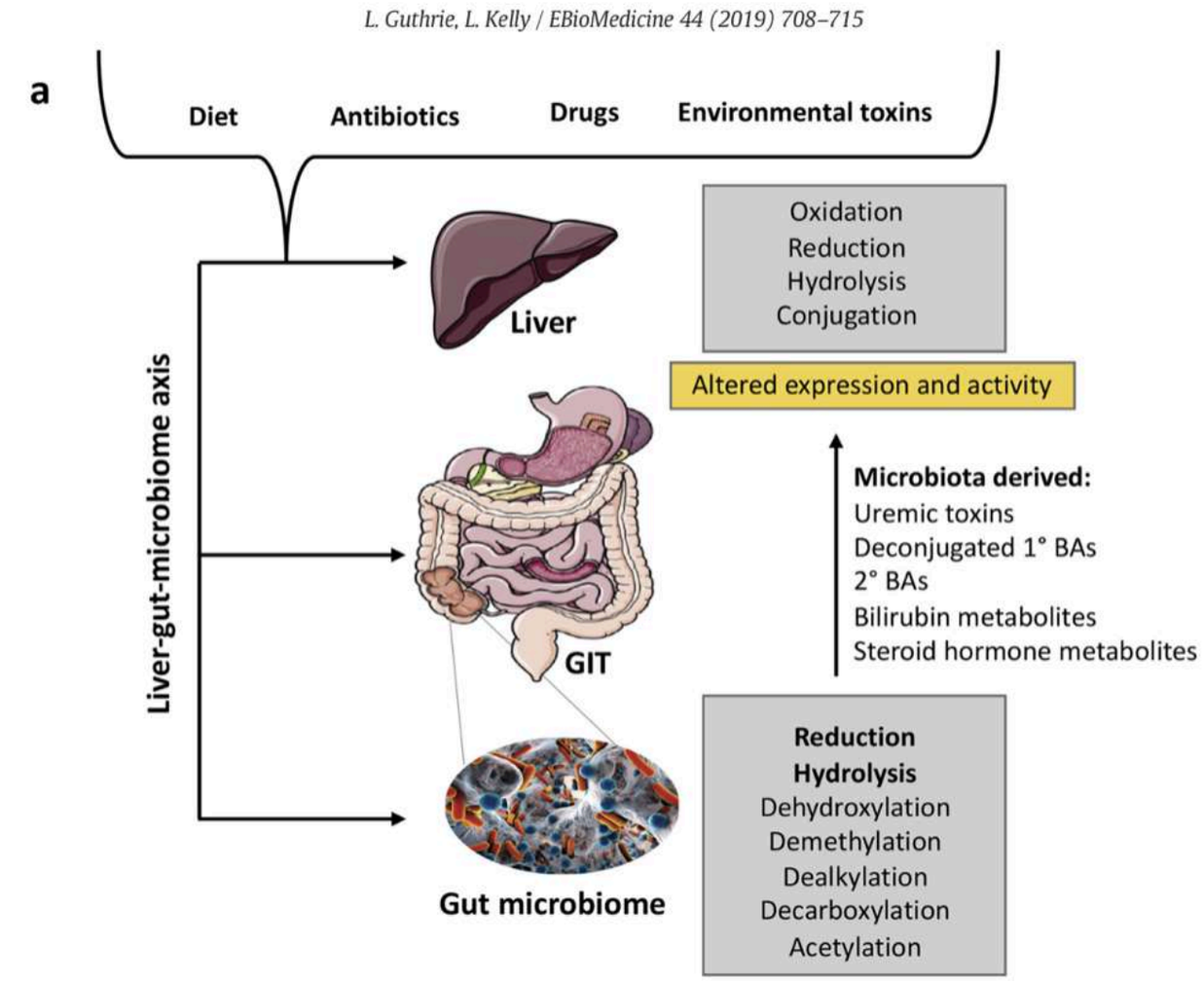
Wang & Jia, 2016



- Sufficient, extensive, sequence data
- High-resolution investigation of association human microbiome and several complex diseases, including type 2 diabetes, obesity, liver cirrhosis, colorectal cancer and rheumatoid arthritis
- Dysbiosis: Imbalance of the microbiota at a body site that is caused by an overgrowth of pathogenic microorganisms or a lack of commensal microorganisms —> disease

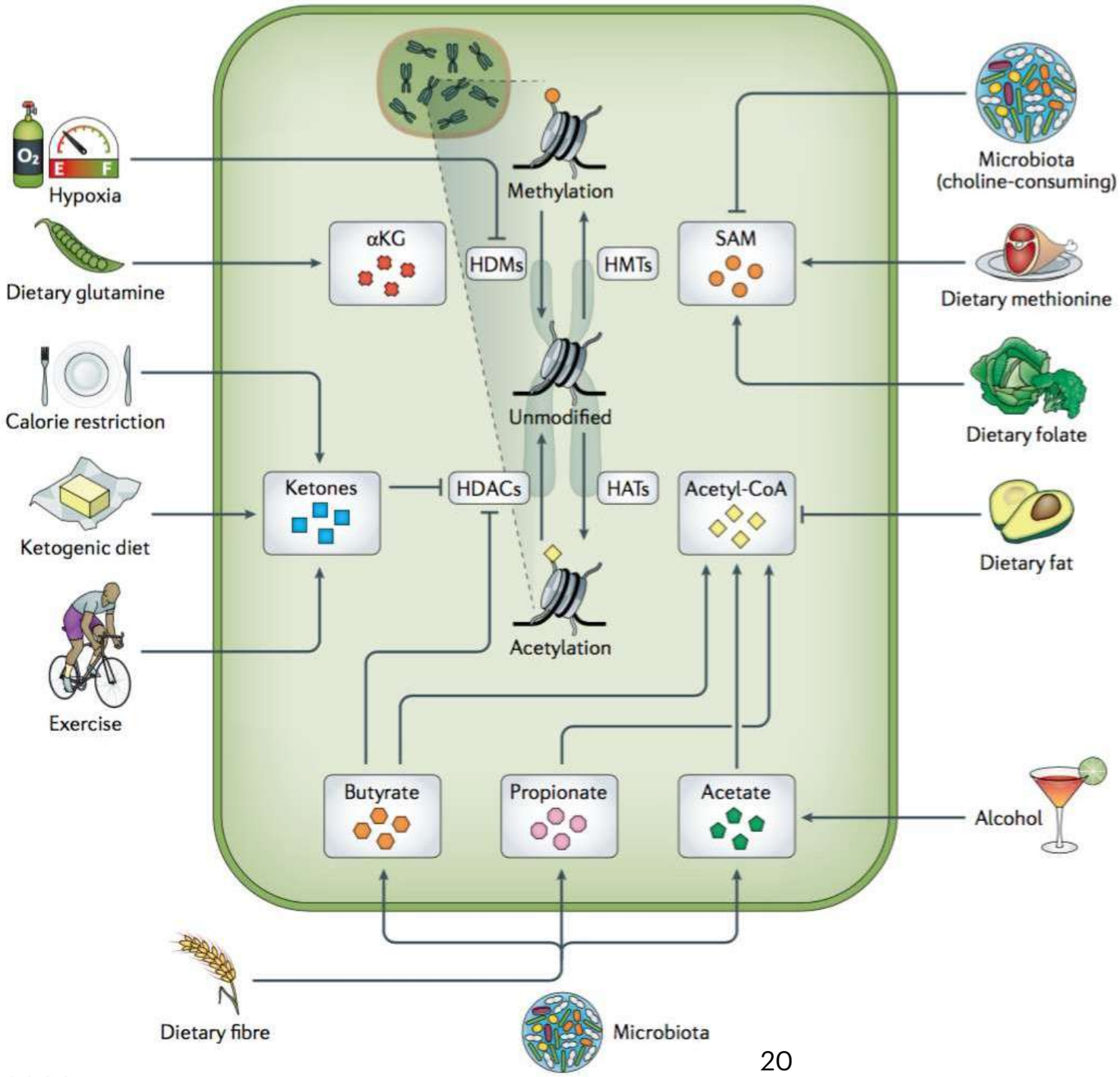
Microbiome to individual medicine

- Translating microbiome research into the clinic requires, in part, a mechanistic and predictive understanding of microbiome-drug interactions
- Human metabolism and individual variation in drug response
- Microbiome chemical mechanisms shape drug metabolism
- Microbiome modulation of drug metabolism enzymes
- Therapeutic drug influences on the gut microbiome



Guthrie & Kelly, 2019

Influences of environmental factors on histone acetylation and methylation via micro biome



S-adenosylmethionine (**SAM**) and acetyl-CoA, that are used by histone methyltransferases (HMTs) and histone acetyltransferases (HATs)

The activity of histone demethylases (**HDMs**) is supported by α-ketoglutarate (αKG), which can be derived from dietary glutamine, and is inhibited by the limited oxygen availability during hypoxia

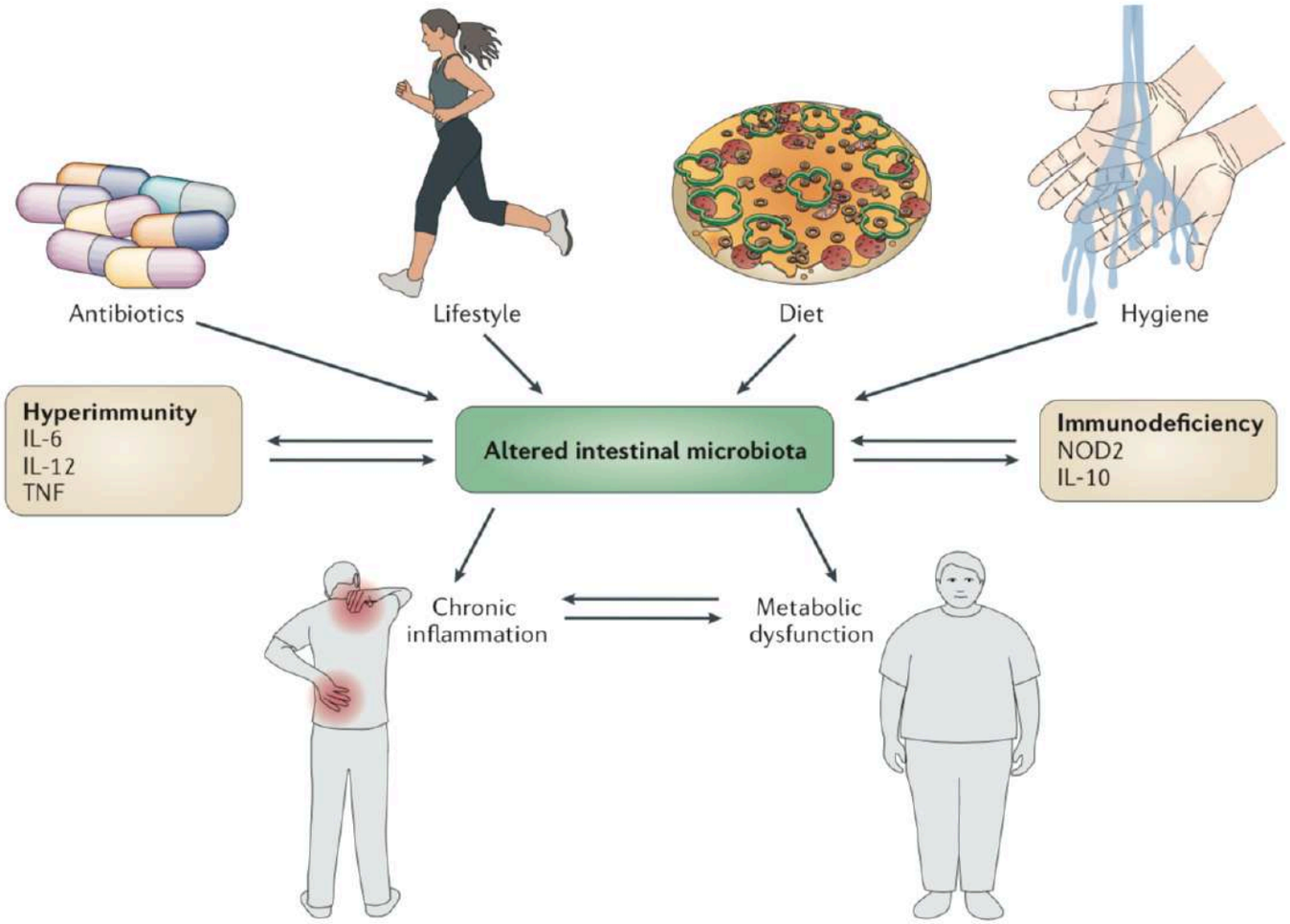
Ketone bodies and short-chain fatty acids (SCFAs) such as acetate, propionate and **butyrate** can provide **acyl-CoA** precursors for histone acylation, while also directly inhibiting the activity of histone deacetylases (HDACs)

Dai et al., 2020

Box 1 | The epigenomes of eukaryotes and bacteria

- In eukaryotes, epigenetic modification of the genome involves DNA methylation[3] and histone modification[4]. Bacteria lack histones, and epigenetic control relies on DNA methylation only[6].
- In eukaryotes, de novo and maintenance forms of DNA methylation are performed by separate enzymes[2]. Bacterial DNA methyltransferases have both de novo and maintenance activities[37].
- In eukaryotes, two main mechanisms exist to erase DNA methylation marks: active demethylation by dedicated proteins (Tet enzymes), and passive demethylation by the hindrance of DNA methylase activity upon DNA replication[35]. In bacteria, DNA demethylation is usually passive[66], and the relevance of active demethylation by DNA repair remains to be evaluated[82].
- In both bacteria and eukaryotes, transcriptional repression by DNA methylation is common[3,6]. Transcriptional activation of bacterial genes under DNA methylation control often involves demethylation (partial or complete, single- or double-stranded) of promoters or regulatory regions[57,72,89,90,94,158].
- The methylated base typically involved in the control of eukaryotic transcription is C^5-methyl-cytosine[3], whereas in bacteria it is often N^6-methyl-adenine[7,14]. However, direct control of bacterial transcription by C^5-methyl-cytosine has been demonstrated recently[126]. Transcriptional control by N^4-methyl-cytosine may also exist[130].
- In multicellular eukaryotes, the DNA methylation pattern of the genome is reprogrammed during gametogenesis and during early embryonic development[2]. In bacteria, reprogramming does not occur, and the DNA methylation pattern can be transmitted unaltered across generations. However, the acquisition and loss of DNA methyltransferase genes[41] and recombinational shuffling of DNA methyltransferase domains[27,33,143] can produce novel methylation patterns in bacterial genomes.
- In both bacteria and eukaryotes, DNA methylation controls the formation of phenotypic variants of genetically identical cells. However, DNA methylation-dependent formation of bacterial cell lineages can show programmed reversion (phase variation)[15,27,93,111].

Factor shaping microbial gut community



- Environmental factors: antibiotics, lifestyle, diet and hygiene preferences
- Host's genetic disposition has a role in influencing gut microbiota composition
- Hyperimmunity (owing to over-representation of pro-inflammatory mediators such as interleukin-6 (IL-6), IL-12 or tumour necrosis factor (TNF))
- Immunodeficiency (owing to mutations in regulatory immune proteins such as NOD2 (nucleotide-binding oligomerization domain protein 2) or IL-10)
- Dysbiosis affects levels of immune mediators and induces both chronic inflammation and metabolic dysfunction

Sommer & Bäckhed, 2013

Secondary metabolite production by gut microbiota association

TABLE 24.2 Biochemical/metabolic contributions of intestinal microorganisms

Process	*Product or enzyme*
Vitamin synthesis	Thiamine, riboflavin, pyridoxine, B_{12}, K
Amino acid synthesis[a]	Asparagine, glutamate, methionine, tryptophan, lysine, and others
Gas production	CO_2, CH_4, H_2
Odor production	H_2S, NH_3, amines, indole, skatole, butyric acid
Organic acid production	Acetic, propionic, butyric acids
Glycosidase reactions	β-Glucuronidase, β-galactosidase, β-glucosidase, α-glucosidase, α-galactosidase
Steroid metabolism (bile acids)	Esterified, dehydroxylated, oxidized, or reduced steroids

[a]Capacity for amino acid biosynthesis inferred from the identification of biochemical pathways encoded in gut metagenomic sequences (Sections 9.8 and 19.8).

Immune system does not properly develop in the **absence** of **microbial** stimulation and that early life exposure to a variety of microorganisms is essential for developing tolerance to beneficial microorganisms and recognizing pathogens as foreign

TABLE 24.3 Small bioactive molecules produced by bacteria in the large intestine

Class	*Compound*	*Example producer*	*Activity*
RiPP[a] (lantibiotic)	Ruminococcin A	*Ruminococcus gnavus*	Antibiotic
RiPP[a] (bacteriocin)	Ruminococcin C	*Ruminococcus gnavus*	Antibiotic
Amino acid metabolite	Indolepropionic acid	*Clostridium sporogenes*	Protective anti-oxidant
Amino acid metabolite	4-Ethylphenylsulfate	Undefined	Neuromodulatory
Amino acid metabolite	Tryptamine	*Ruminococcus gnavus*	Neurotransmitter
Volatile fatty acid	Propionic acid	*Bacteroides* spp.	Immunomodulatory[b]
Oligosaccharide	Polysaccharide A	*B. fragilis*	Immunomodulatory[b]

[a]Ribosomally synthesized and post-translationally modified peptides.
[b]These small molecules promote colonization by normal microbiota.

Gut as a second brain

Madigan et al. 2018

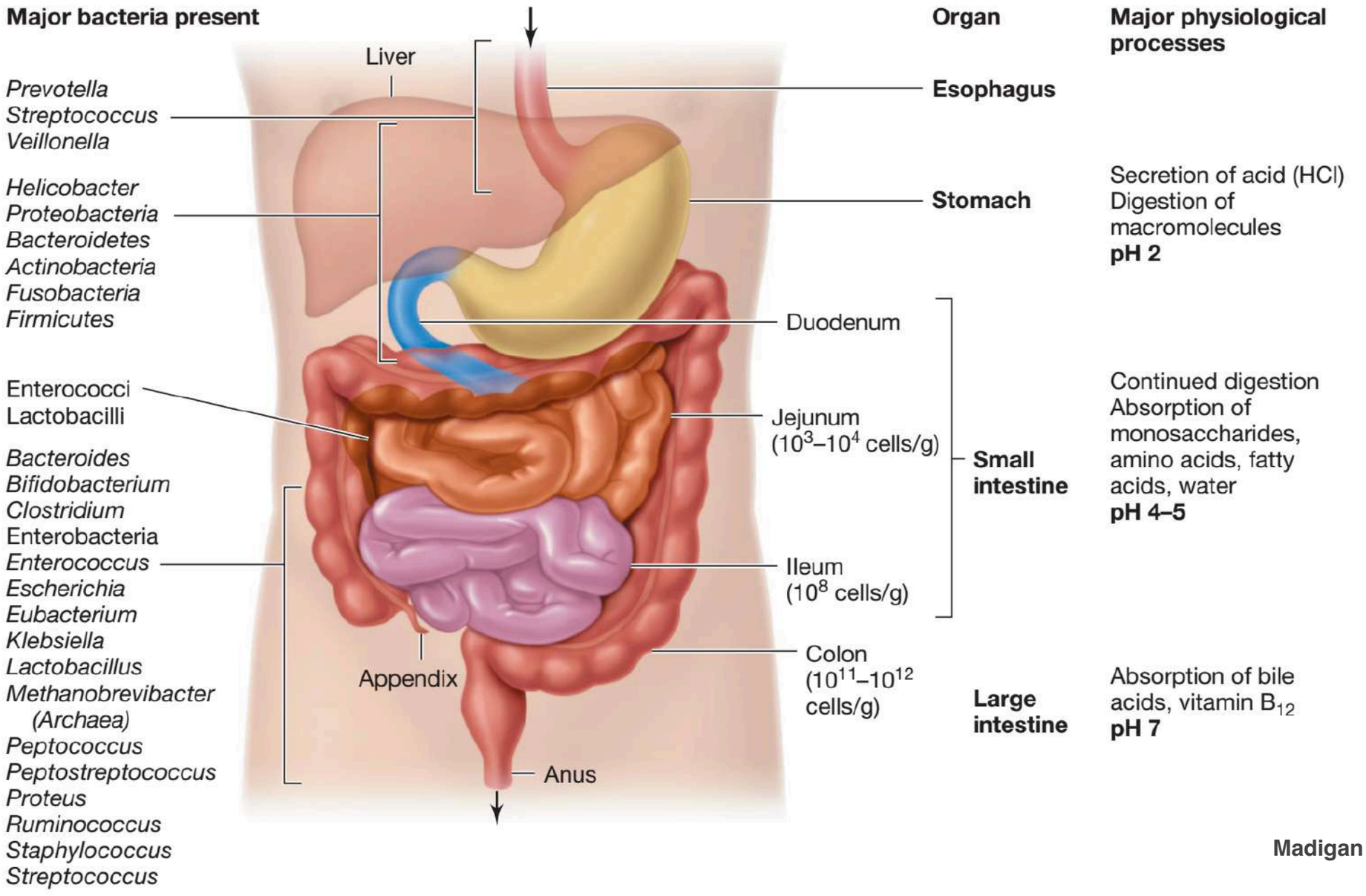
Gut-microbes association

Changing in space and time

Changing with age host

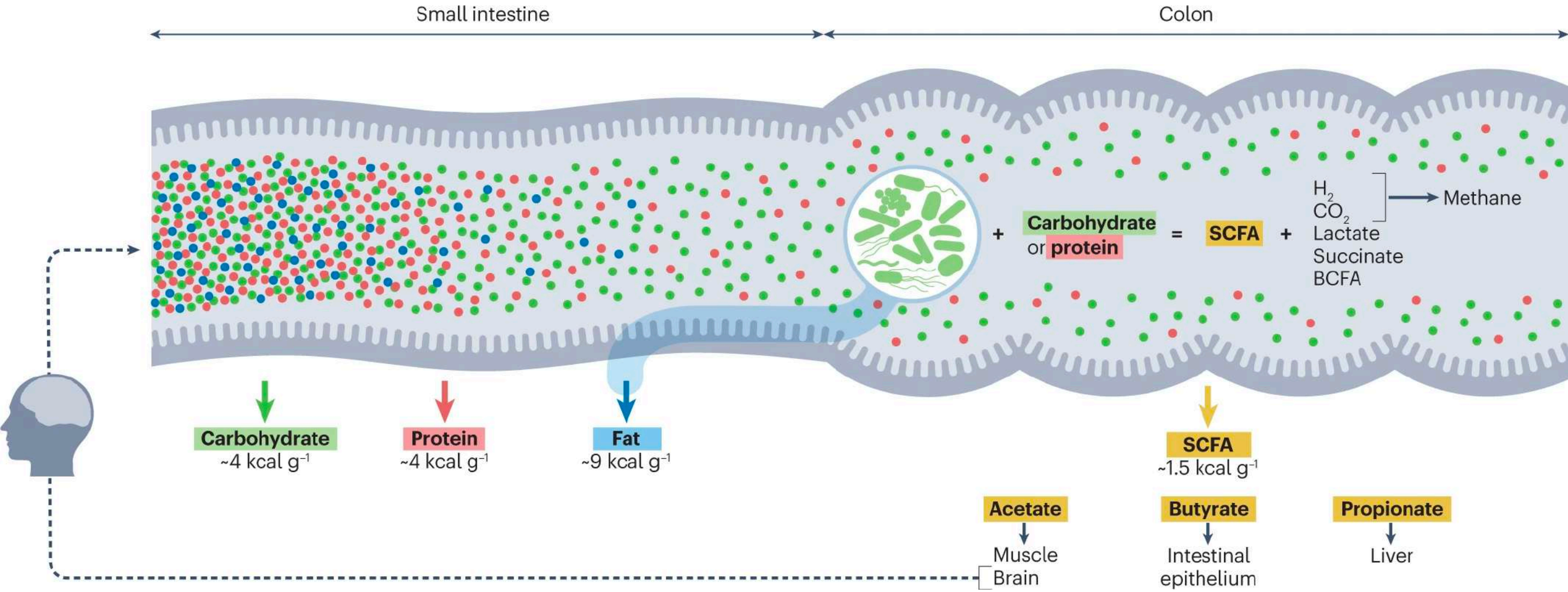
Changing with food ingested and drugs

Ever-changing microbial communities and abundance



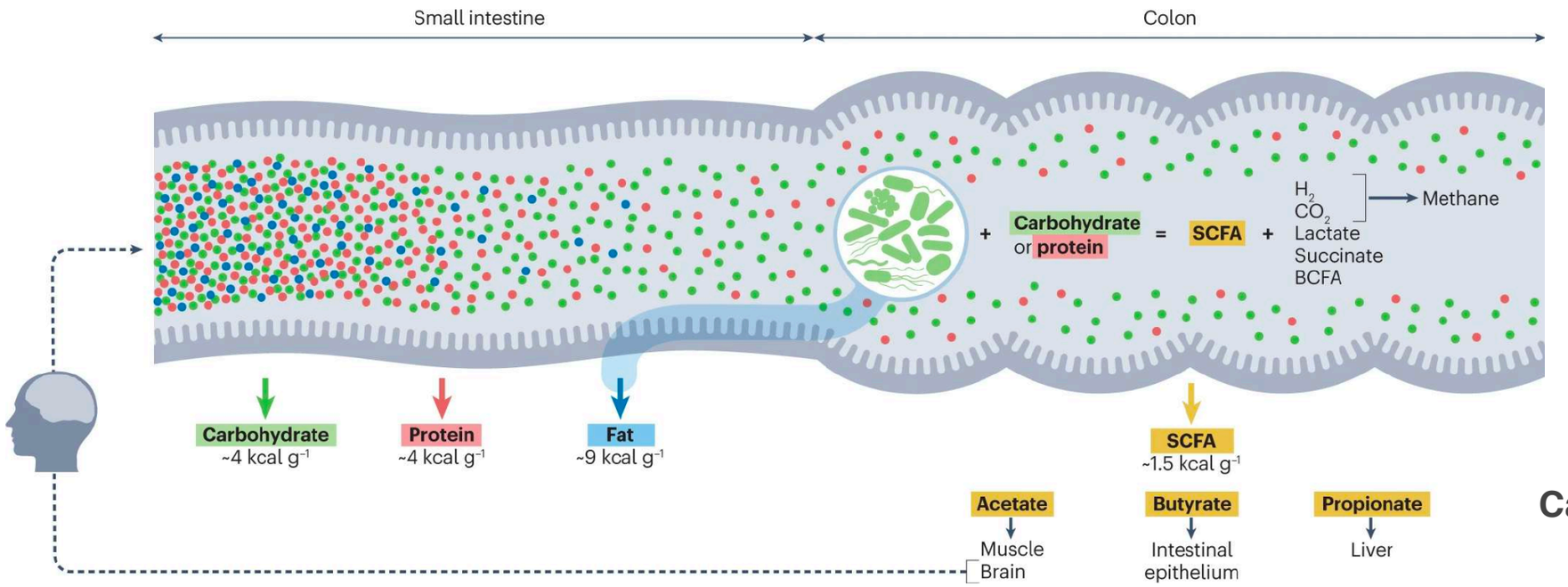
Madigan et al. 2018

Gut microbiome enhances dietary energy harvest



Carmody & Bisanz, 2023

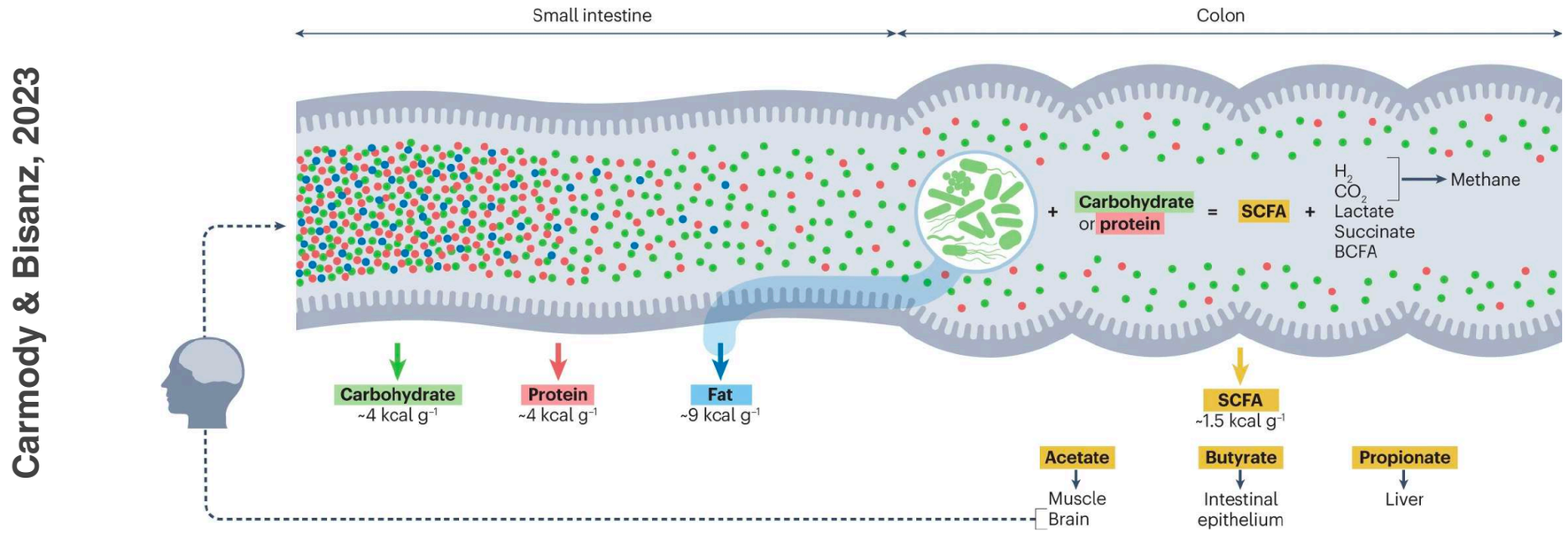
Gut microbiome enhances dietary energy harvest



Carmody & Bisanz, 2023

Macronutrients available for breakdown by host enzymes are digested in the small intestine
Small intestinal macronutrient absorption supplies the host with energy predictable by biochemistry (carbohydrate, ~4 kcal g^{-1}; protein, ~4 kcal g^{-1}; fat, ~9 kcal g^{-1})
Dietary **fat** is readily absorbed in the proximal small intestine —> fat digestion canonically depends exclusively on host enzymes, but there are evidence of gut microbiome contributions to small intestinal lipid absorption
Microorganisms augment carbohydrate and protein digestion
The fractions of carbohydrate and protein digested in the small intestine vary with macronutrient structural form (for example, higher for sugar versus fibre), meal composition (for example, higher for fibre-poor versus fibre-rich meals), thermal processing (for example, higher for cooked foods) and physical processing (for example, higher for smaller particle sizes)
Nutrients that escape small intestinal digestion undergo fermentation by the colonic gut microbiota, producing an array of metabolites with energetic implications
The gut microbiome produces branched-chain fatty acids (BCFAs) from dietary valine, leucine and isoleucine, plus other organic acids such as lactate and succinate

Gut microbiome enhances dietary energy harvest



Undigested carbohydrates are the principal fuel for microbial **fermentation**, from which the gut microbiome **generates the short-chain fatty acids (SCFAs) acetate, butyrate and propionate**

SCFAs are absorbed by the host and contribute to energy metabolism in diverse tissues, with acetate supporting muscle and brain, butyrate supplying up to 60–70% of the energetic needs of the colonic epithelium and propionate used in hepatic gluconeogenesis

Energy returns from SCFAs have been estimated at ~1.5 kcal g^{-1} < than half the rate for carbohydrates digested in the small intestine

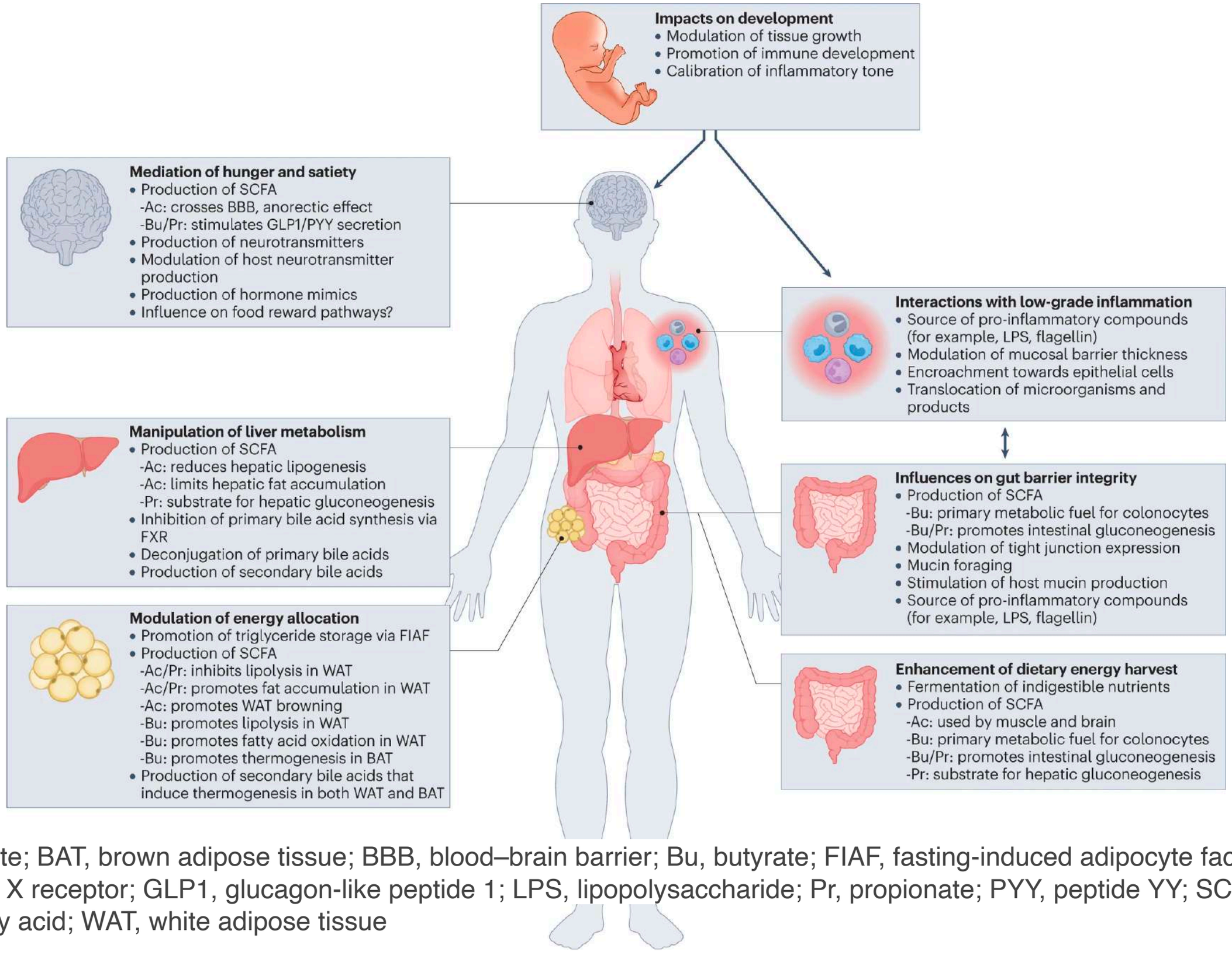
More energy is harvested by the host when nutrients are digested directly versus fermented

SCFAs account for ~5–10% of daily energy requirements in industrialized populations and almost certainly a >> fraction in populations with minimally processed and/or fibre-rich diets

SCFAs were long appreciated primarily as vehicles for energy salvage and have potent signalling functions that modulate energy intake, energy utilization and inflammation

Host metabolites, including bile acids and immune factors , also interact bidirectionally with the gut microbiome and influence its contributions to energy balance

Mechanisms of gut microbial influence on host energy status

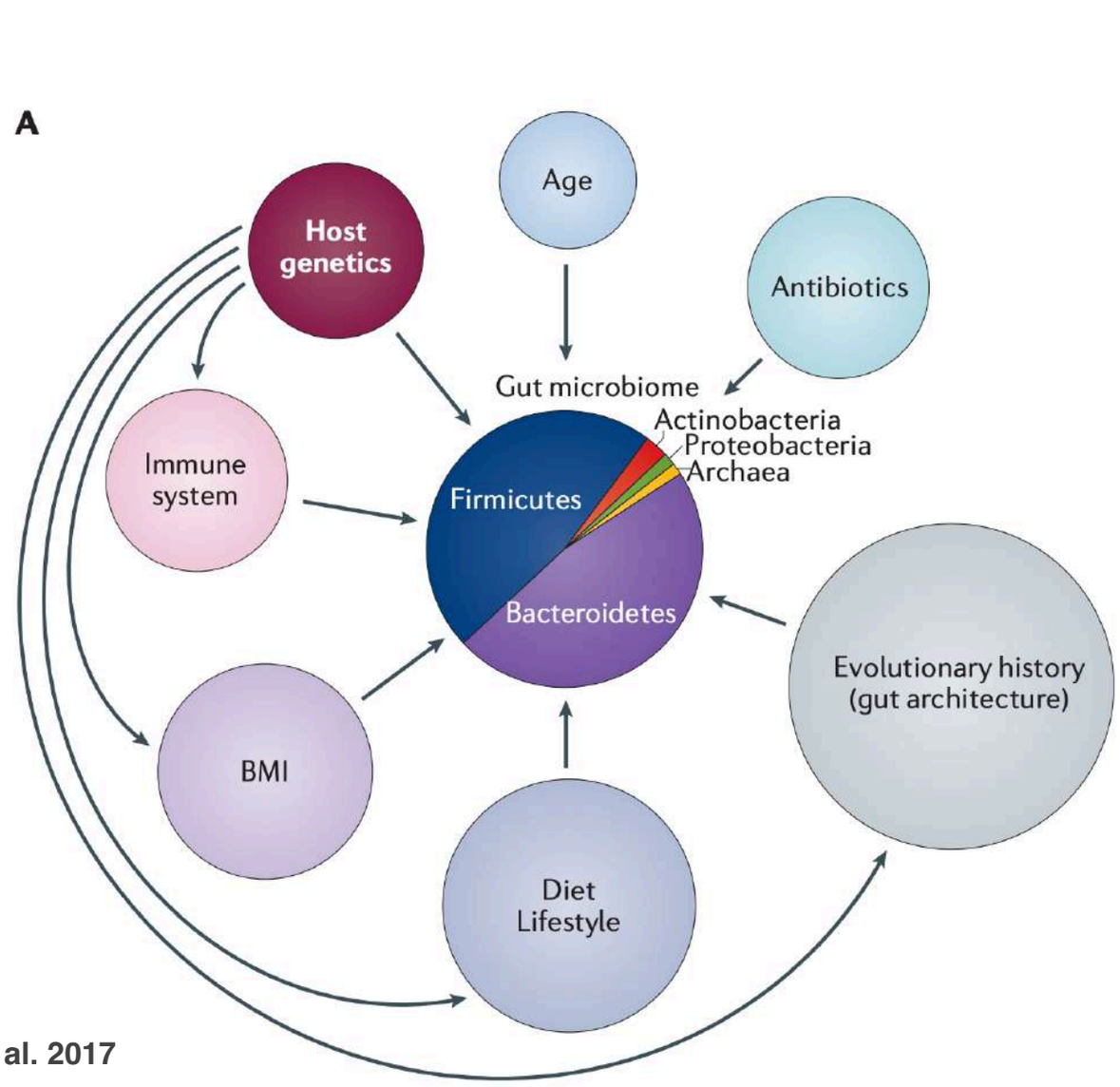


Carmody & Bisanz, 2023

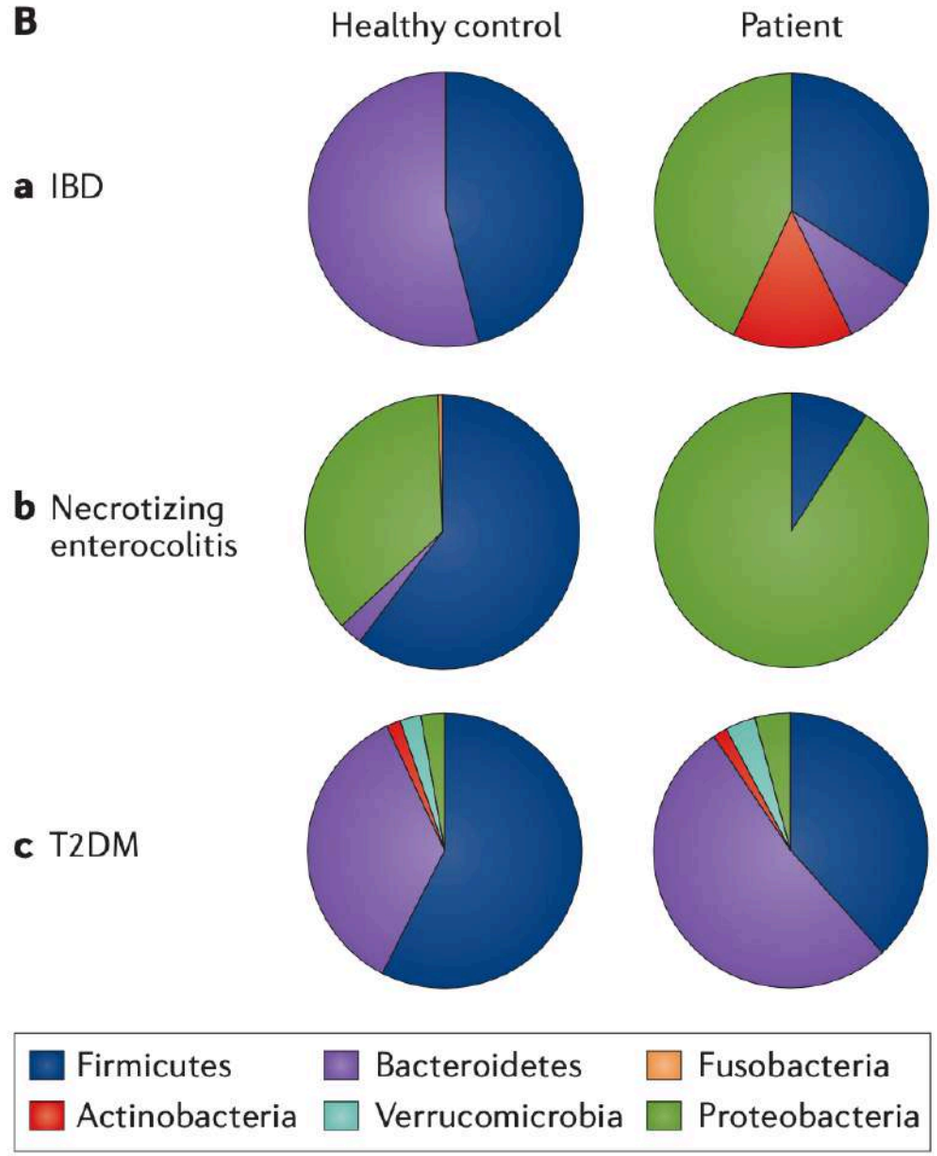
Ac, acetate; BAT, brown adipose tissue; BBB, blood–brain barrier; Bu, butyrate; FIAF, fasting-induced adipocyte factor; FXR, farnesoid X receptor; GLP1, glucagon-like peptide 1; LPS, lipopolysaccharide; Pr, propionate; PYY, peptide YY; SCFA, short-chain fatty acid; WAT, white adipose tissue

Dysbiosis

- Changes of interactions among microbes due to changes in communities
- Dysbiosis of the gut microbiome has been implicated in multiple diseases:
- Inflammatory bowel disease (IBD)
- Necrotizing enterocolitis (in premature infants)
- Type 2 diabetes mellitus (T2DM)



Hall et al. 2017



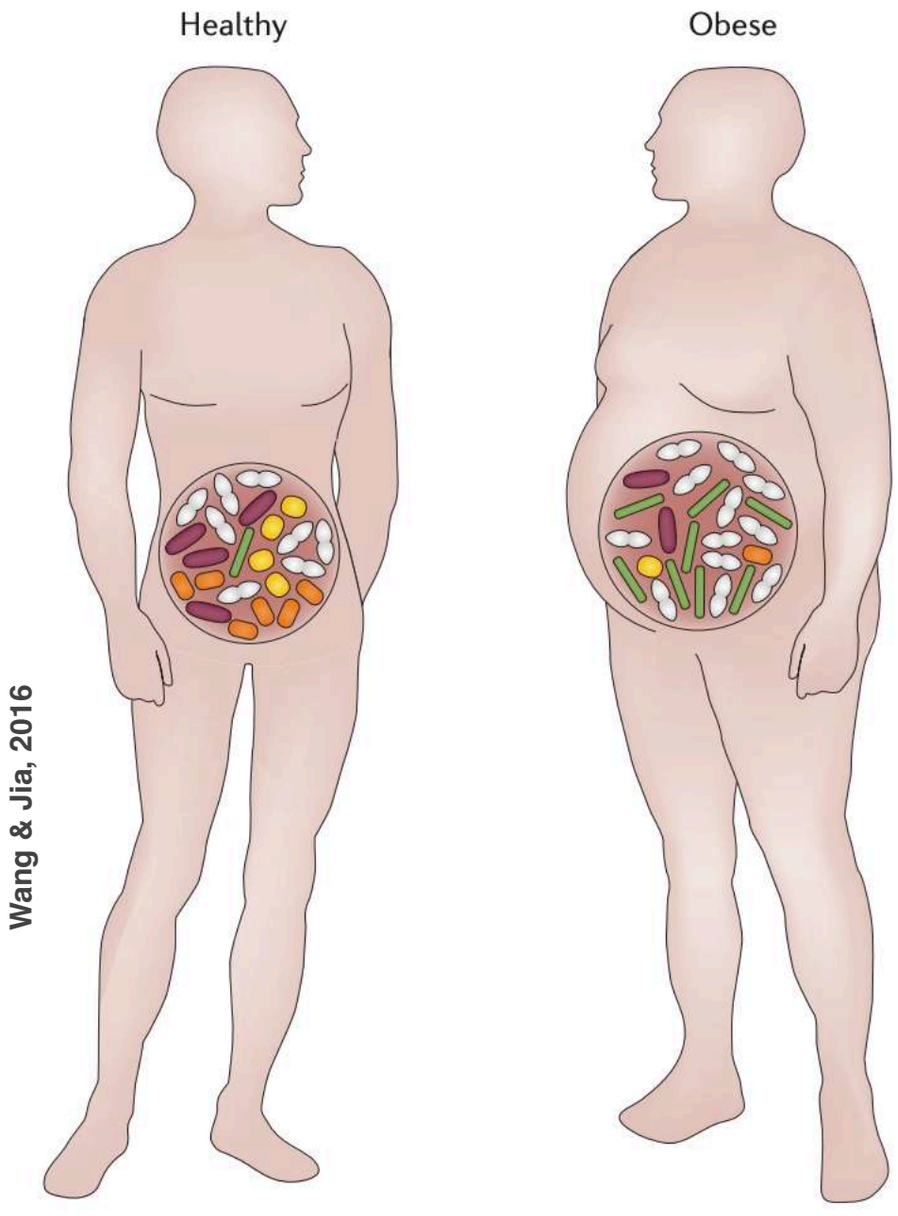
Representative studies linking human conditions to the microbiome

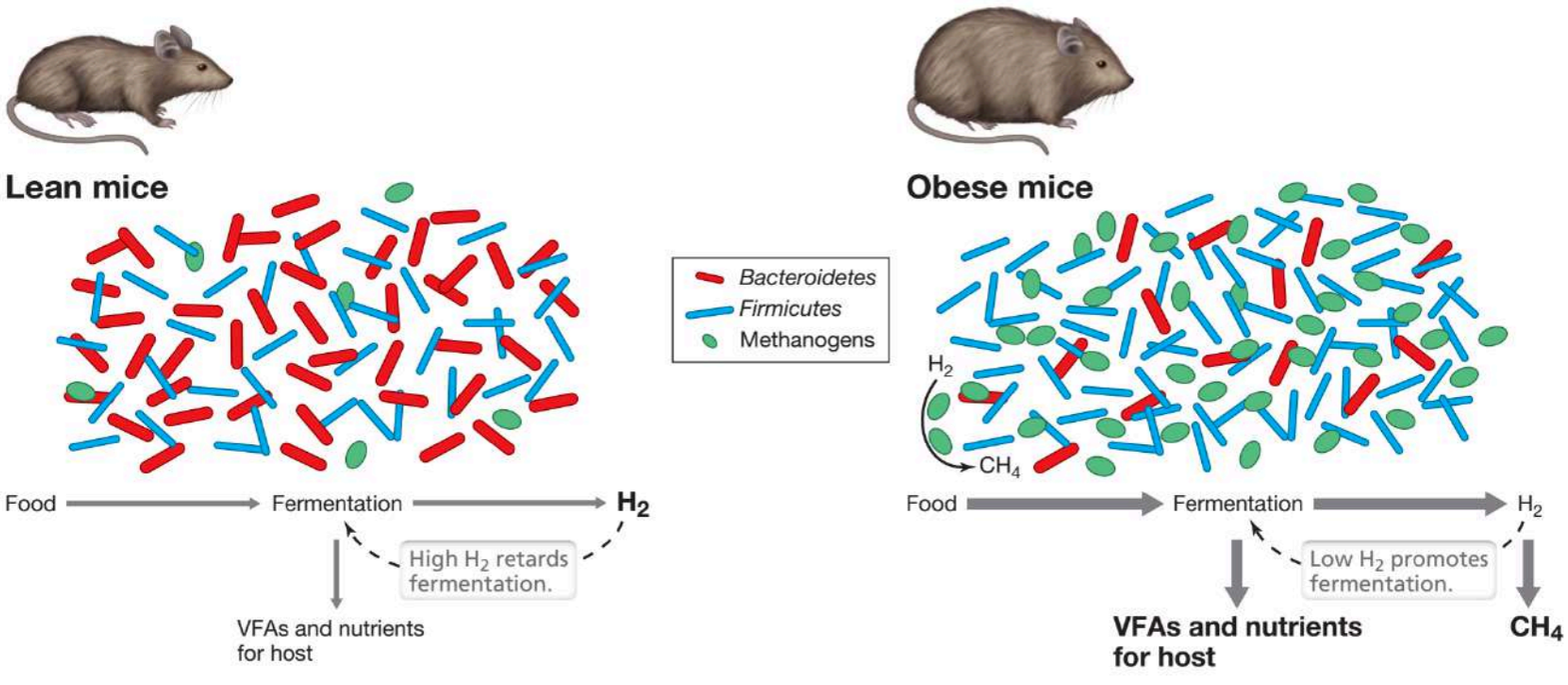
Condition or disease	Microbiome alteration	Potential or known mechanism	Comments	Refs
Obesity	Greater abundance of pathobionts and Firmicutes	Calorie harvesting, inflammation, modulating satiety, regulating adipogenesis	Controversial microbial links to complex, that is, multifactorial, disease	157
Type 2 diabetes	As for obesity, with signals related to *Prevotella copri* and *Akkermansia muciniphila*	Unclear; liver signalling, branched-chain amino acids?	Initial success with faecal microbiota transplantation not maintained in later studies	158
Inflammatory bowel disease	Reduced abundance of Christensenellaceae, *Coriobacteriaceae*, *Faecalibacterium prausnitzii*; higher abundance of Actinomyces, *Veillonella*, *Escherichia coli*	Products of colonic inflammation stimulate anaerobic respiration, driving microbiome further towards a pro-inflammatory type	Meta-analysis concedes lack of a unifying taxon signature for inflammatory bowel disease; once inflammation is triggered, the microbiome may be irrelevant for treating inflammatory bowel disease	159,160
Irritable bowel syndrome	*Ruminococcus gnavus* and Lachnospiraceae are more abundant, *Barnesiella intestinihominis* and *Coprococcus catus* depleted	Pathophysiology may involve a reduction of luminal pH by excessive fermentation and sensitization of the enteric nervous system by inflammation	Not all patients with irritable bowel syndrome have an altered microbiome; disruption of the diet–microbiome–metabolome connectivity is a feature of those who do	161,162
Colorectal cancer	Presence of *Fusobacterium nucleatum* and other oral biofilm-forming pathobionts is a feature of tumour microbiome	Inflammation, DNA breakage, mutagenesis	Microbiome alterations linked to colon cancer relate to known risk factors such as diet and inflammation; microbiome also influences the responsiveness of cancers to checkpoint immunotherapy	10
Cardiovascular disease	Bacterial taxa capable of generating trimethylamine from carnitine, choline and glycine betaine	Trimethylamine is a substrate for liver production of trimethylamine oxide, an atherogenic metabolite	Initial controversy due to inverse relationship between choline intake and cardiovascular disease but prospects for druggable targets	7,9,163
Cognitive function, behaviour and mood	Diverse observations and metabolites reported but a catalogue of gene products with neuroactive potential identified	Effects on neurodevelopment, neuroplasticity, degree of myelination, peptide binding to immune cells and vagus nerve endings, other brain signalling effects	Plausible leads but a paucity of compelling human studies	8,164

Gosh et al., 2022

Dysbiosis: obesity and altered microbiome

- Heritable species are partially responsible for the altered microbiome composition in obesity
- Obesity is associated with **differential abundance of specific microbial species and metabolism**
- *Christensenella minuta*, *Akkermansia muciniphila, Methanobrevibacter smithii* are under-represented in obesity
- *Blautia*, over-represented in obesity

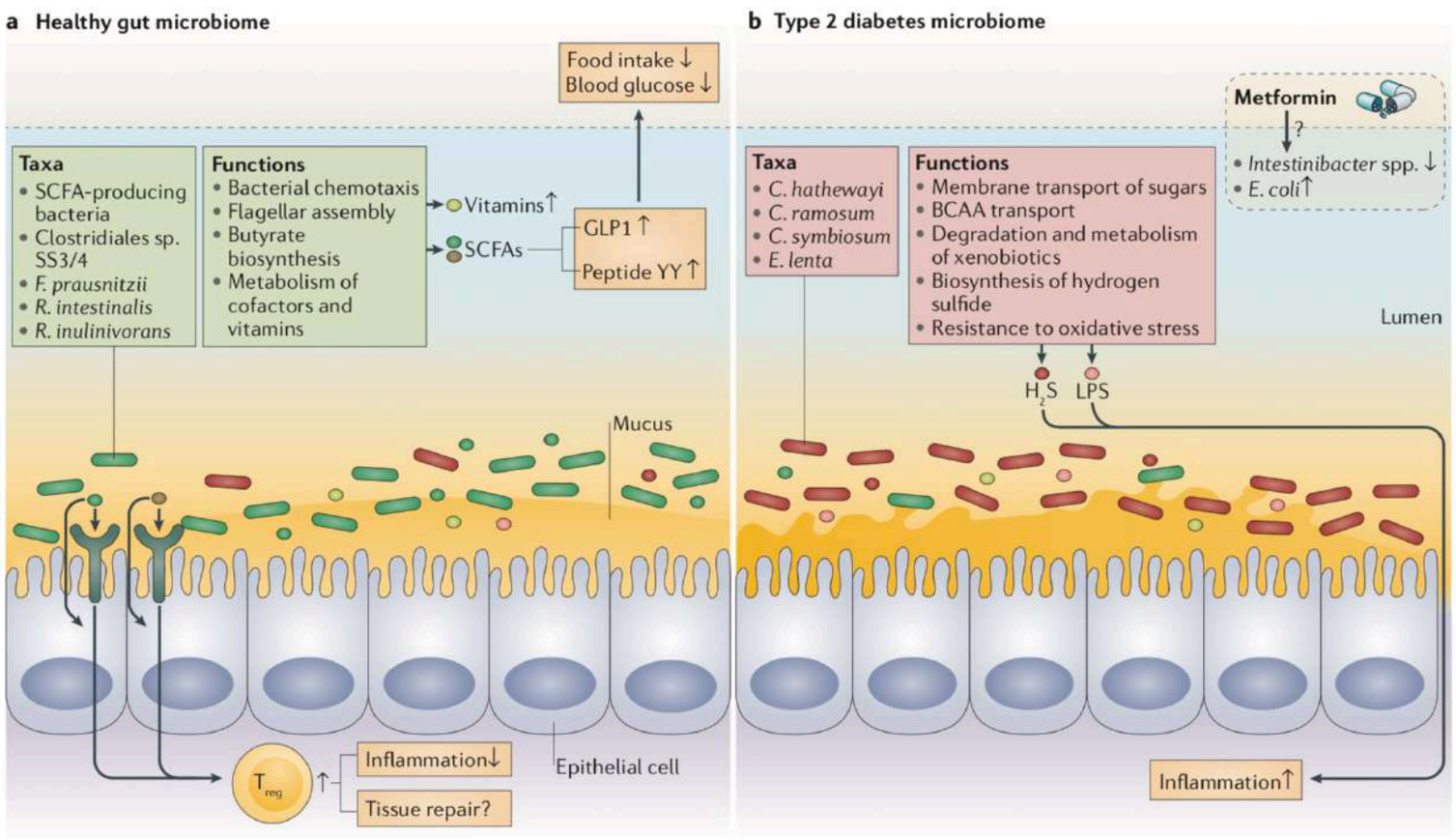




Madigan et al. 2018

Dysbiosis: Gut-microbiome - type 2 diabetes

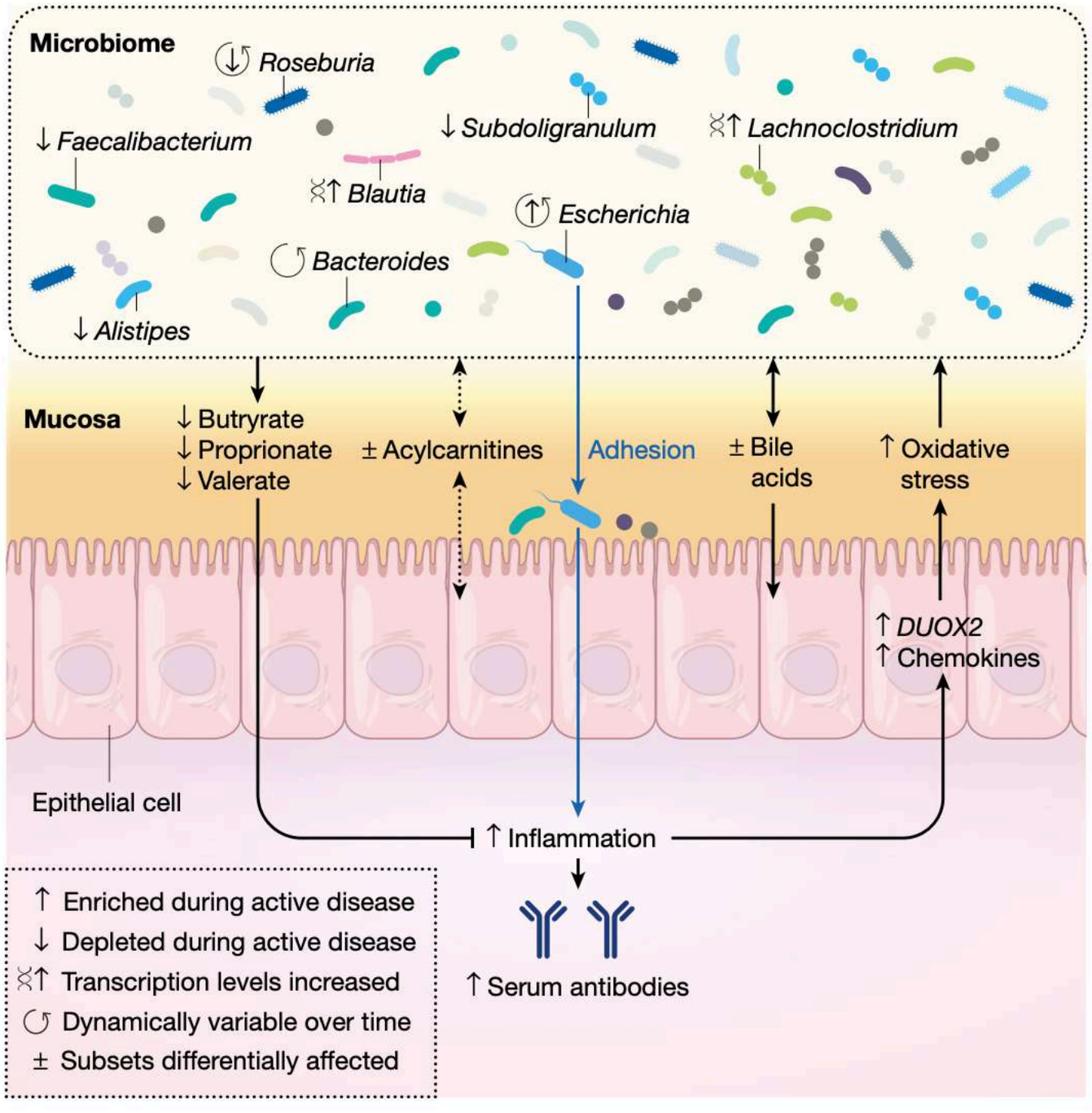
- **Healthy** individuals: gut microbiome enriched for taxa with increased capacity for **short-chain fatty acids** (**SCFAs**) production—> **intestinal integrity, energy homeostasis, signalling through host receptors to induce regulatory T cells, which restricts inflammation may even promote tissue repair**
- SCFAs stimulate secretion of glucagon-like peptide 1 (GLP1), peptide YY by intestinal L cells to control glucose homeostasis and regulate food intake
- **Type 2 diabetes**: increase production of **hydrogen sulfide and lipopolysaccharide** (LPS) could stimulate **inflammation** and **production of BCAA (branched-chain amino acid)**
- Gut microbiomes of individuals with type 2 diabetes who were treated with anti-diabetic drug metformin showed a decrease of *Intestinibacter* spp. an increase of *Enterobacteriaceae* family, such as *E. coli*



Wang & Jia, 2016

C.= *Clostridium*

Dysbiosis: Host–microbiome dynamics in IBD

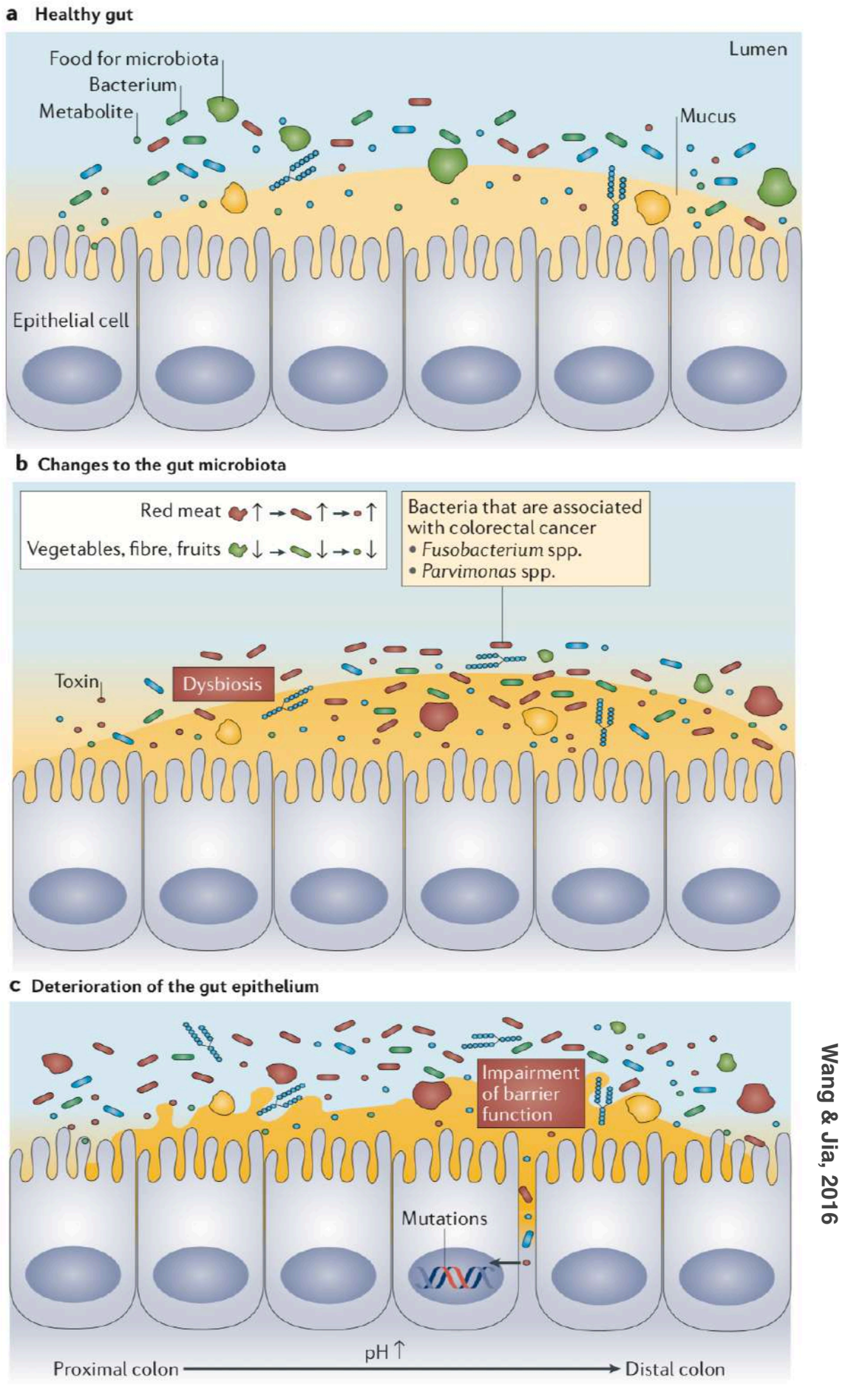


- **Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis**
- Network of mechanistic associations identified several key components that are central to the alterations seen in IBD.
- Octanoyl carnitine, several lipids and short-chain fatty acids, the taxa *Faecalibacterium*, *Subdoligranulum*, *Roseburia*, *Alistipes*, and *Escherichia*, and host regulators of interleukins

iHMP, 2019

Dysbiosis: colorectal cancer

- Some **bacterial species** that are **usually of low abundance** in the gut
- **Abundance shift in response to lifestyle or dietary changes,** such as an **increase** in the consumption of **red meat** and a **decrease** in the consumption of **fruits, vegetables and fibre**
- Some bacterial species that are most commonly described as anaerobic oral bacteria, such as *Fusobacterium* spp. and *Parvimonas micra* may play a role
- **Functional changes** in the gut microbiome might involve an **increase in the production of carcinogens** through processes such as **amino acid fermentation and the metabolism of bile acids**
- By contrast, **bacterial species that produce the metabolites butyrate and lactate**, which facilitate the **maintenance of the colonic epithelium**, can be **depleted** in the gut microbiomes of individuals with colorectal cancer
- **Dysbiosis of the gut microbiota can result in an impairment of gut barrier function, which increases the exposure of the gut epithelium to microorganisms and their metabolites mutagens that might promote carcinogenesis**



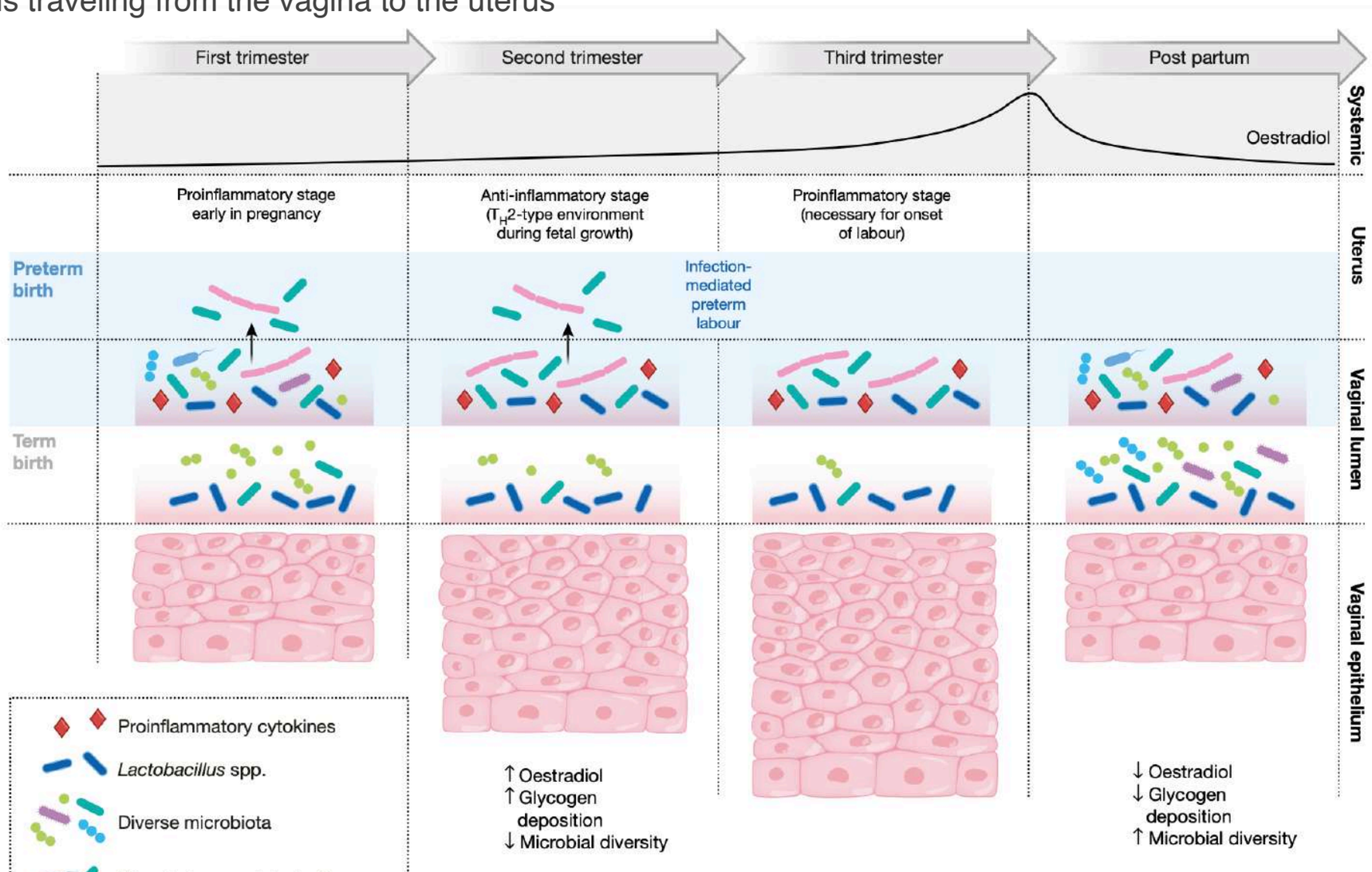
Wang & Jia, 2016

Dysbiosis: Vaginal microbiome in pregnancy and preterm birth

As **pregnancy** progresses, with **predictable changes in systemic oestradiol levels**, the uterine and **vaginal environments** undergo various **changes**

The **uterus switches** from an **early pro-inflammatory** condition **to** an **anti-inflammatory** condition in the second trimester, and then back **to a pro-inflammatory** condition before the onset of **labour**

Specific changes in the microbiome of the vaginal lumen can be associated with preterm birth, possibly through mechanisms involving microorganisms traveling from the vagina to the uterus

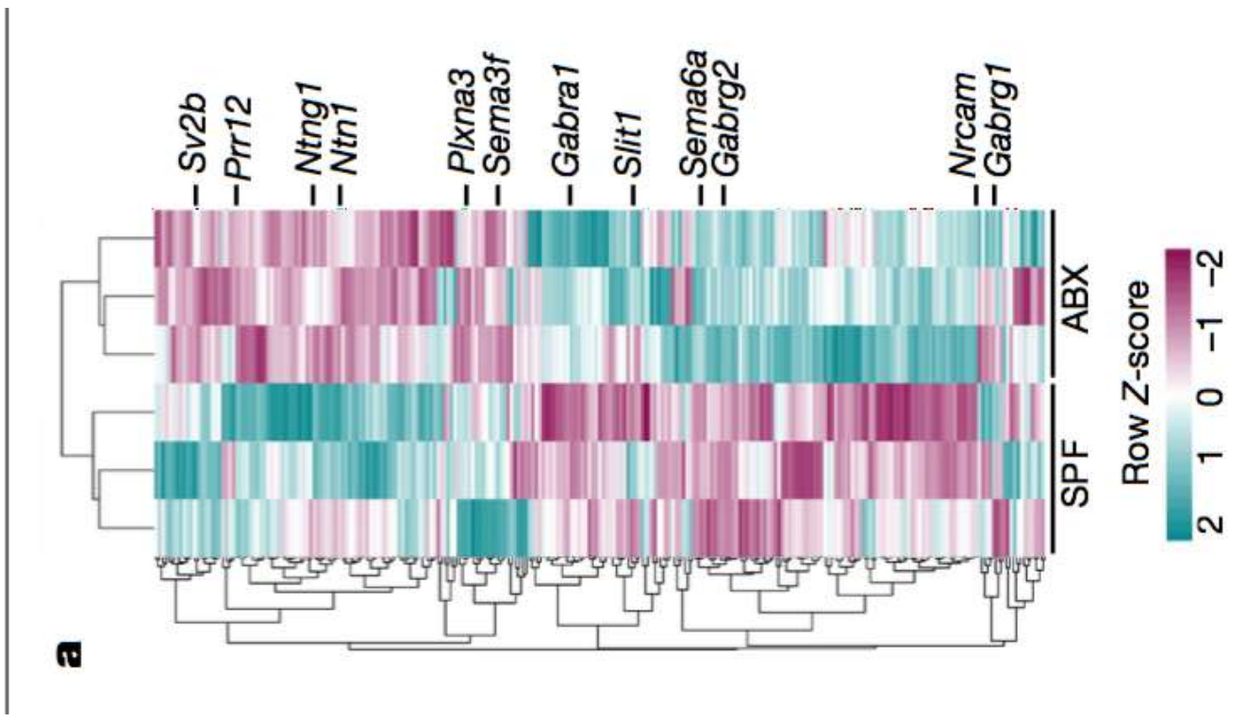


iHMP, 2019

The maternal microbiome modulates fetal neurodevelopment in mice

‘**Dysbiosis’ of the maternal gut microbiome**, in response to challenges such as infection, **altered diet and stress during pregnancy**, has been increasingly associated with **abnormalities in brain function and behaviour of the offspring**

Manipulation of the **maternal microbiome and microbial metabolites** during pregnancy yielded adult o spring with altered tactile sensitivity in two aversive somatosensory behavioural tasks

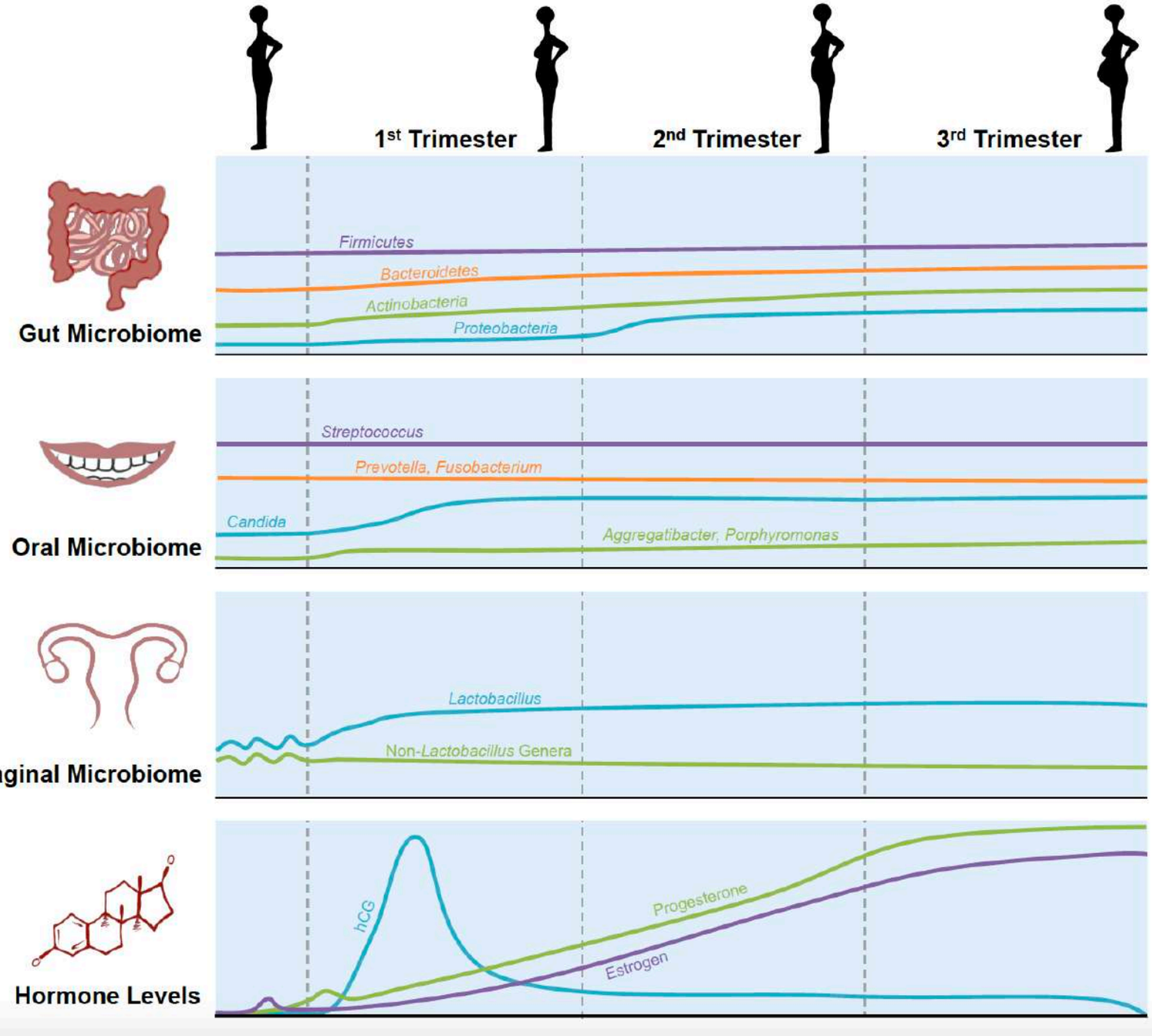


SPF: specific-pathogen-free

Genes that are differentially expressed in E14.5 brains from offspring of SPF and ABX dams

Vuong et al., 2020

Microbial changes during pregnancy



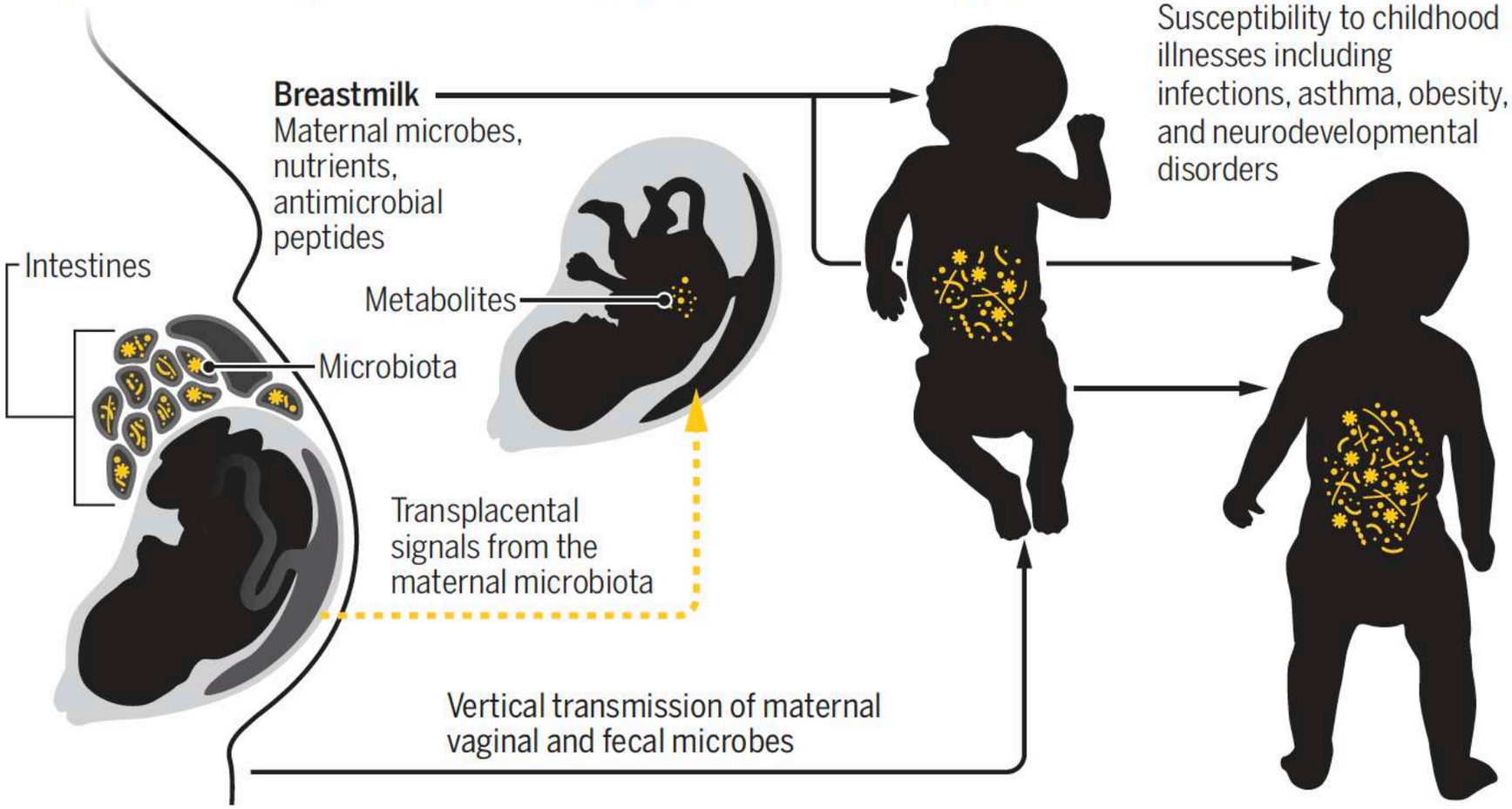
human Chorionic Gonadotropin

Amir et al, 2020

Maternal microbiota in pregnancy and early life

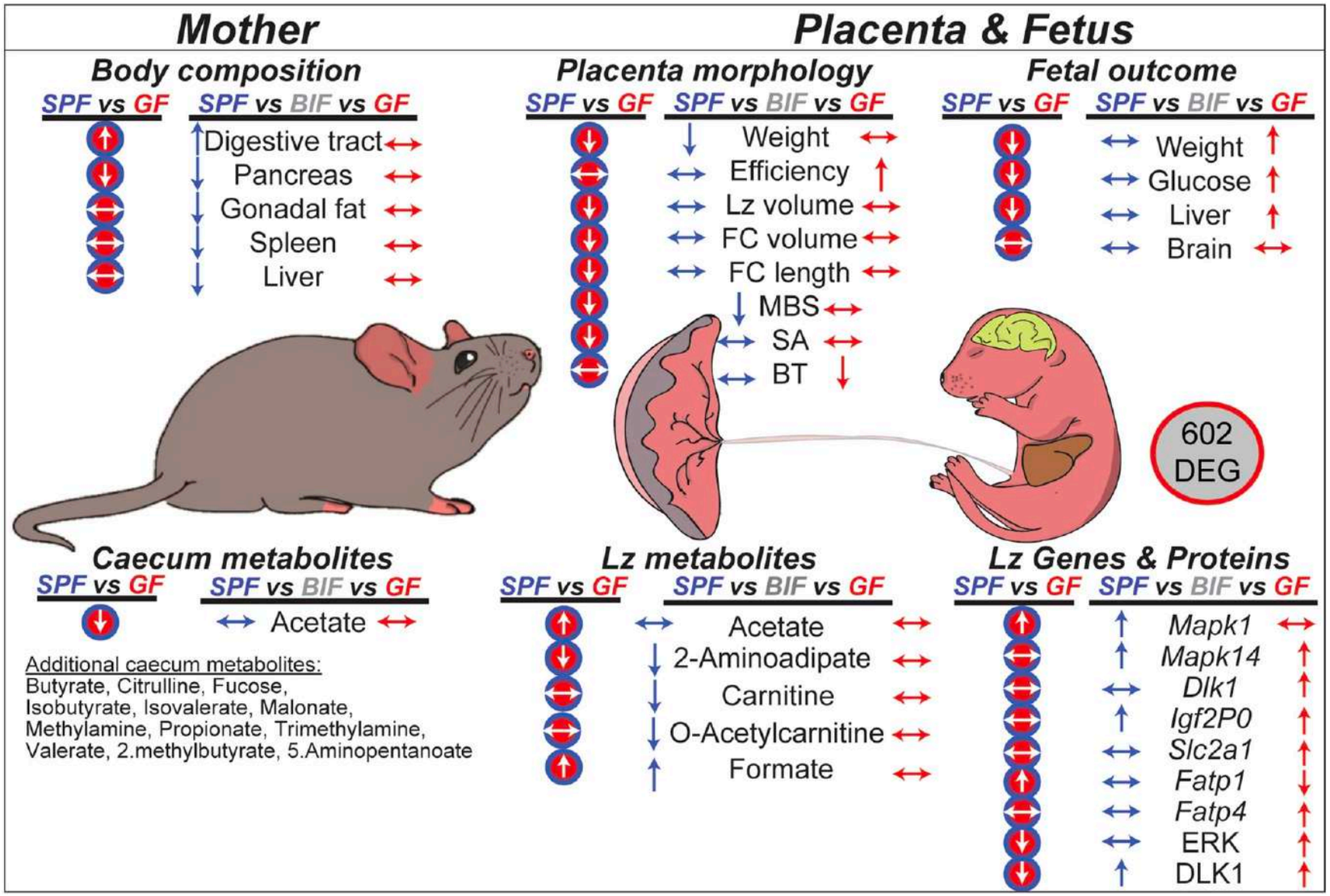
Effects of the maternal microbiota in pregnancy and early life

Through effects on early-life colonization, immune development, and neurodevelopment, the maternal microbiota regulates susceptibility to a number of childhood illnesses and can vertically transmit dysbiosis-mediated pathologies.



McDonald & McCoy, 2019

Maternal gut microbiota *Bifidobacterium* promotes placental morphogenesis, nutrient transport and fetal growth in mice



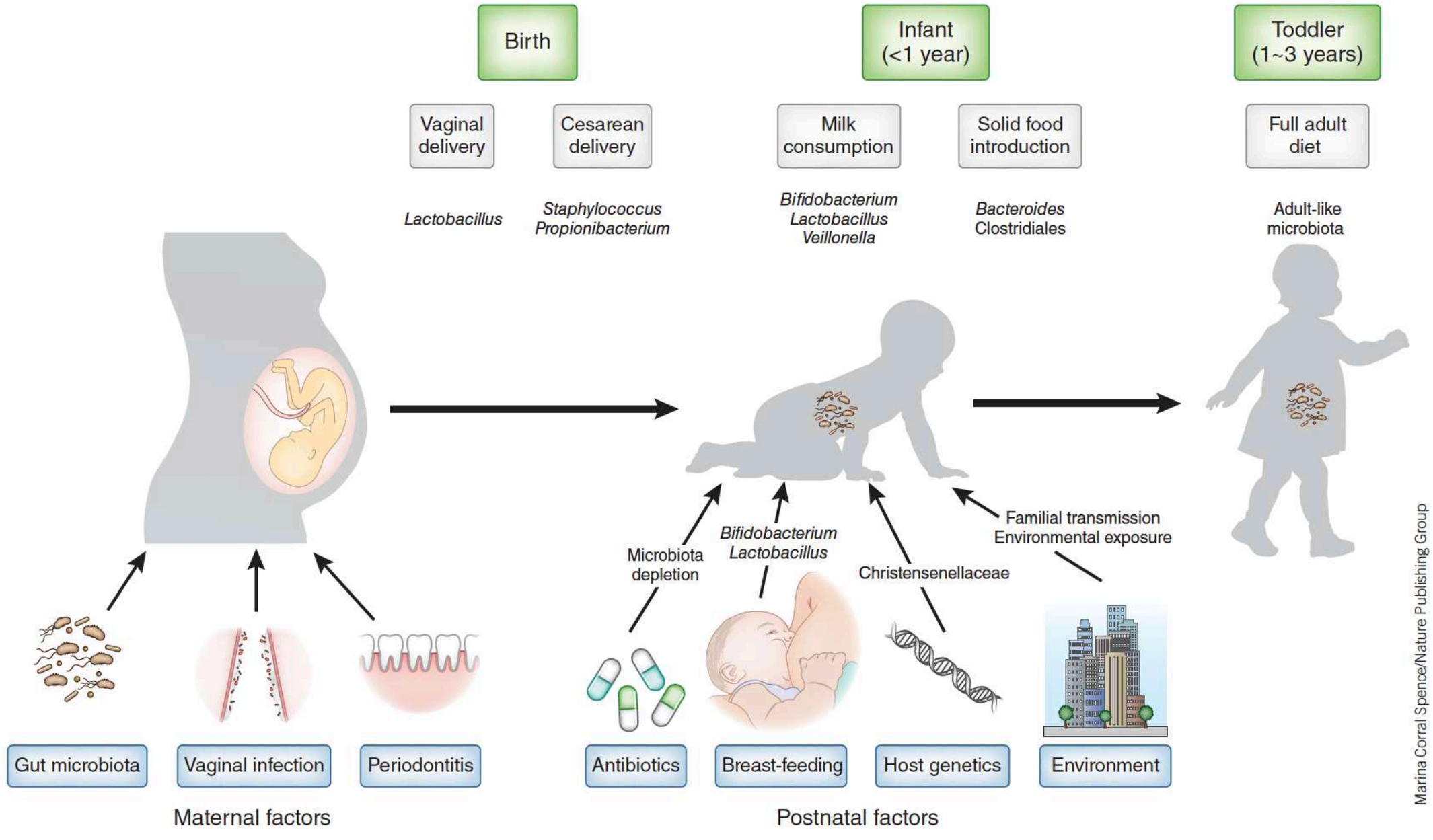
Lopez-Tello et al, 2023

SPF specific-pathogen-free mouse,
GF germ-free mouse,
BIF germ-free mouse treated with *B. breve* UCC2003,
Lz labyrinth zone,
MBS maternal blood spaces,
FC fetal capillaries,
SA surface area for exchange,
BT barrier thickness,
DEG differentially expressed genes

Lacking maternal gut microbiota aside from inducing changes in the maternal digestive tract, pancreas and caecum metabolites, has important implications **for the correct growth of the fetus and its placenta**

Bifidobacterium induces changes in the maternal compartment that **affect the structure, metabolome and function of the placenta** in association with alterations in fetal metabolism, growth and hepatic transcriptome

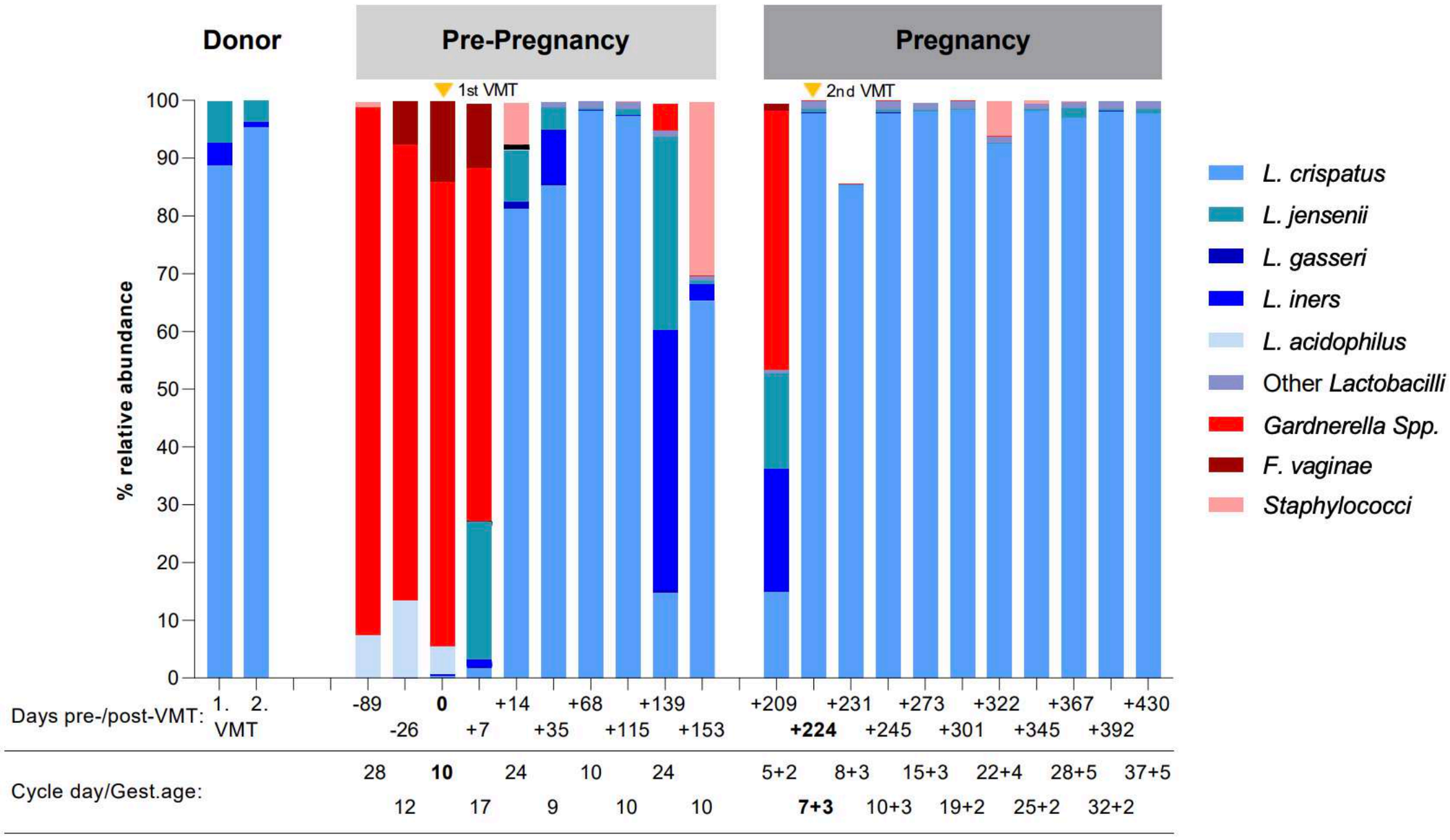
Factors shaping the neonatal microbiome



Tamburini et al, 2016

Antibiotic-free vaginal microbiota transplant with donor engraftment, dysbiosis resolution and live birth after recurrent pregnancy loss: a proof of concept case study

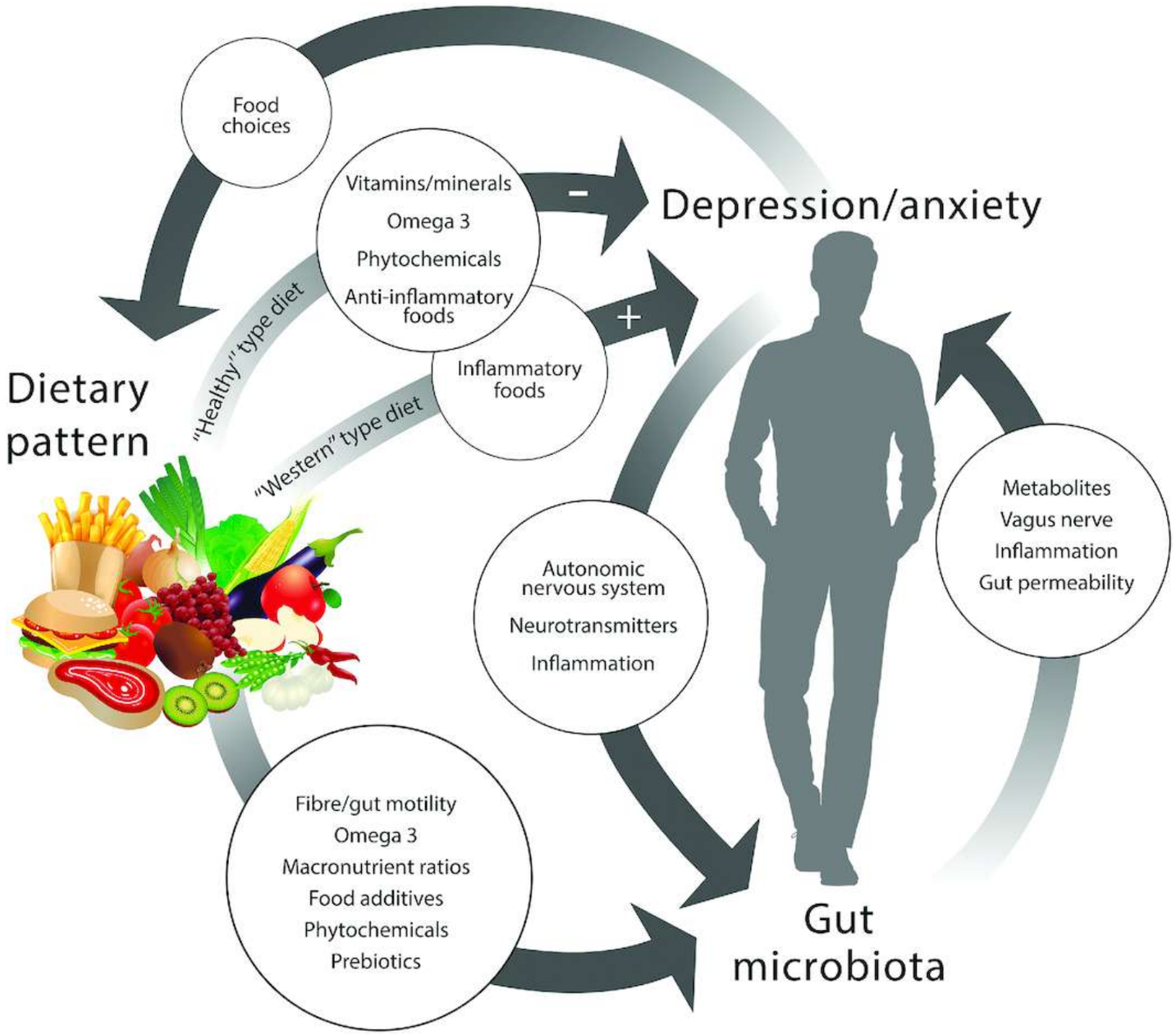
Vaginal Microbiota Transplantation (VMT)



Wrønding et al., 2023

Gut-Brain Axis

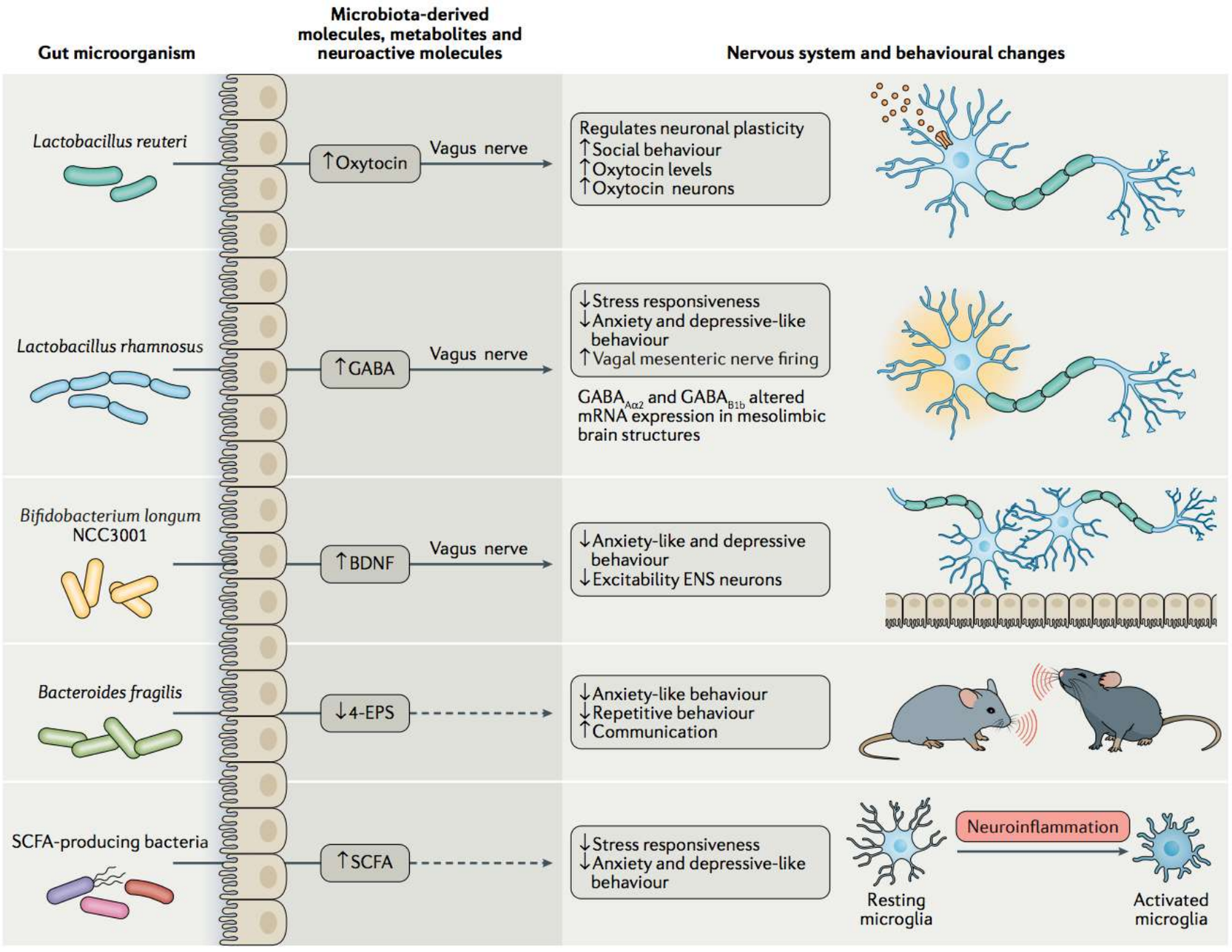
- “**Healthy**” dietary patterns, characterized by an **abundance of vegetables, fruits, cereals, nuts, seeds**, and pulses, as well as moderate amounts of dairy, eggs, and fish and unsaturated fats, including the Mediterranean diet, Japanese diet, and Norwegian diet
- “**Western**” dietary pattern, consisting of **sweet and fatty foods, refined grains, fried and processed foods, red meat, high-fat dairy products, and low fruit and vegetable** intake, is associated with higher **depression** incidence
- **Food molecules influence brain via gut-brain axis**



Bear et al., 2020

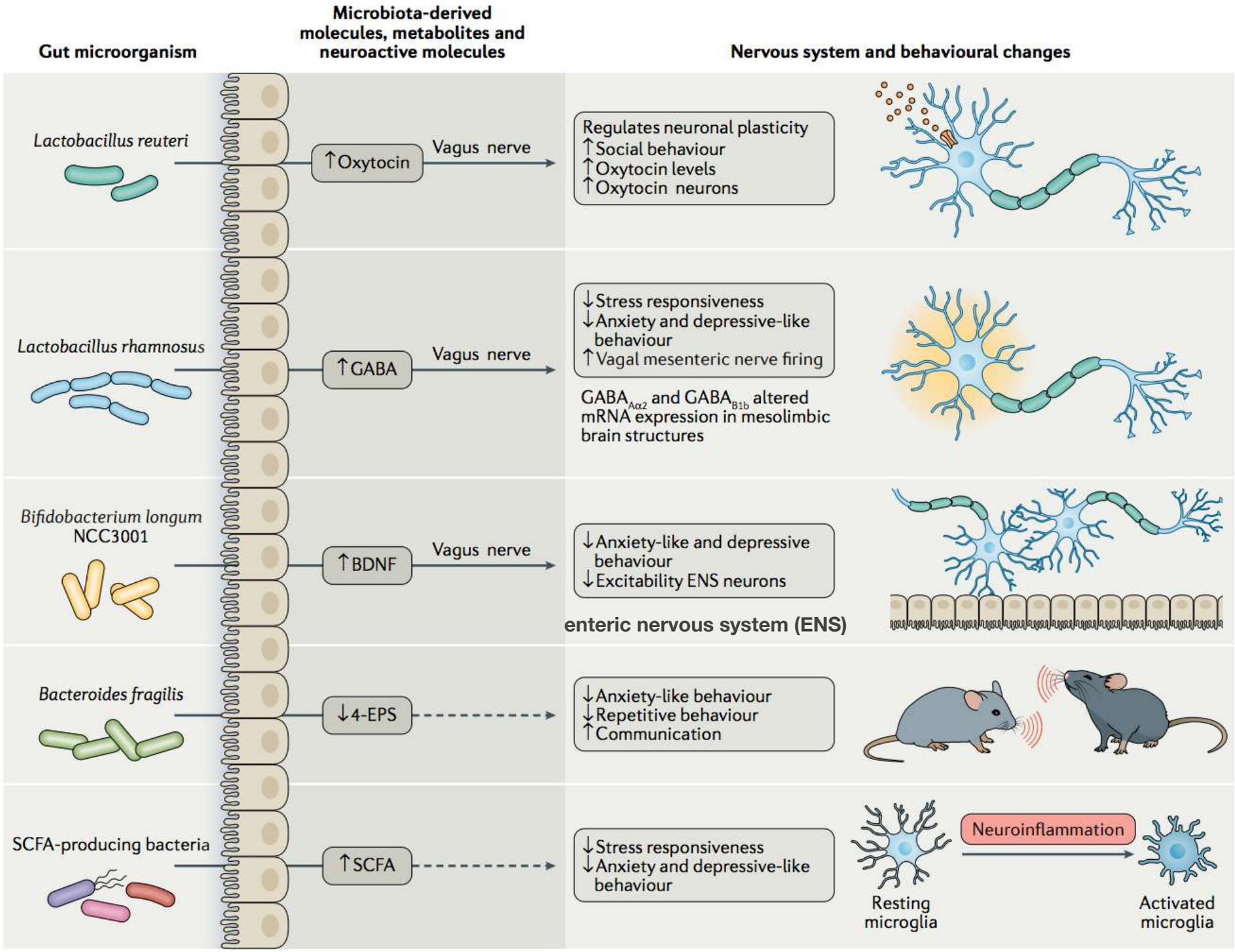
Microbiota and microbial-derived molecules modulate host behaviour and nervous system function

Culture and uncultured based-approach



Morais et al., 2020

Microbiota and microbial-derived molecules modulate host behaviour and nervous system function



γ-aminobutyric acid (GABA)

Brain-derived neurotrophic factor (BDNF)

4-ethylphenylsulfate (4-EPS)

Short-chain fatty acids (SCFAs)

Morais et al., 2020

TABLE 1 Examples of published literature evidence (from in vitro, animal, and human studies) of components within dietary patterns related to depression in humans or emotional behaviors in animals, which directly affect the host but also interact with the gut microbiota[1]

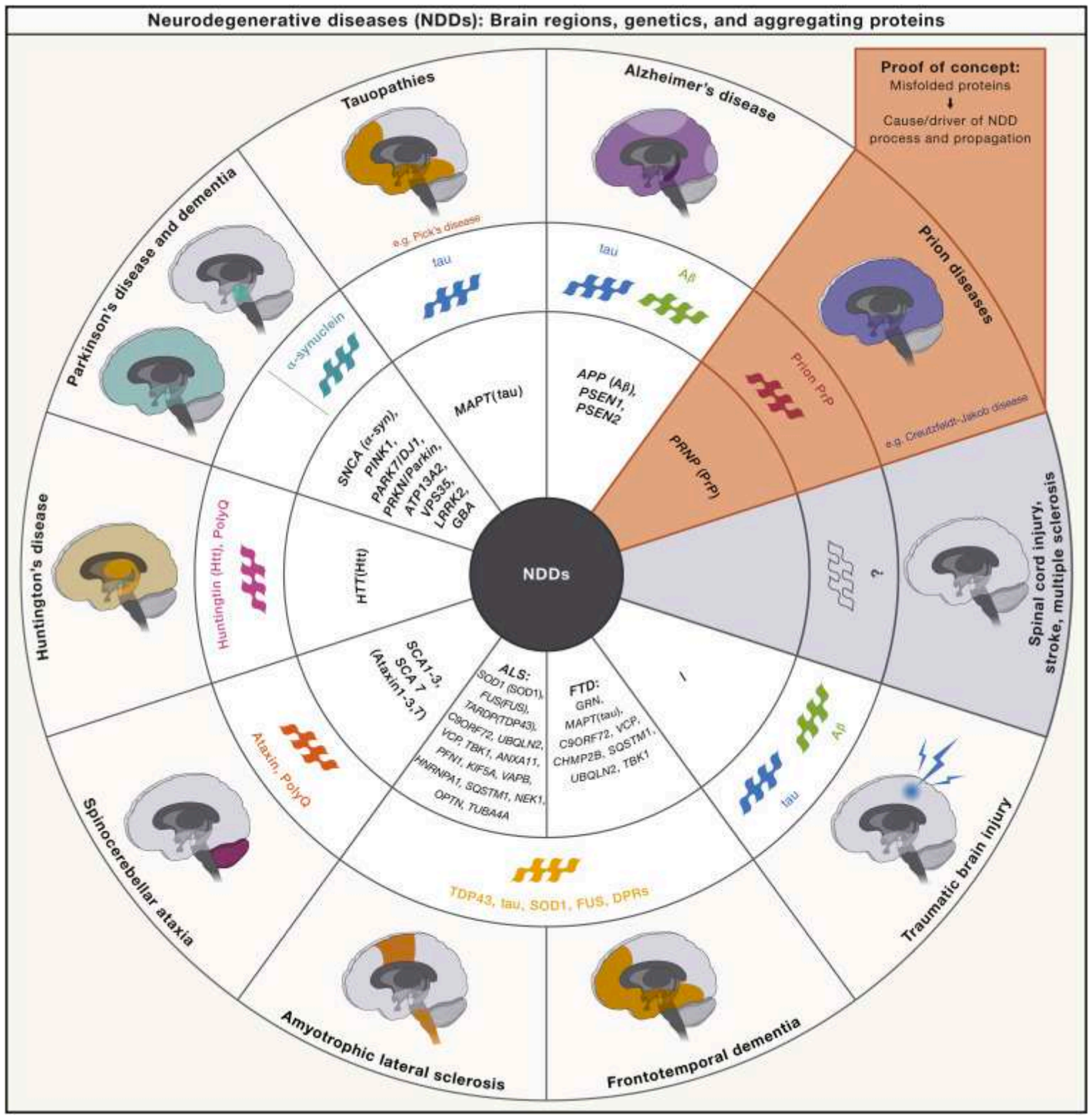
Dietary component	Effect	Summary	Subject	Ref.
Phytochemicals				
Cocoa polyphenols	Affected mood	In an RCT in adults, 500 mg supplement for 30 d increased self-rated calmness and contentedness compared with placebo.	Human	Pase et al. (183)
	Altered microbial growth	A 6-wk diet with 10% cocoa in rats caused a decrease in *Bacteroides*, *Clostridium*, and *Staphylococcus* genera in feces.	Animal	Massot-Cladera et al. (184)
		In vitro digestion with 1 g cocoa powder/60 mL water. 38.6% of phenols were solubilized, and an increase in *Bifidobacteria*, *Lactobacilli*, and butyrate was found.	In vitro	Fogliano et al. (185)
	Altered immune function	A 6-wk diet with 10% cocoa in rats caused an altered toll-like receptor pattern and increased gastrointestinal immunoglobin A secretion.	Animal	Massot-Cladera et al. (184)
Blueberry extract (anthocyanins)	Affected mood and cognition	In a BCT, in children and young adults, a single drink containing 253 mg anthocyanins increased positive but did not change negative affect scores using the "Positive and Negative Affect Scale" compared with a placebo drink.	Human	Khalid et al. (186)
		A 5% blueberry drink given to rats for 8 wk protected against cognitive impairment during chronic mild stress.	Animal	Guo et al. (187)
	Altered host metabolites	Decreased plasma norepinephrine and dopamine concentrations, and brain concentrations of antioxidant compounds due to 8 wk of chronic mild stress were attenuated by a 5% blueberry drink.	Animal	Guo et al. (187)
Fiber (prebiotic)				
GOS, PDX, and FOS	Attenuated stress-induced behaviors and mood, and gene expression in the brain	Male rats were fed diets containing GOS + PDX for 4 wk and then underwent inescapable stressors. The prebiotic reduced stress-induced exaggerated freezing and deficit in escape latency, and attenuated c-fos mRNA in parts of the brain.	Animal	Mika et al. (188)
		Male and female rats underwent early-life stress (maternal separation model). Prebiotic supplementation of GOS + FOS for 5 wk after the stress attenuated stress-induced deficits in spatial memory and locomotion, but not anxiety-like behaviors.	Animal	McVey Neufeld et al. (189)
		RCT, patients with depression: 8 wk supplementation with 5 g GOS resulted in decreases in scores on the Beck Depression Inventory compared with placebo.	Human	Kazemi et al. (190)
		Healthy volunteers given either FOS or GOS daily for 3 wk. Salivary cortisol awakening response and emotional bias (attention to negative information) were decreased after GOS but not FOS.	Human	Schmidt et al. (191)
	Altered the gut microbiota	Prebiotic diet of GOS + FOS increased *Lactobacillus rhamnosus* and also *Lactobacillus* spp.	Animal	Mika et al. (188)
		44 elderly subjects, given 5.5 g/d GOS or placebo for 10 wk in a double-blind, placebo-controlled, crossover study. Increase in *Bifidobacterium* spp., *Lactobacillus Enterococcus* spp., *Clostridium coccoides–Eubacterium rectale*, and a decrease in *Bacteroides* spp., *Clostridium histolyticum* group, *Escherichia coli*, and *Desulfovibrio* spp.	Human	Vulevic et al. (192)
	Altered immune function	Increases in immune function, including reduced proinflammatory cytokines and increased anti-inflammatory cytokines, phagocytosis, and NK cell activity.	Human	Vulevic et al. (192)
Wheat arabinoxylan	May counteract effects of high-protein diet on the gut microbiota	In pigs fed a 4-wk Western-type diet, added soluble fiber (wheat arabinoxylan) increased carbohydrate fermentation and reduced protein fermentation and fermentation products such as ammonia.	Animal	Williams et al. (193)

Dietary component	Effect	Summary	Subject	Ref.
Vitamins/minerals				
Vitamin D	Regulated gut physiological processes	Vitamin D receptors in the gut regulate processes including epithelial barrier function and immune processes.	Review	Barbáchano et al. (194)
	Associated with changes in the gut microbiota	Plasma 25-hydroxyvitamin D and vitamin D supplementation in women in their 36th week of pregnancy were measured, and compared with fecal samples in their 1-mo-old infants. Increased concentrations of both were associated with decreased *Bifidobacterium* spp. and *Clostridium difficile* and increased *B. fragilis*.	Human	Talsness et al. (182)
Magnesium	Dietary deficiency altered behavior	30 mice fed a magnesium-restricted diet for 6 wk had increased immobility in the forced swim test and increased hippocampal IL-6 compared with mice fed a normal diet.	Animal	Winther et al. (179)
	Associated with changes in the gut microbiota	The cecal gut microbiota was also altered, with cluster analysis showing significant differences between the diets.		
Vitamin A	Associated with changes in the gut microbiota and the gut mucosal barrier	A vitamin A–deficient diet in rats increased total bacteria, decreased *Lactobacillus* spp., and increased *Escherichia coli*. Mucin-producing goblet cells were altered and expression of toll-like receptors was increased.	Animal	Amit-Romach et al. (195)
		Vitamin A deficiency in children aged 1–12 mo with persistent diarrhea showed significantly different gut microbiota than in those with normal serum vitamin A concentrations.	Human	Lv et al. (196)
Macronutrients				
ω-3 fatty acids	Immunomodulatory	The metabolic and inflammatory effects in wild-type mice fed a diet with a high ratio of ω-6 to ω-3 were able to be prevented with antibiotic treatment, or by cohousing mice with *Fat-1* transgenic mice, which endogenously produce ω-3 fatty acids.	Animal	Kaliannan et al. (176)
	Increased endogenous antimicrobial defenses	*Fat-1* mice were found to produce increased intestinal alkaline phosphatase, an endogenous antimicrobial compound, which reduced gut permeability and LPS production.	Animal	Kaliannan et al. (176)
	Restored gut dysbiosis	*Fat-1* transgenic mice were found to be protected against gut dysbiosis and obesity caused by a Western-style diet after early-life antibiotic exposure.	Animal	Kaliannan et al. (197)
		Supplementation of 100–250 mg/d ω-3 FA (80% EPA, 20% DHA) for 12 wk to female rats reversed stress-induced gut dysbiosis.	Animal	Pusceddu et al. (177)
	Increased gut microbial metabolites (SCFAs)	An 8-wk open label trial using an EPA/DHA supplement drink or capsule in adult males and females reversibly increased SCFA-producing bacteria including *Bifidobacterium*, *Roseburia*, and *Lactobacillus*.	Human	Watson et al. (198)
	Deficiency affected mood as well as the gut microbiota	An ω-3 FA–deficient diet in pregnant mice and their male offspring resulted in an elevated ratio of *Firmicutes* to *Bacteroidetes* in the offspring, along with altered behavior and immune function.	Animal	Robertson et al. (178)
		Increased depressive behavior (immobility in forced swim test), decreased sociability (three chamber test), isolation-induced ultrasonic vocalizations in adulthood, and decreased memory (novel object recognition test) in both adolescence and adulthood. Increased contextual fear conditioning.		

Dietary component	Effect	Summary	Subject	Ref.
High fat, particularly saturated fat	Altered microbiota composition	A high-fat diet in mice decreased *Ruminococcaceae* and increased *Rikenellaceae* compared with a carbohydrate diet.	Animal	Daniel et al. (199)
		Increase in *Firmicutes*, particularly the family *Erysipelotrichaceae*, and decrease in *Bacteroidetes* in mice fed a high-fat diet.	Animal	Fleissner et al. (200)
		Mice fed a low-fat diet who switched to a high-fat diet had a significant shift in microbiome composition within 1 d. Increased *Firmicutes*, particularly the *Erysipelotrichi* class, *Bacilli*, and decreased *Bacteroidetes*.	Animal	Turnbaugh et al. (201)
		BALB/c mice fed a high-fat diet showed alterations in the gut microbiota including an increase in *Firmicutes*, particularly in the families Rumunococcaceae and *Lachnospiraceae*, a decrease in the *Bacteroidetes* phylum, and a resulting decrease in the ratio of *Bacteroidetes* to *Firmicutes*.	Animal	Pyndt Jørgensen et al. (202)
	Altered anxiety-like behavior	Mice fed a high-fat diet displayed less burrowing (anxiety-like) behavior, and displayed reduced memory in the Morris water maze test compared with mice fed a control diet. The diets were not isocaloric, and the high-fat diet mice also gained more weight.	Animal	Pyndt Jørgensen et al. (202)
High-fat, high-sugar diet	Altered microbiota composition	A Western-style diet in humanized mice resulted in increased *Erysipelotrichi* class (mainly *Clostridium innocuum*, *Eubacterium dolichum*, and *Catenibacterium mitsuokai* genera) and *Bacilli* class (mainly *Enterococcus* spp. genera). The microbial shift occurred after only a single day.	Animal	Turnbaugh et al. (201)
High-sugar diet	Positive change in behavior when the gut microbiota was not altered	A high-sucrose diet did not alter the gut microbiota in BALB/c mice compared with a control diet and did alter some behaviors, but in a positive direction (increased latency to immobility in the forced swim test, less goal-orientated burrowing, and less anxiety-like behavior in the triple test).	Animal	Pyndt Jørgensen et al. (202)
Red meat	Modified gut microbiota composition	A comparison between a diet rich in red meat or whole grains (10-wk crossover trial) showed that increased red meat consumption increased the genera *Clostridium* spp. from the phylum *Firmicutes*.	Human	Foerster et al. (203)
	Microbial metabolism of heme-rich meat increases oxidative compounds	Comparison of meat types varying in heme content (beef, pork, chicken) in an in vitro digestion model showed that heme-rich meat caused higher concentrations of the nitrosoxide compound–derived DNA adduct O^6-carboxymethylguanine.	In vitro	Vanden Bussche et al. (204)
Food additives				
Emulsifiers CMC and P80	Altered gut microbiota composition	C57Bl/6J mice were given either CMC or P80 emulsifiers at 1% in their drinking water from weaning until 3 mo old. The gut microbiota was altered by the treatment. Interestingly the outcomes differed between males and females. In males, *Firmicutes* phylum and *Oscillospria*, *Coprococcus*, and *rc4_4* genera were reduced, as well as reduced *Dorea* with P80, and reduced *Bacteroides*, *Burkholderia*, *Clostridium*, and *Veillonella* with CMC. In females, *Bacteroides*, Sphingomonadales, *Sphingomonas*, and *Ruminococcus* were reduced, and there was an increase in *Anaeroplasma* with P80, and the *Proteobacteria* phylum and *Clostridium* and *Burkholderia* genera with CMC.	Animal	Holder et al. (205)
	Altered anxiety-like behavior	Treatment with emulsifiers decreased sociability in the 3-chamber test in females only, and increased locomotion in the Elevated Plus Maze in males only. No difference found in forced swim test or light-dark box.		

[1] BCT, blinded crossover trial; CMC, carboxylmethylcellulose; FOS, fructooligosaccharide; GABA, γ-aminobutyric acid; GOS, galactooligosaccharide; PDX, polydextrose; P80, polysorbate 80; RCT, randomized controlled trial.

Neurodegenertive disease

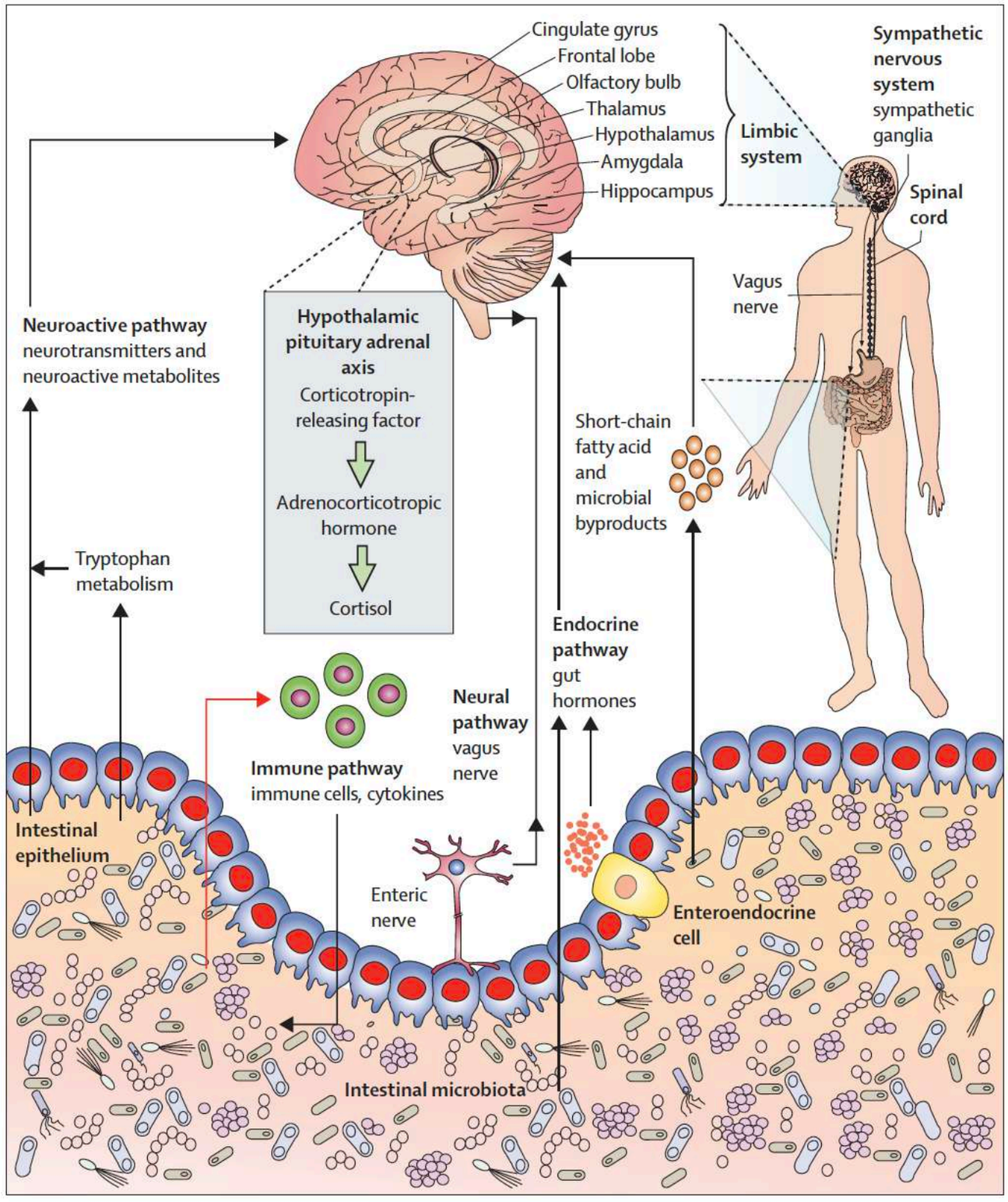


Neurodegenerative diseases (NDDs) are a heterogeneous group of neurological disorders adversely affecting the lives of millions of people worldwide and entail the progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS)

Characteristic aggregating proteins, genes linked to and affected brain regions in NDDs

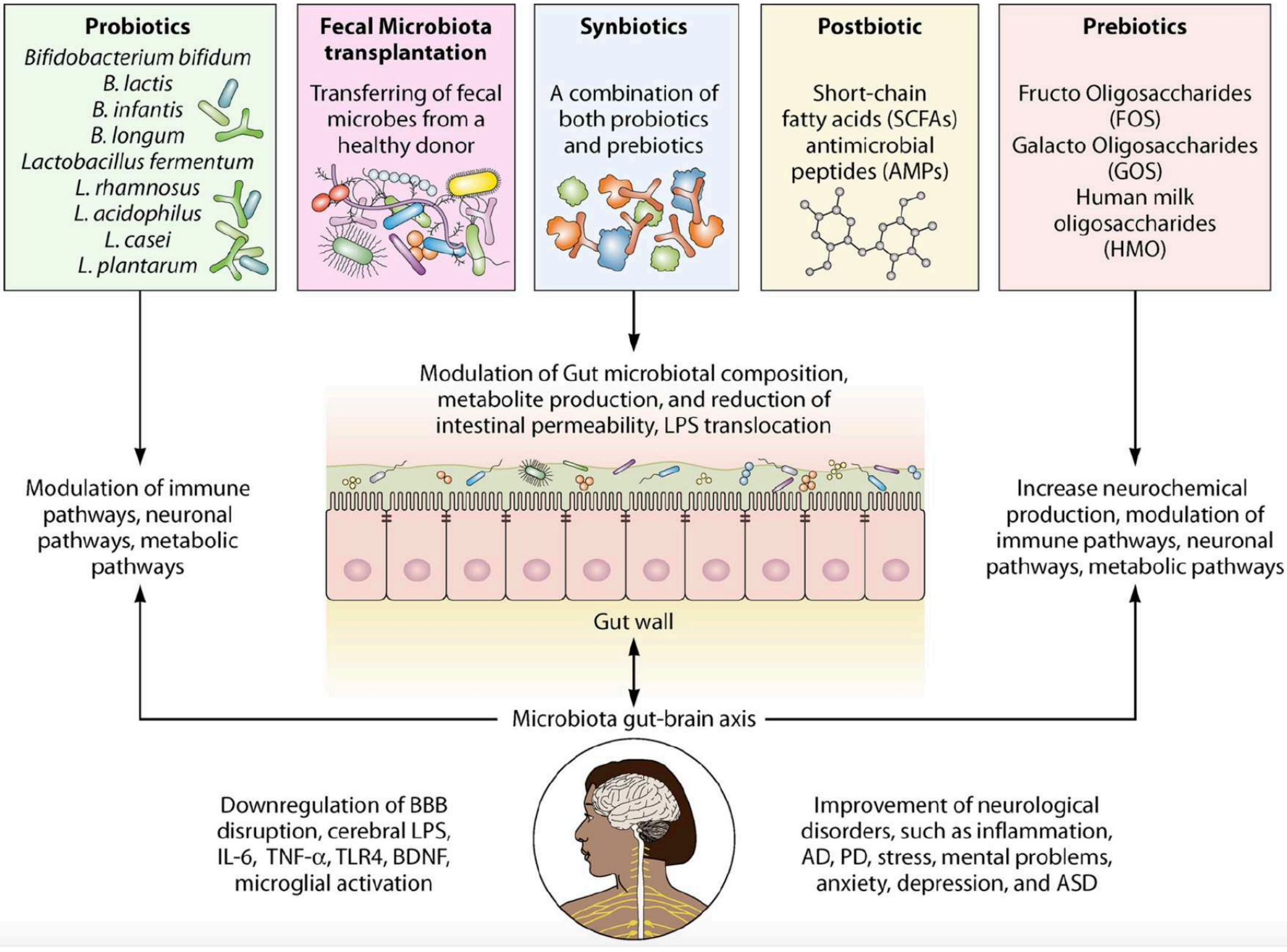
Willson III et al., 2023

Pathways of communication between the microbiota and the brain



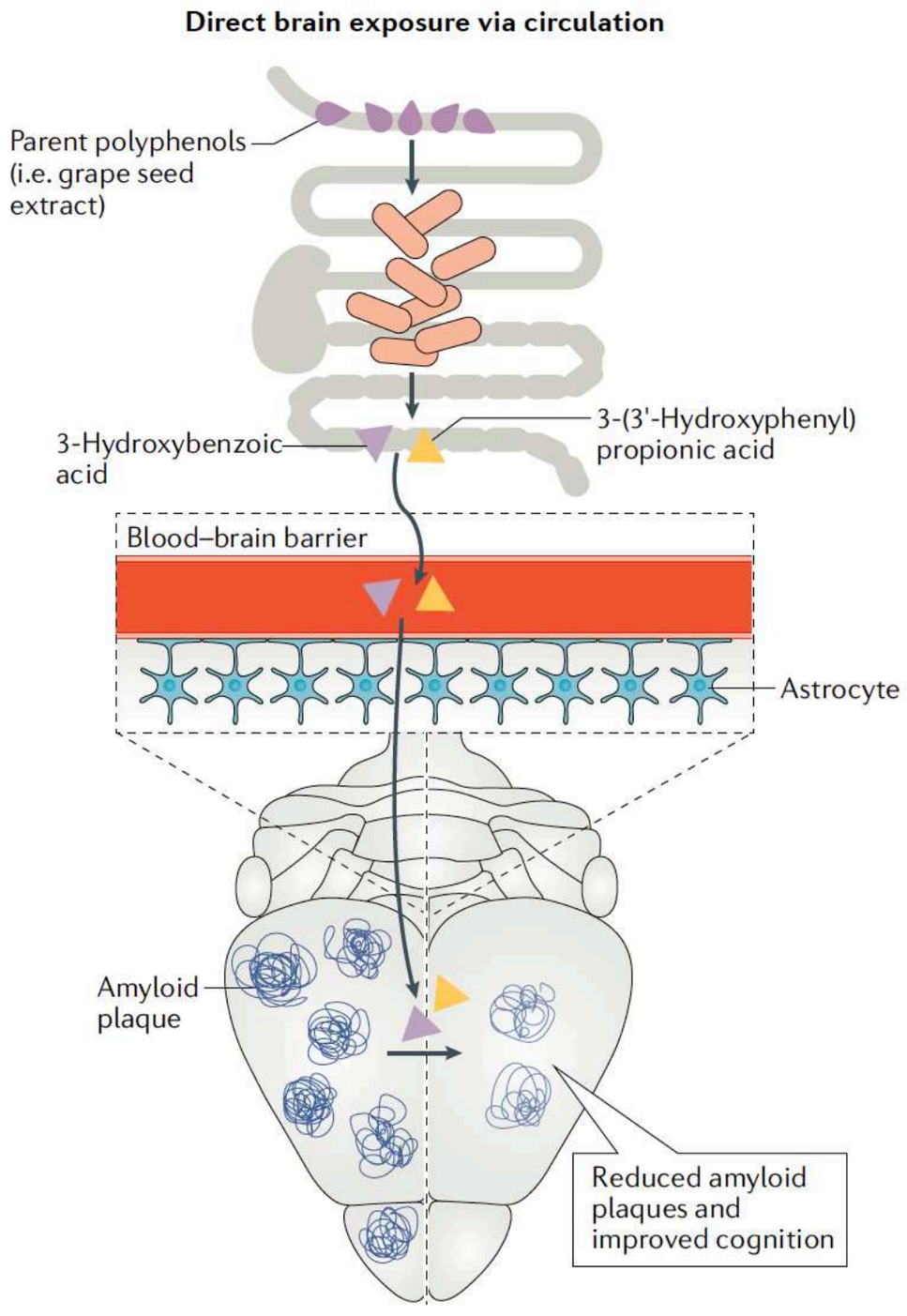
Cryan et al., 2019

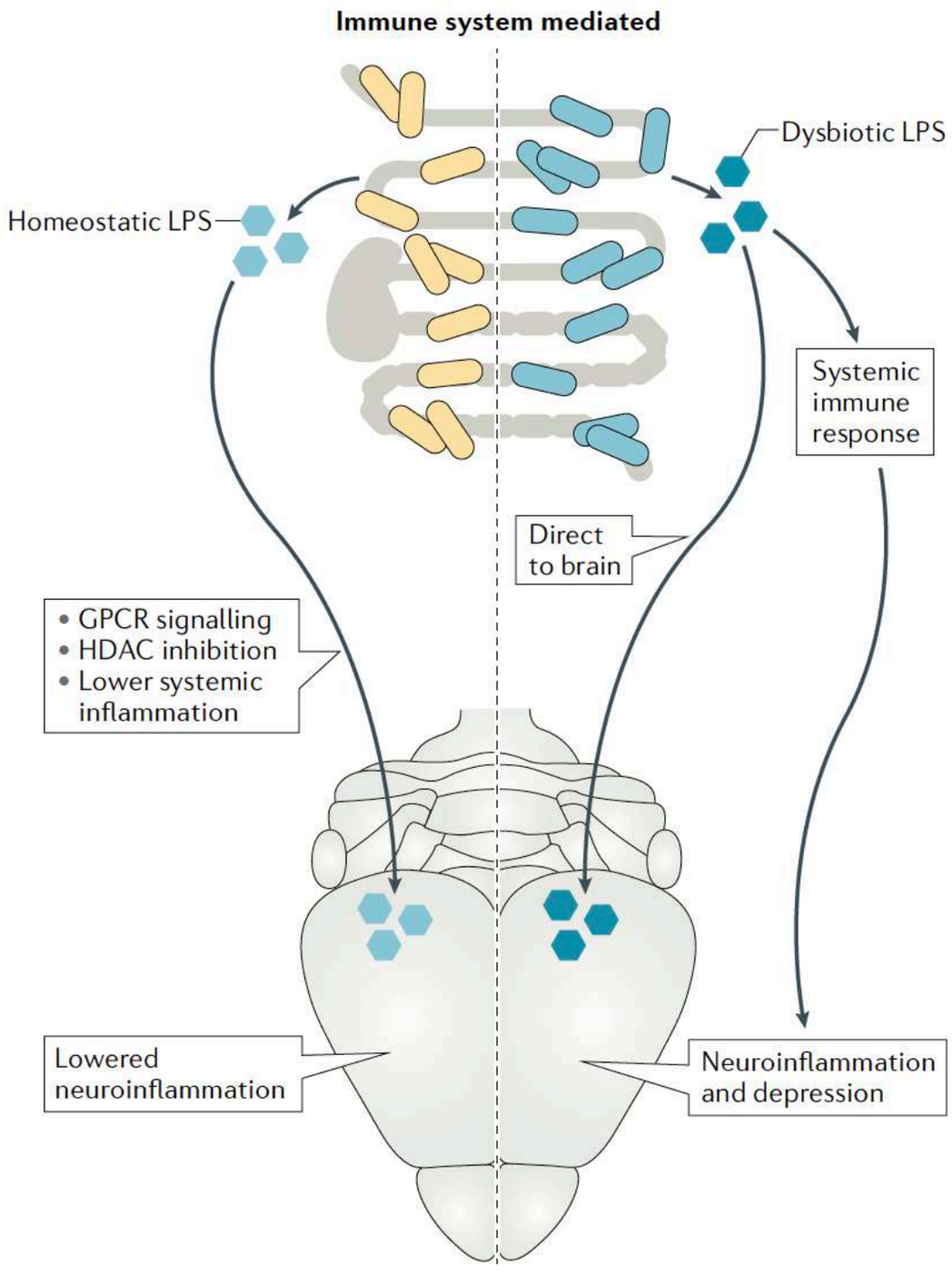
Modulation of gut microbiota by therapeutic microbial interventions



Sorboni et al., 2022

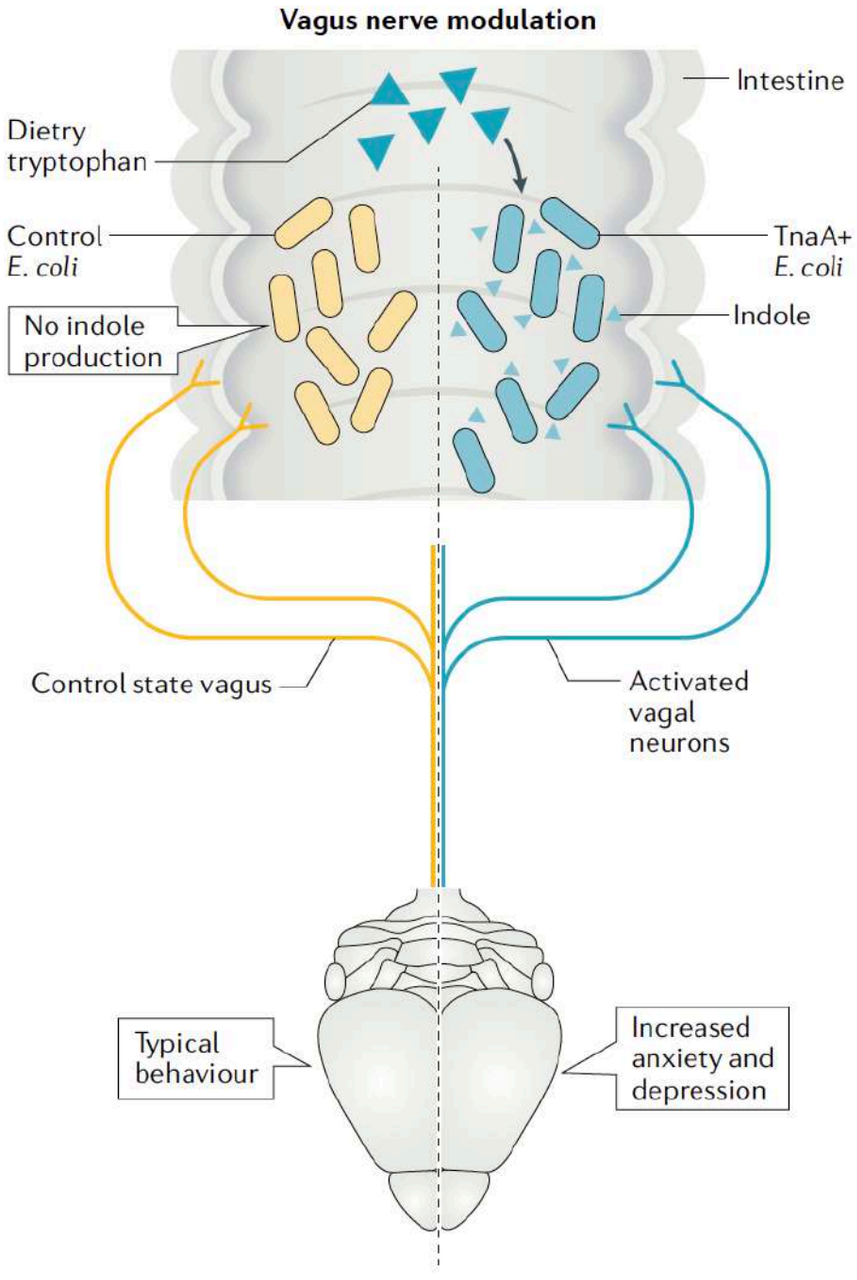
Mechanistic examples of the routes of gut–brain communication

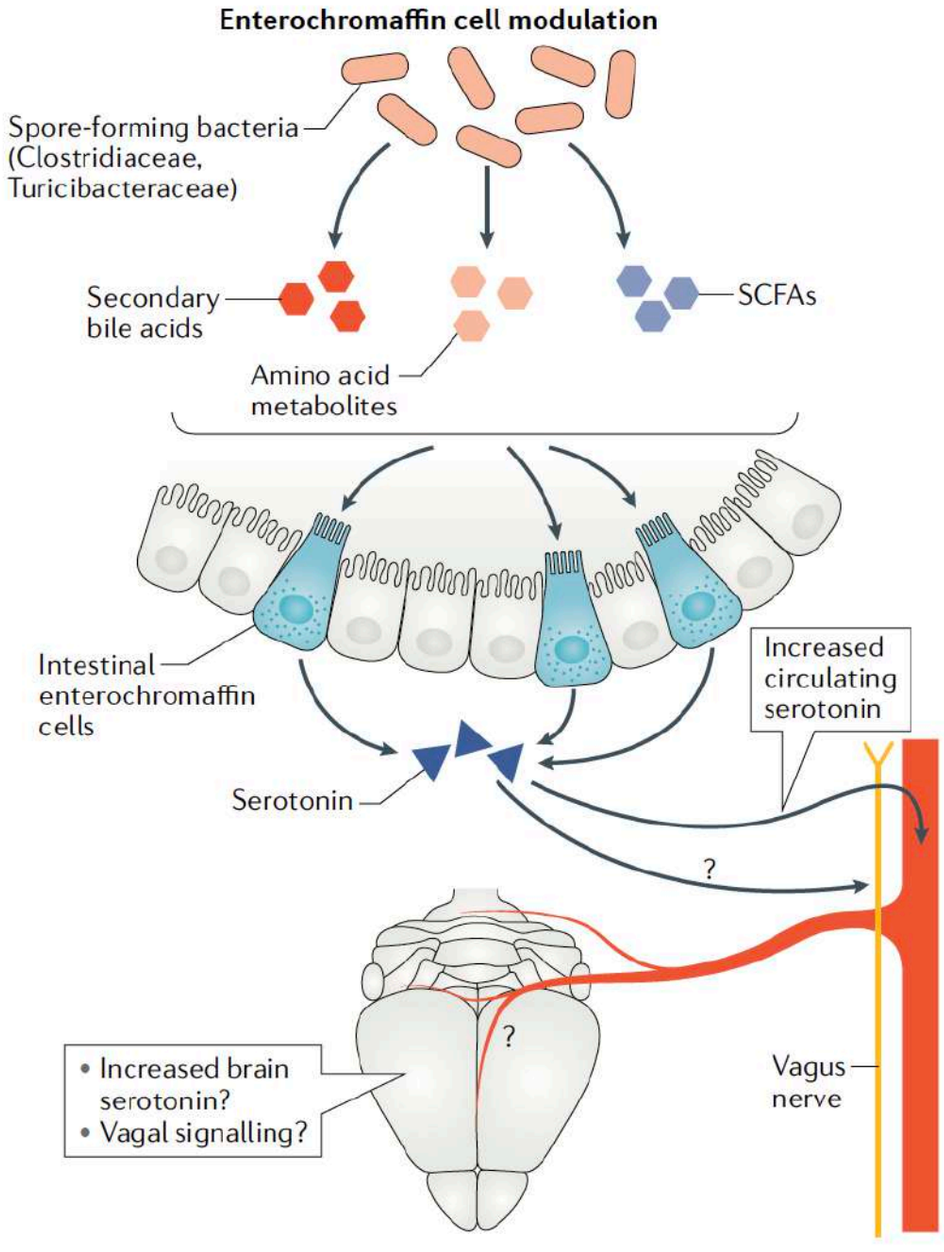




Needham et al., 2020

Mechanistic examples of the routes of gut–brain communication





Needham et al., 2020

Gut microbial molecules in behavioural and neurodegenerative conditions

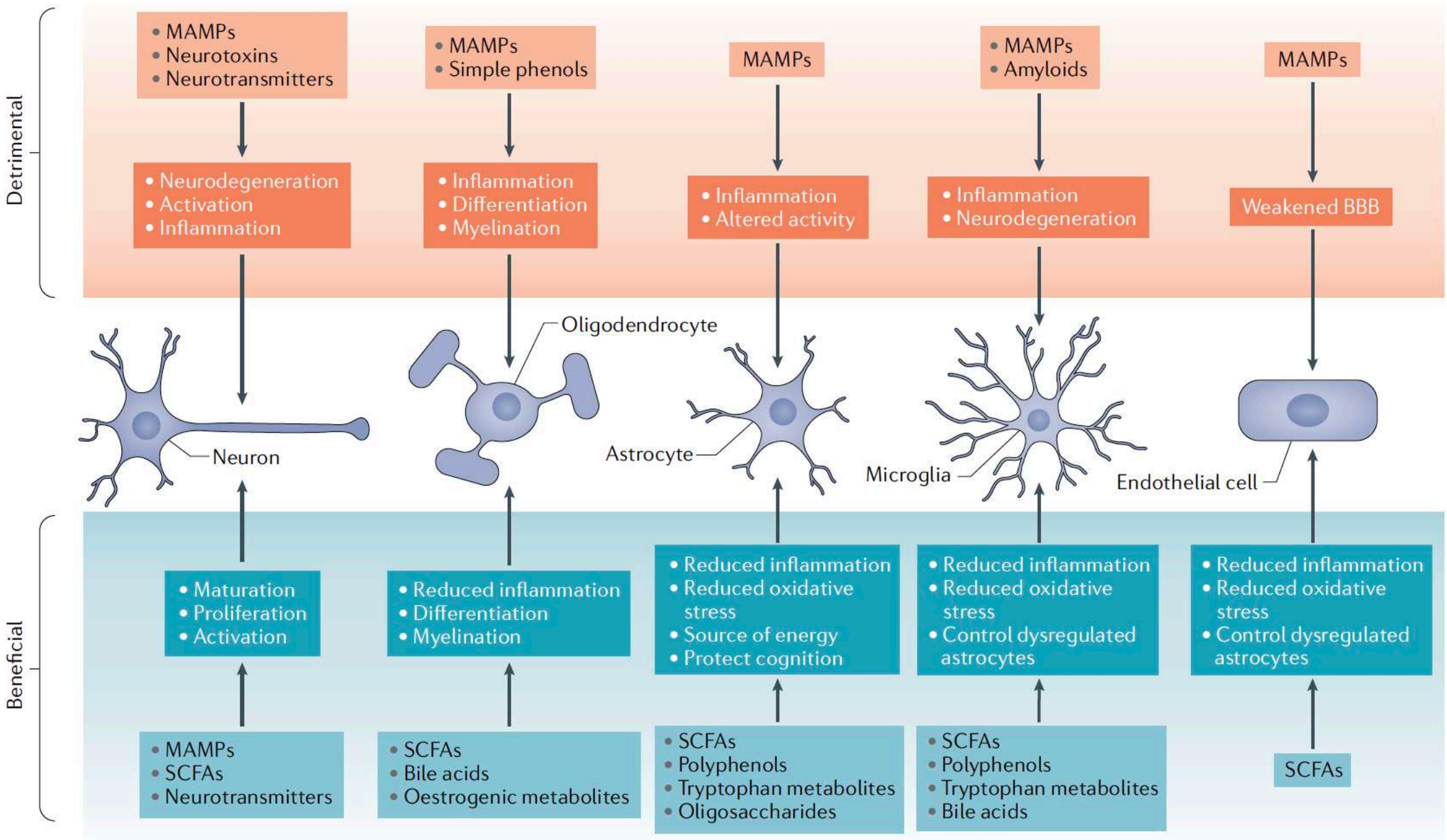
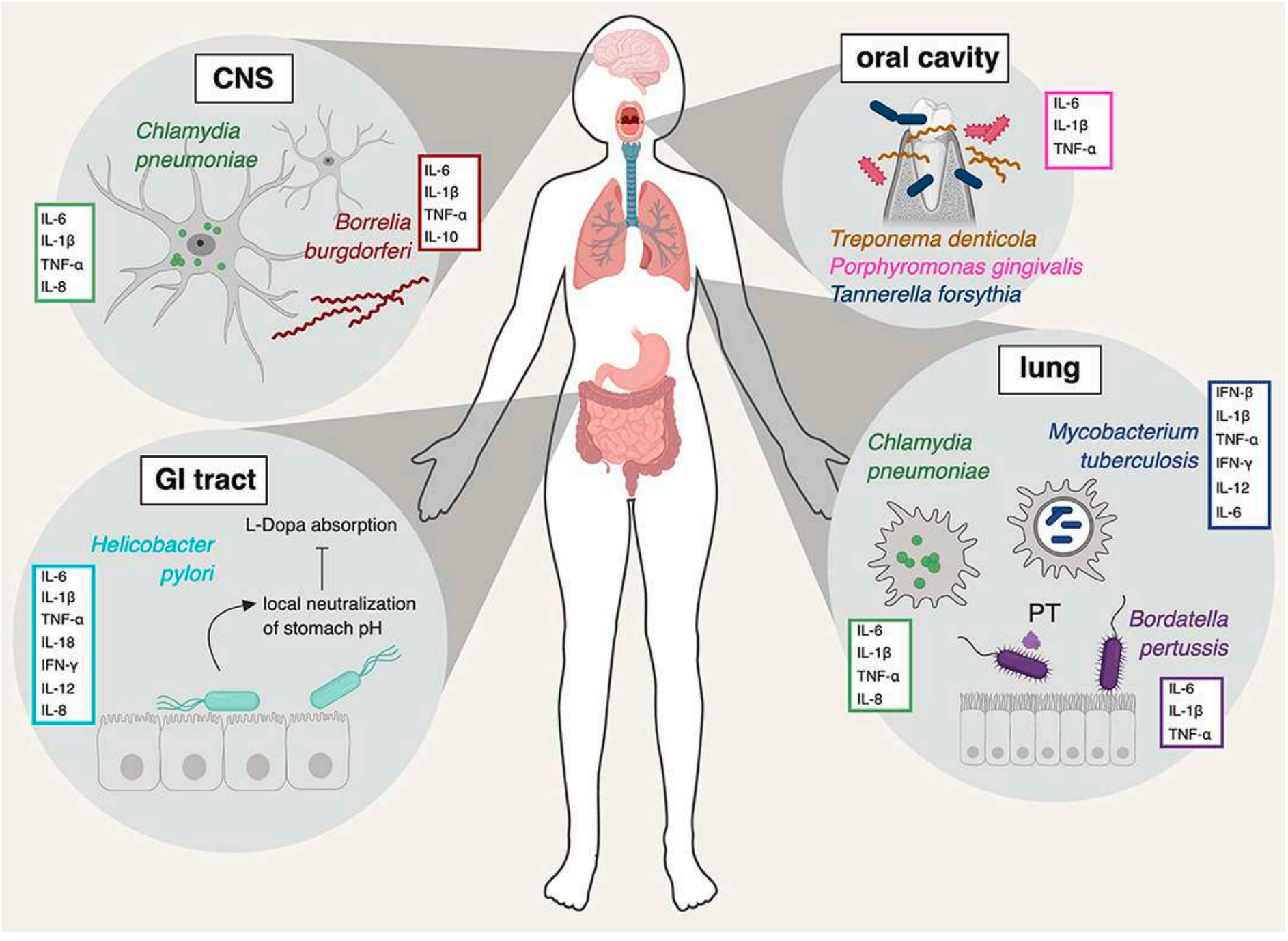


Fig. 4 | **Brain cell-specific effects of microbial metabolites.** Some microbial metabolites have known cellular targets in the brain. The beneficial and detrimental effects of these interactions are summarized. BBB, blood–brain barrier; MAMPs, microorganism-associated molecular patterns; SCFAs, short-chain fatty acids.

Needham et al., 2020

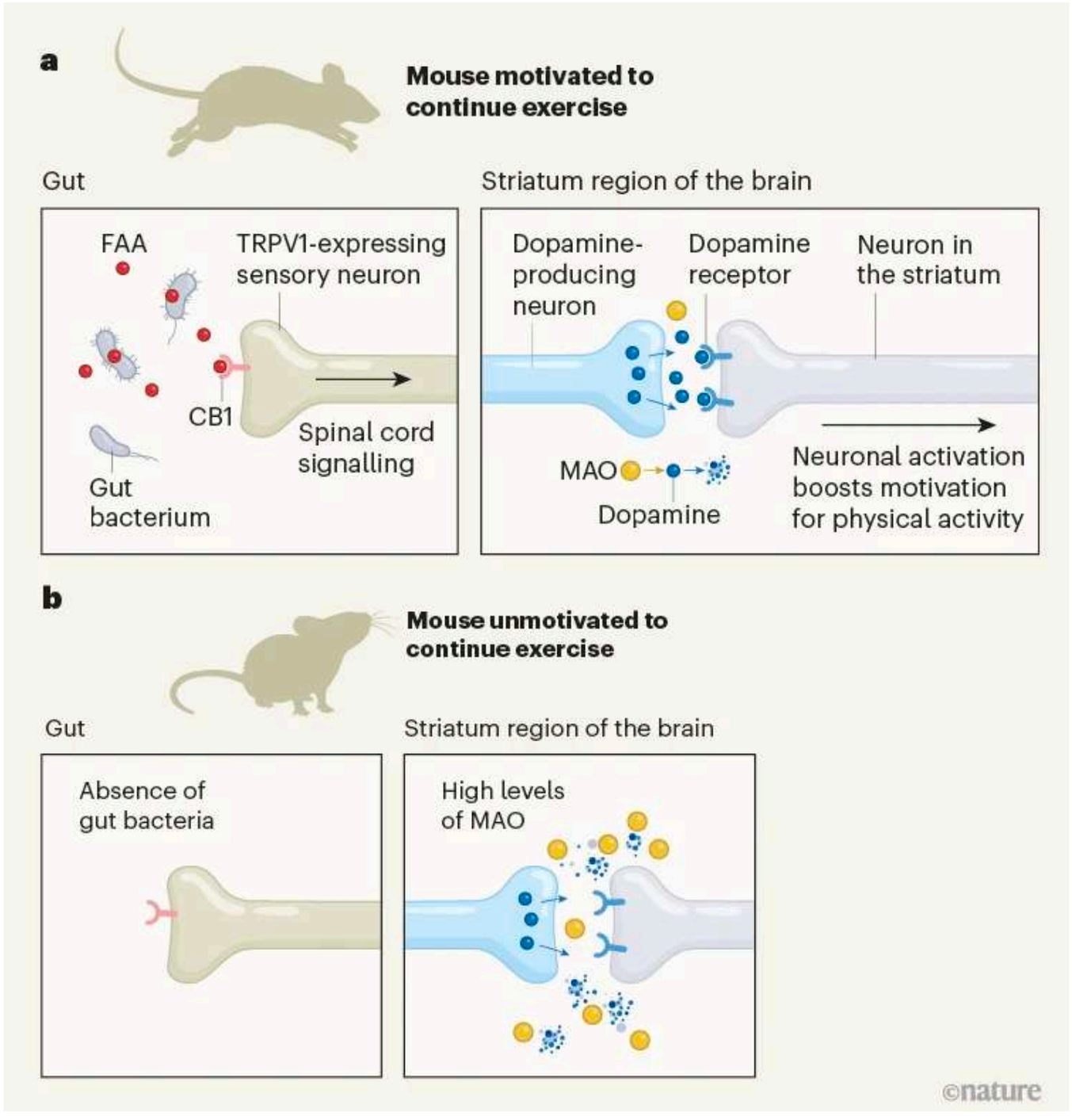
Different bacterial species that have been implicated in neuroinflammation



https://asm.org/articles/2021/january/microbes-on-the-mind-a-complex-role-in-neurodegene

Patrick et al., 2019

Gut microbes shape athletic motivation

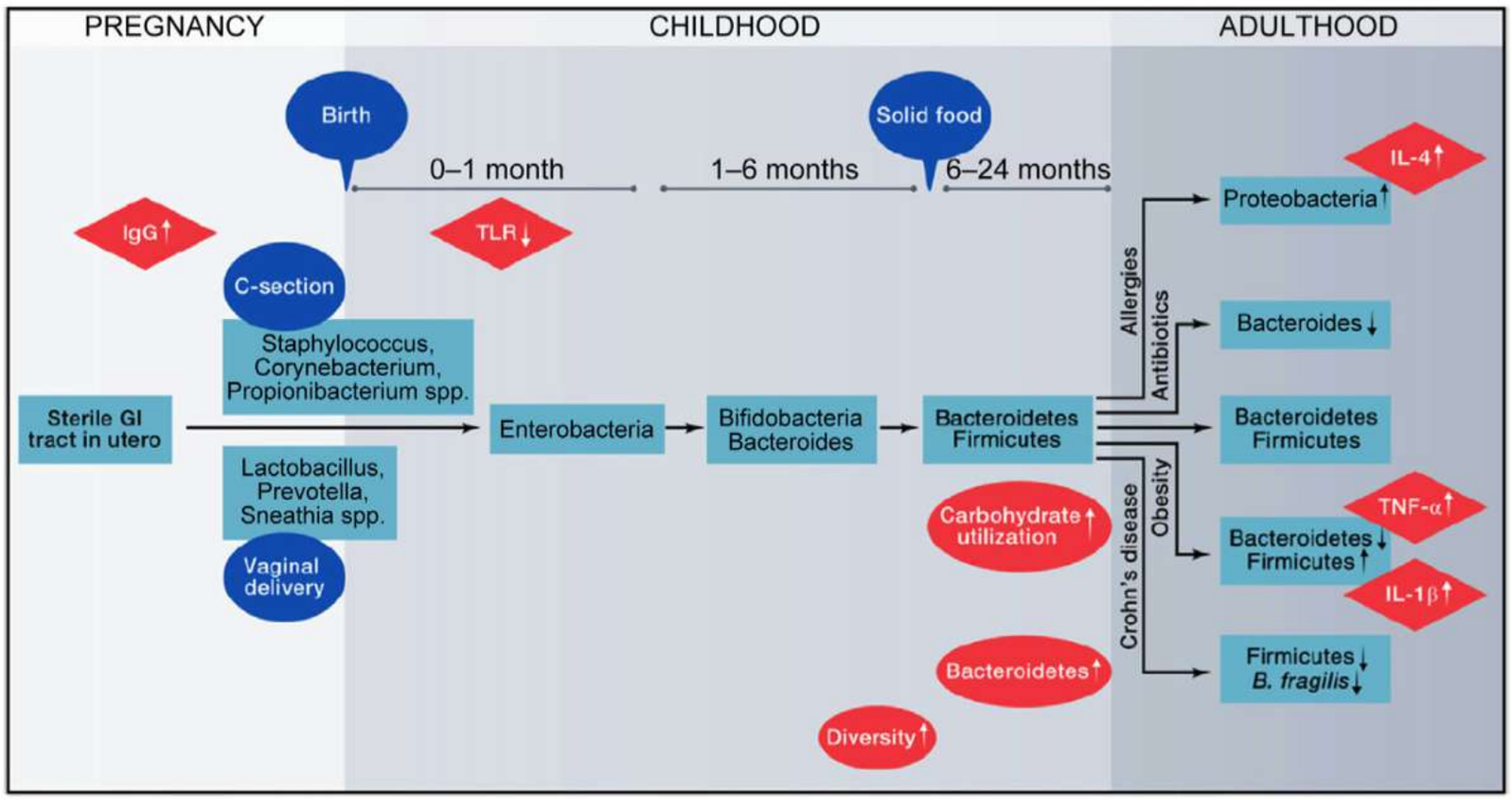


- Certain gut **bacteria** in mice **produce** molecules called **fatty acid amides (FAA)**, which **bind** to the **cannabinoid 1 receptor (CB1)** and thereby **activate sensory neurons** in the gut that express the protein TRPV1
- These neurons connect to the brain through the **spinal cord**
- Activation of these neurons results in **decreased expression of the enzyme monoamine oxidase (MAO) in the striatum region of the brain**; this enzyme **can degrade dopamine** and other neurotransmitter molecules
- **Dopamine-producing neurons induce an exercise-dependent surge of the molecule**, which then activates neurons in the striatum that have dopamine receptors
- **This triggering of neuronal activity in the striatum aids the motivation for exercise**
- In the **absence of gut bacteria**, the sensory neurons in the gut are not excited. The **level of MAO then remains high**, which blunts dopamine signalling in the striatum and results **in a premature termination of physical exercise**.

Dohnalová et al., 2022

Host colonization: a microscale battle

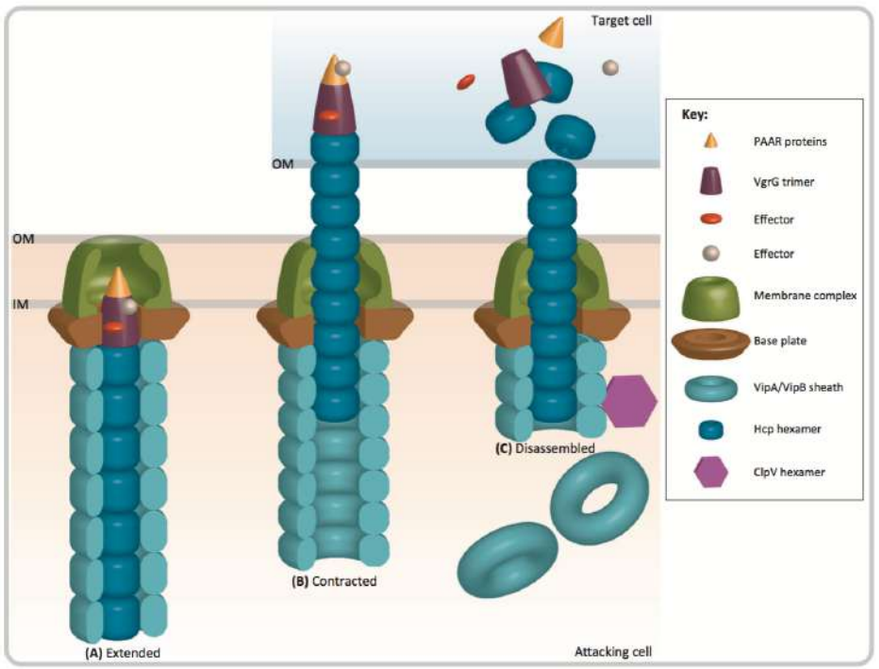
- Human babies are colonized during passage through the birth canal by environmental microorganisms (for example, from the mother's vagina or skin) and during breast feeding by microorganisms present in the milk
- Highly oxidative environment in GI tract of the newborn: first, **facultative anaerobic** bacteria such as proteobacteria, which are thought to adjust the environmental conditions by decreasing the oxygen concentration then **anaerobic microorganisms** (*Bacteroides* and members of the phyla *Actinobacteria* and *Firmicutes)*
- During the first year of life, the intestinal microbiota composition is simple and fluctuates widely between individuals and over time
- **Microbial signatures** stabilize and start to resemble the 'adult state' when the infant reaches **1–2 years of age**
- Development of the microbiota. The gastrointestinal tract of the fetus is sterile until birth, after which the newborn is initially colonized. depending on delivery mode, the initial communities tend toward a skin-like (cesarean section) or a vaginal-like (vaginal delivery) configuration
- As the infant grows, and with the introduction of solid foods, the microbiota diversity increases, and the community converges toward an adult-like state. At the same time, the immune system "learns" to differentiate between commensal and pathogenic bacteria
- By adulthood, a relatively stable community composition (but varying between different individuals) is achieved, dominated mostly by Bacteroidetes and Firmicutes



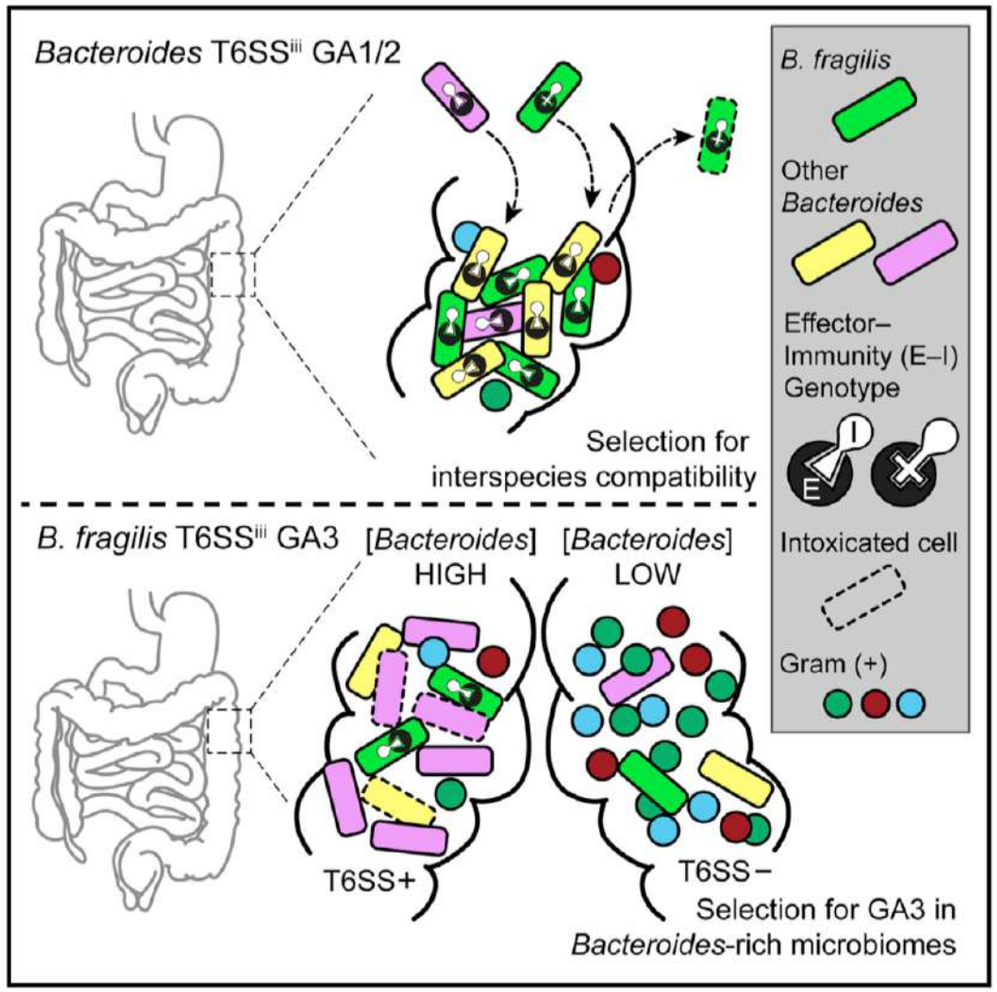
Watson & Søreide, 2017

Intense microbial competition in human colonization phase

- Bacteria experience pervasive competition from surrounding cells
- A prevalent pathway mediating the transfer of toxic proteins between bacteria is the type VI secretion system (T6SS)
- T6SS activity typically results in growth arrest or the lysis of competitor cells
- Hard completion during early stage of infant colonization
- Selection of genotypes over time
- Competition by the mean of cell-death using T6SS



Joshi et al. 2017 for T6SS



Verster et al., 2017 for Bacteroidetes

Fecal transplant

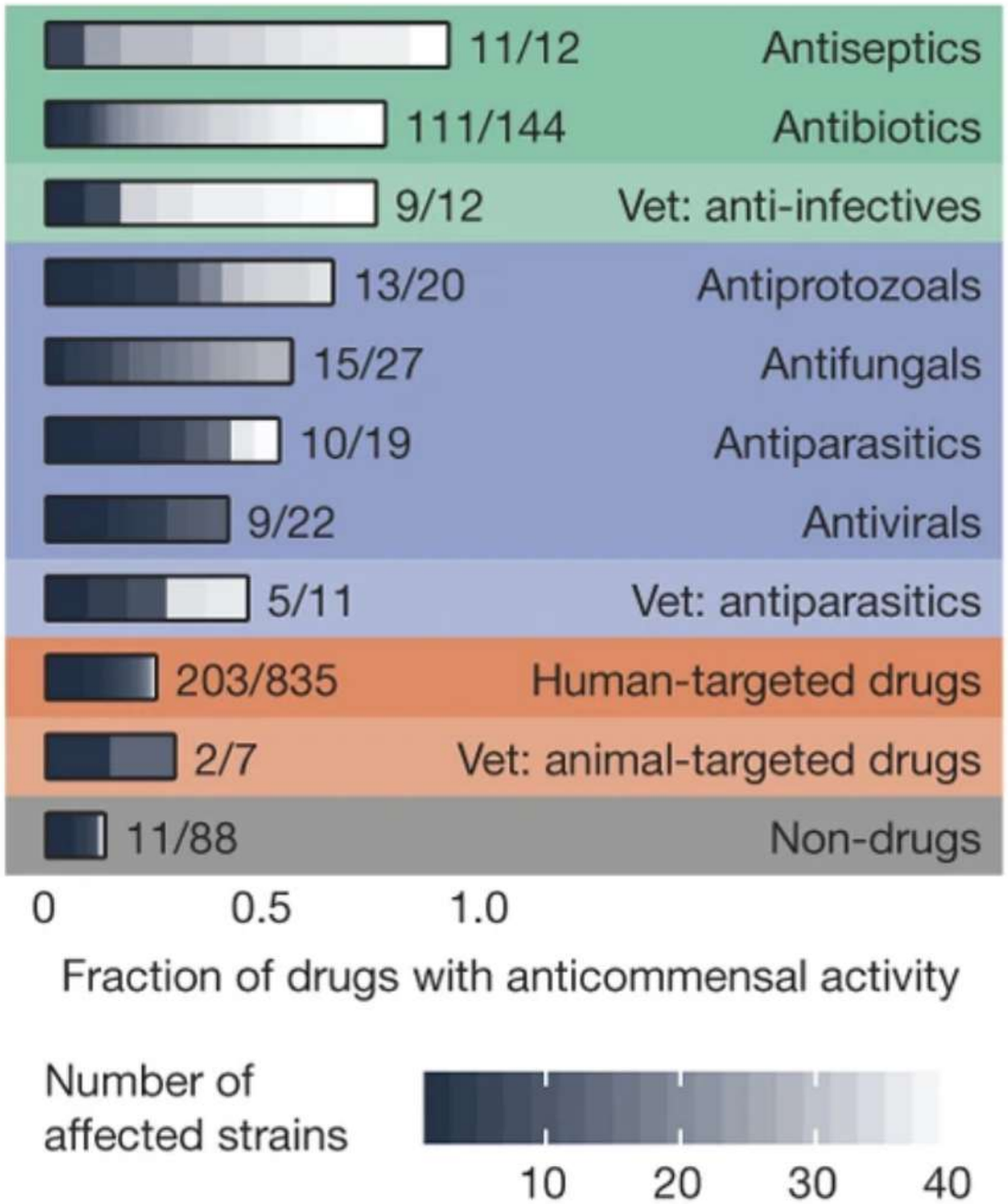
- Finding that thousands of bacterial species, viruses and fungi live in people, and are an integral part of human biology, has challenged medicine's view of microorganisms solely as agents of infectious disease
- The discovery that dietary fibre stimulates the particular groups of bacteria that produce key host-signalling molecules (such as short-chain fatty acids) is leading to the development of nutrition-based approaches to treating and restoring people's microbiomes —> **PROBIOTIC a "live microorganism which, when administered in adequate amounts, confer a health benefit on the host & PREBIOTIC APPROACH promotes the ingestion of certain plant compounds (e.g. carbohydrate for good fermenters in colon) as microbial growth stimulants with the idea that they will nurture healthy gut bacteria**
- Transplantation has been found to be more than 90% effective in the treatment of recurring *Clostridium difficile* infections (current care standard is repeated doses of antibiotics)
- Some cancer treatments activate the immune system —> new approach to these has emerged with the discovery that efficacy is related to specific members of the patient's gut microbiome

Extensive impact of non-antibiotic drugs on human gut bacteria

1,197 pharmaceuticals marketed drugs against 40 representative gut bacterial strains, and found that 24% of the drugs with human targets, including members of all therapeutic classes, inhibited the growth of at least one strain *in vitro*

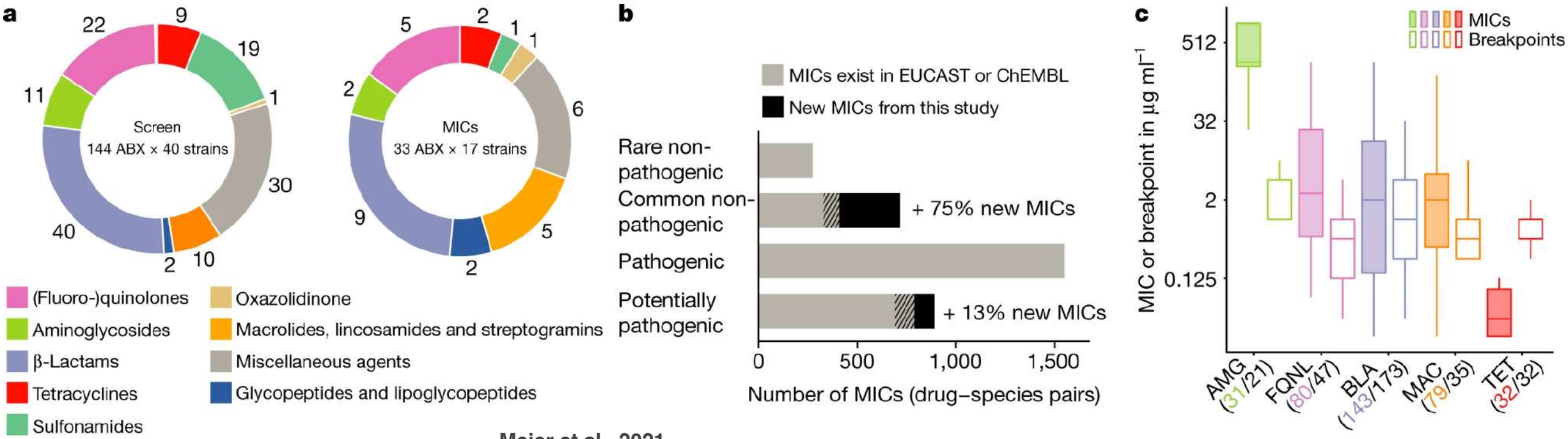
Drugs designed to target human cells and not microbes, such as **antidiabetics** (metformin), **proton pump inhibitors** (PPIs), **nonsteroidal anti-inflammatory drugs** and **atypical antipsychotics** (AAPs), has been associated with changes in microbiome composition

Anaerobic growth, modified GAM broth, 20 μM drug



Meier et al., 2018

Activity spectrum of antibiotic classes on human gut commensals



Meier et al., 2021

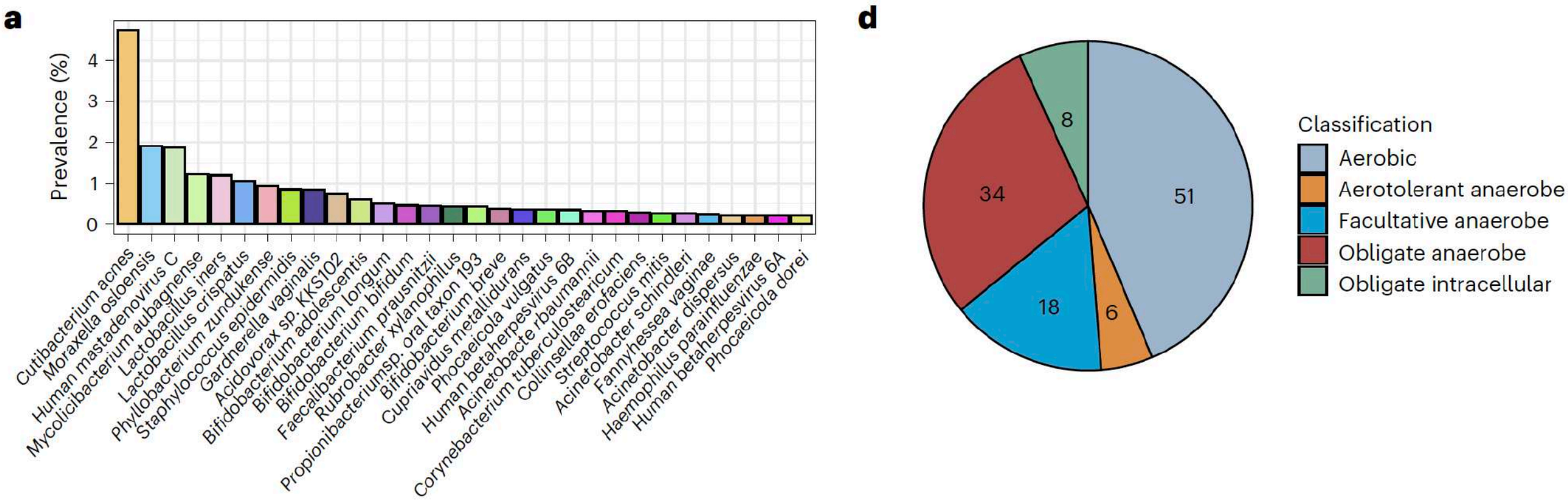
- **Macrolides showed a strong effect on gut commensals** and inhibited all tested microorganisms but not *C. difficile;* **bacteriostatic** antibiotics—that is, they **inhibit bacterial growth but do not kill** (at high numbers) —> community shift
- **β-lactams exhibited strain-specific activity** and are known to **kill bacteria (bactericidal)**, patchy results —> community shift
- Gut commensal bacteria studied (anaerobic growth, modified GAM broth22) had slightly higher MICs than those reported for pathogens (aerobic growth, Mueller–Hinton agar)
- **Tetracyclines** were the exception, **inhibiting commensals at significantly lower concentrations**

Microbes in human blood

Human blood is conventionally considered sterile but recent studies suggest the presence of a blood microbiome in healthy individuals

Commensals associated with the gut (n = 40), mouth (n = 32) and genitourinary tract (n = 18), and were distinct from pathogens detected in hospital blood cultures

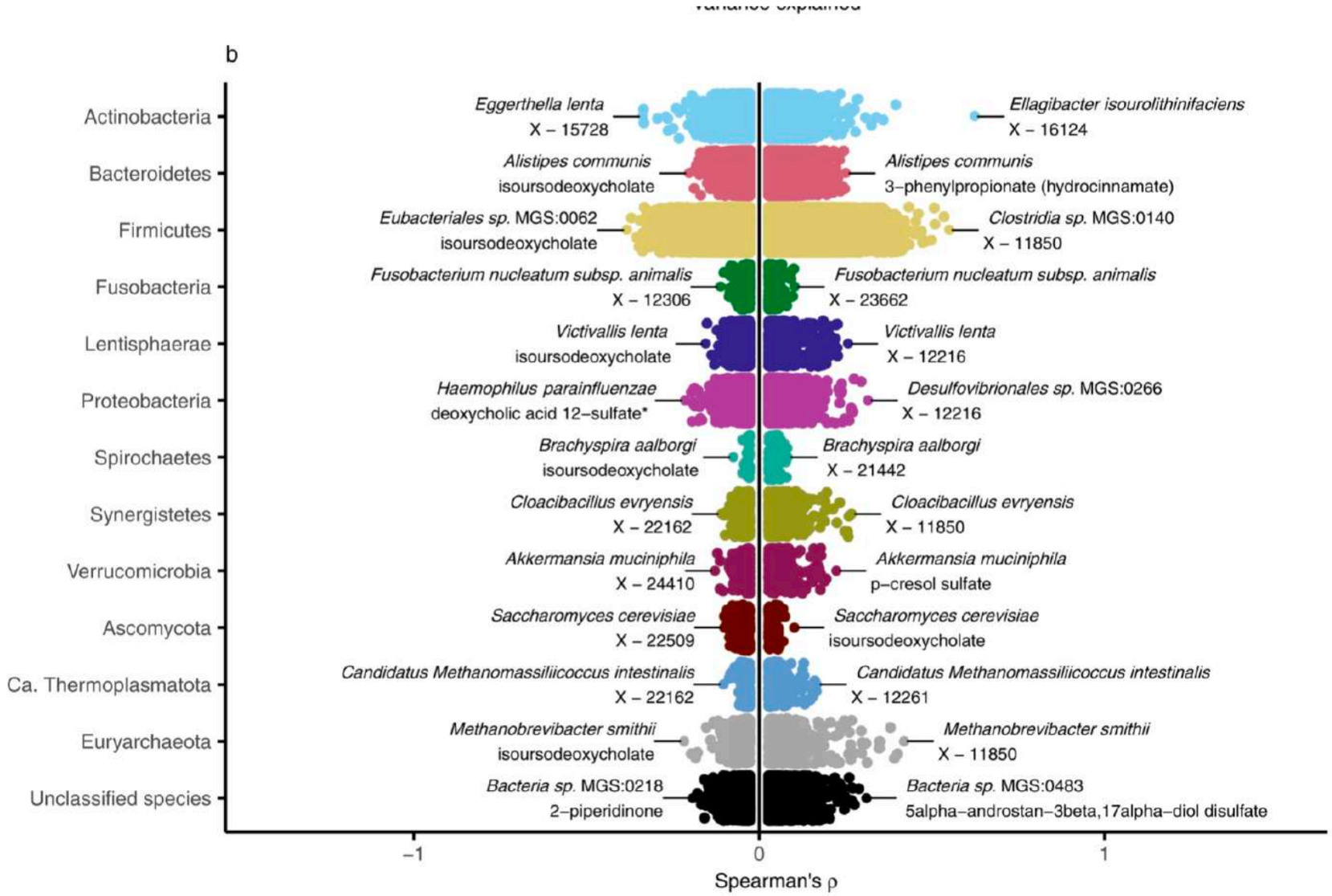
No co-occurrence patterns between different species were observed and no associations between host phenotypes and microbes were found



Tan et al., 2023

Metabolome

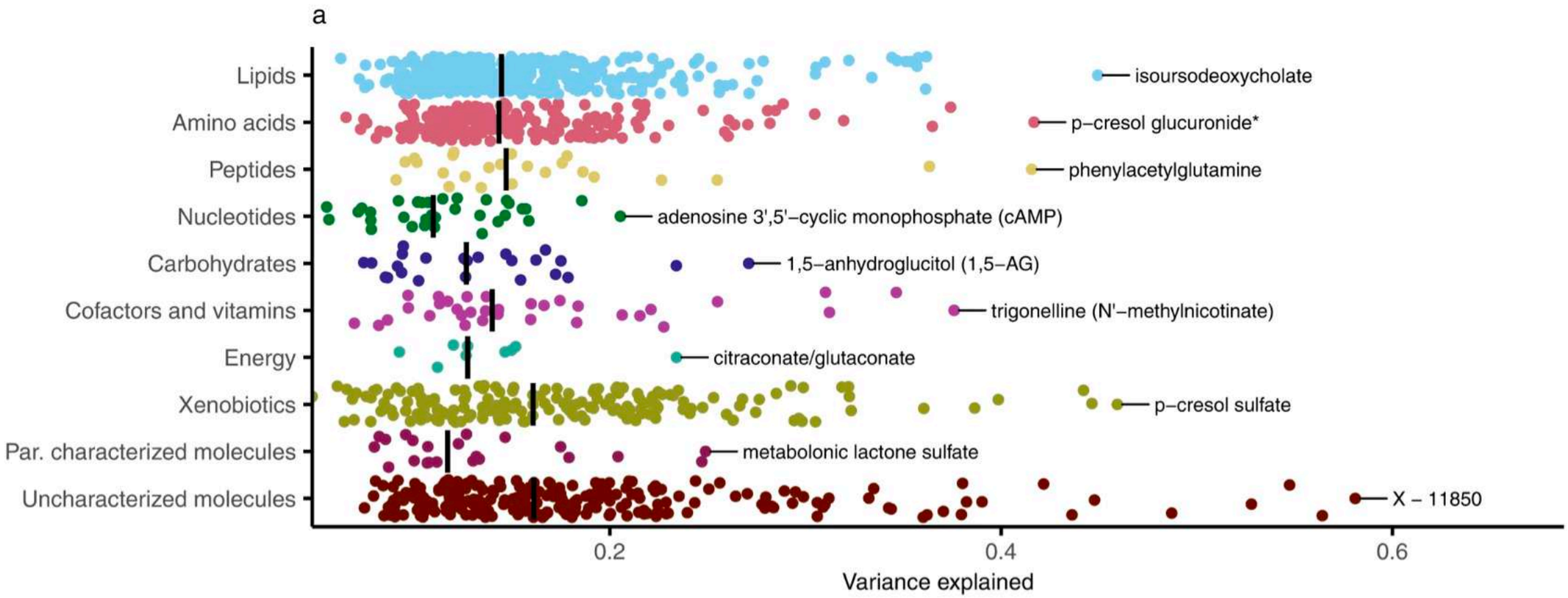
- Gut microbiota produce and modify a number of **molecules**, some of which are taken up into the **bloodstream**
- Characterization of the interactions between gut microbiota and host plasma metabolites could provide crucial insights into the effects of the gut microbiota on human health
- **Some species correlated with one or more metabolites**



Dekkers et al., 2022

Human plasma metabolite signatures of gut microbiome composition

- Modification of the composition of **small molecules in plasma**, i.e. the plasma metabolome, has been suggested as a **potential mediator of gut microbiota effects on human health**



Dekkers et al., 2022

Microbial volatile organic compounds in intra-kingdom and inter-kingdom interactions

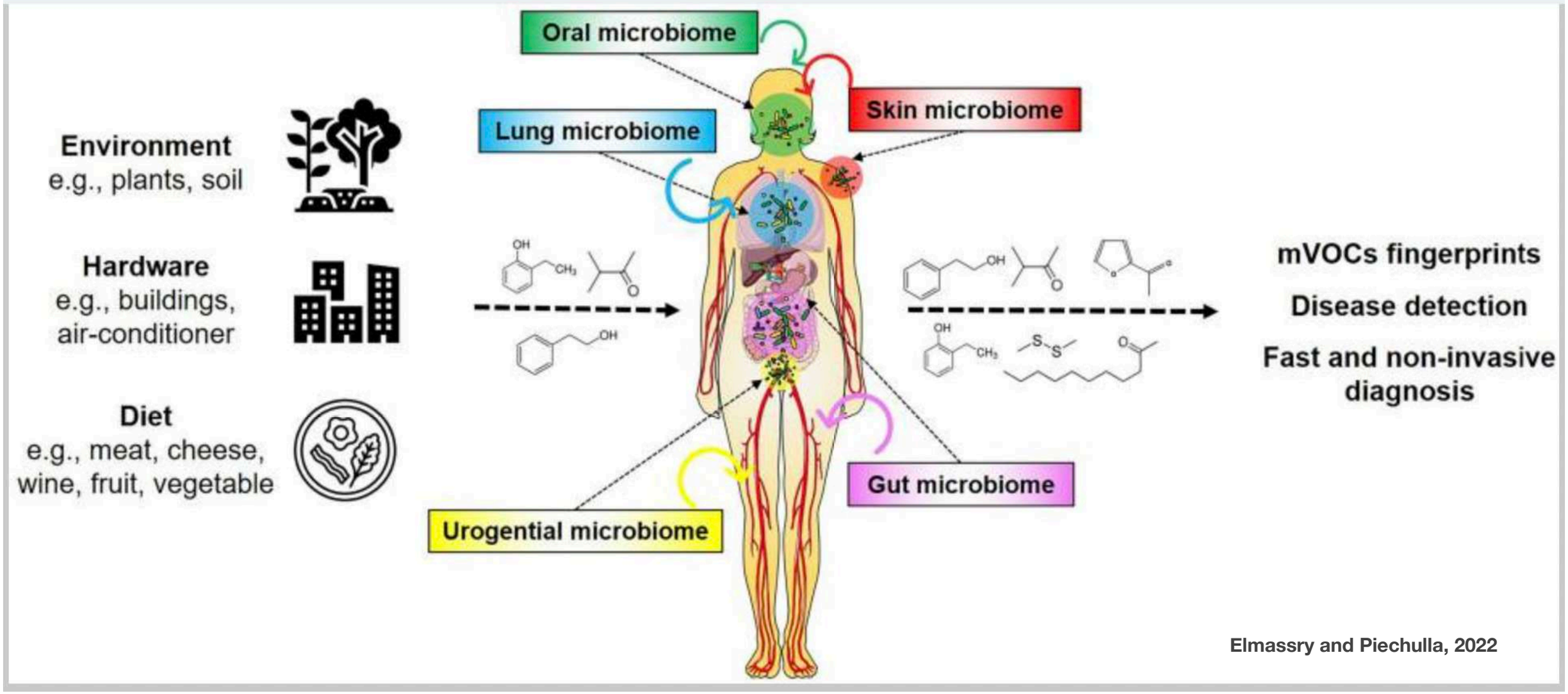
Microorganisms (bacteria, archaea, fungi and protists) use chemical signals as a primary source of information —> quorum sensing

Signals in intra-kingdom and inter-kingdom interactions at low concentration and over long distances (>20 cm)

Microbial volatiles are compounds that can be detected in the **gas phase** of a microbial culture

Unique physico-chemical properties: they are **small molecules (<300 Da)**, with up to two functional groups and the ability to easily **diffuse in air and water**

Volatilomes of Bacterial Infections in Humans



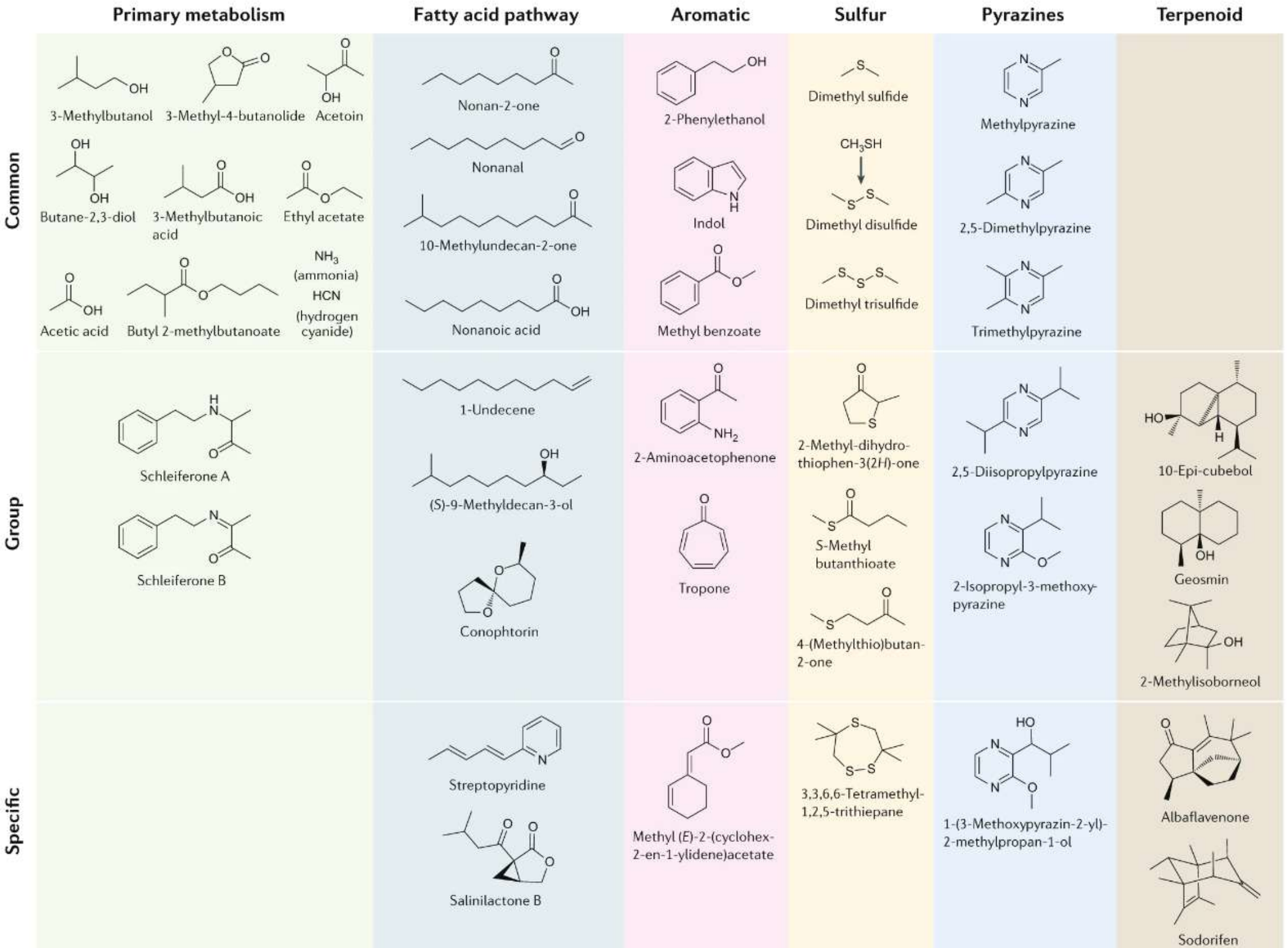
- mVOCs and the human holobiont
- Microorganisms appear universal in the environment
- Microbes produces many compounds, including volatiles
- Volatiles influence and affect humans
- mVOCs released of the human microbiomes are potential biomarkers for non-invasive diagnosis.

Pathogen	Infection	Volatiles	Specimen	References
Clostridioides difficile	Gastrointestinal	2-furancarboxaldehyde; 5-methyl-2-furancarboxaldehyde	Feces	Probert et al., 2004
		propan-1-ol; 3-methylbutanal; ethyl propionate; hexanoic acid; *p*-cresol; dodecane; indole		Patel et al., 2019
Vibrio cholerae		dimethyl disulfide; *p*-menth-1-en-8-ol		Garner et al., 2009
Campylobacter jejuni		1-octen-3-ol		Garner et al., 2007
Helicobacter pylori		hydrogen nitrate; hydrogen cyanide	Breath	Lechner et al., 2005
Staphylococcus aureus	Respiratory	undecane; 1,4-pentadiene; acetone		Neerincx et al., 2016
Pseudomonas aeruginosa		methyl thiocyanate		Shestivska et al., 2011
		hydrogen cyanide		Gilchrist et al., 2013; Smith et al., 2013
		2-aminoacetophenone		Scott-Thomas et al., 2010
		2-hexanone	Sputum	Goeminne et al., 2012

Pseudomonas aeruginosa		2-nonanone		Savelev et al., 2011
		2-butanone; 3-methyl-2-butanone	Bronchoalveolar lavage	Nasir et al., 2018
Acinetobacter baumannii		1-undecene; nonanal; decanal; 2,6,10-trimethyl-dodecane; 5-methyl-5-propyl-nonane; longifolene; tetradecane; 2-butyl-1-octanol	Breath	Gao et al., 2016
Mycobacterium tuberculosis		naphthalene; 1-methyl-cyclohexane; 1,4-dimethyl-cyclohexane		Phillips et al., 2007
		methyl phenyl-acetate; methyl nicotinate; methyl p-anisate; o-phenylanisole		Syhre and Chambers, 2008
Escherichia coli	Bloodstream	dimethyl sulfide; carbon disulfide; ethanol; acetaldehyde; methyl butanoate	Blood	Umber et al., 2013
		indole		Zhong et al., 2019; Chingin et al., 2015
		acetaldehyde; ethanol; acetone; hydrogen sulfide; methanethiol; dimethyl sulfide		Allardyce et al., 2006
Pseudomonas aeruginosa		acetic acid; acetone		Allardyce et al., 2006
		1-vinyl aziridine; trimethylamine		Chingin et al., 2015
Staphylococcus		butyric acid; isovaleric acid		Chingin et al., 2015

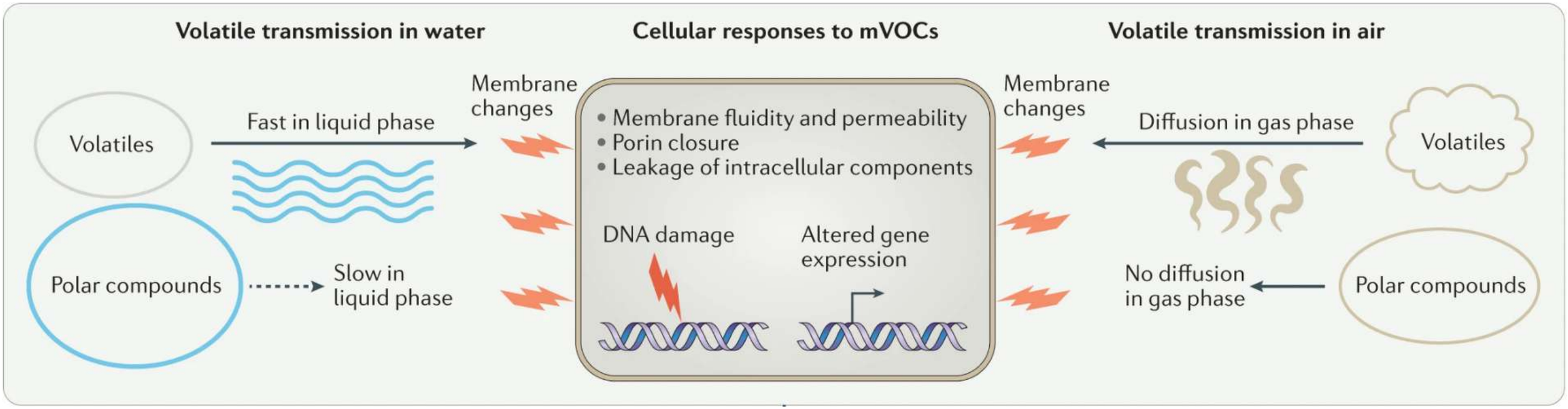
Staphylococcus aureus	acetaldehyde; ethanol; ammonia; methanethiol; dimethyl sulfide	Allardyce et al., 2006
Acinetobacter baumannii	trimethylamine	Chingin et al., 2015
Streptococcus pneumoniae	acetaldehyde; ethanol; acetone; dimethyl sulfide	Allardyce et al., 2006
Neisseria meningitidis	acetone; dimethyl disulfide	Allardyce et al., 2006

Major biosynthetic pathways of microbial volatile organic compounds



Weisskopf et al., 2021

Modes of diffusion of microbial volatiles



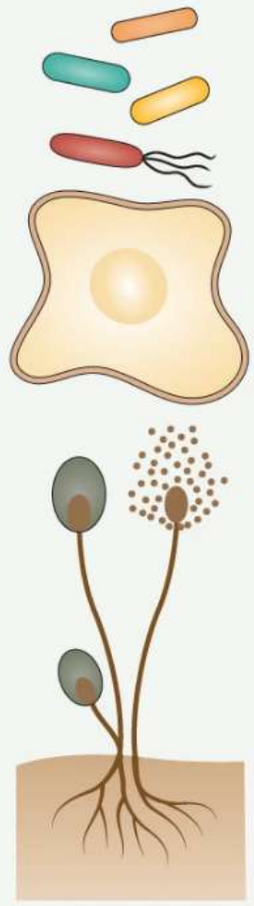
In bacteria, mVOCs have also been shown to modulate **antibiotic resistance** (for example, 1-methylthio-3-pentanone, 2-aminoacetophenone and trimethylamine), **quorum sensing** (for example, dimethyl disulfide and dimethyl trisulfide) and **biofilm formation** (for example, indole and 1-butanol)

Weisskopf et al., 2021

Responses in microorganisms, plants and animals to mVOCs

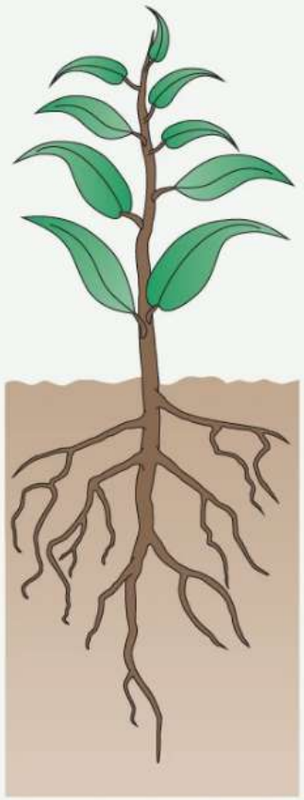
Microbial responses to mVOCs

↑↓ Growth
↑↓ Motility
↑↓ Virulence
↑↓ Explanatory behaviour
↑ Antibiotic resistance
↑ Prey sensing
↑ Expression of stress response genes
↑ Production of secondary metabolites
↓ Quorum sensing
↓ EPS production
↓ Biofilm
↓ Sporulation
↓ Ergosterol synthesis



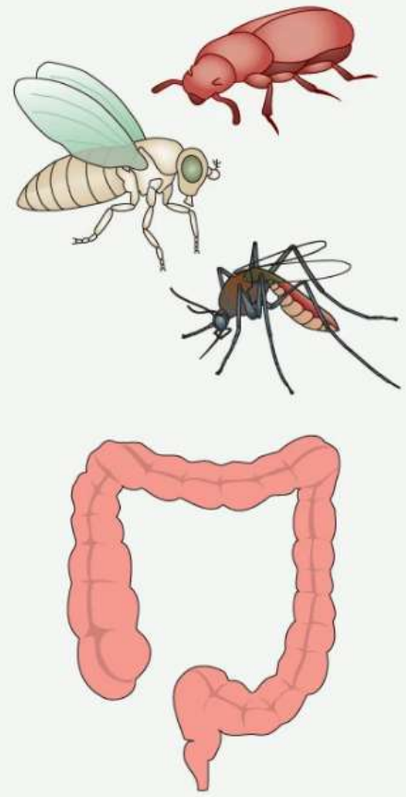
Plant responses to mVOCs

↑↓ Shoot growth
↑ Secondary root growth
↓ Primary root growth
↑ Sulfur uptake
↑ Iron uptake through:
↑ Acidification
↑ Reductase
↑ Transport
↑ Induced systemic resistance
↑ Tolerance to salt stress through:
↑ Compatible solute production
↓ Root Na^+ uptake
↑ Shoot Na^+ extrusion
Inorganic volatile-induced killing
↓ Early response to bacterial elicitors



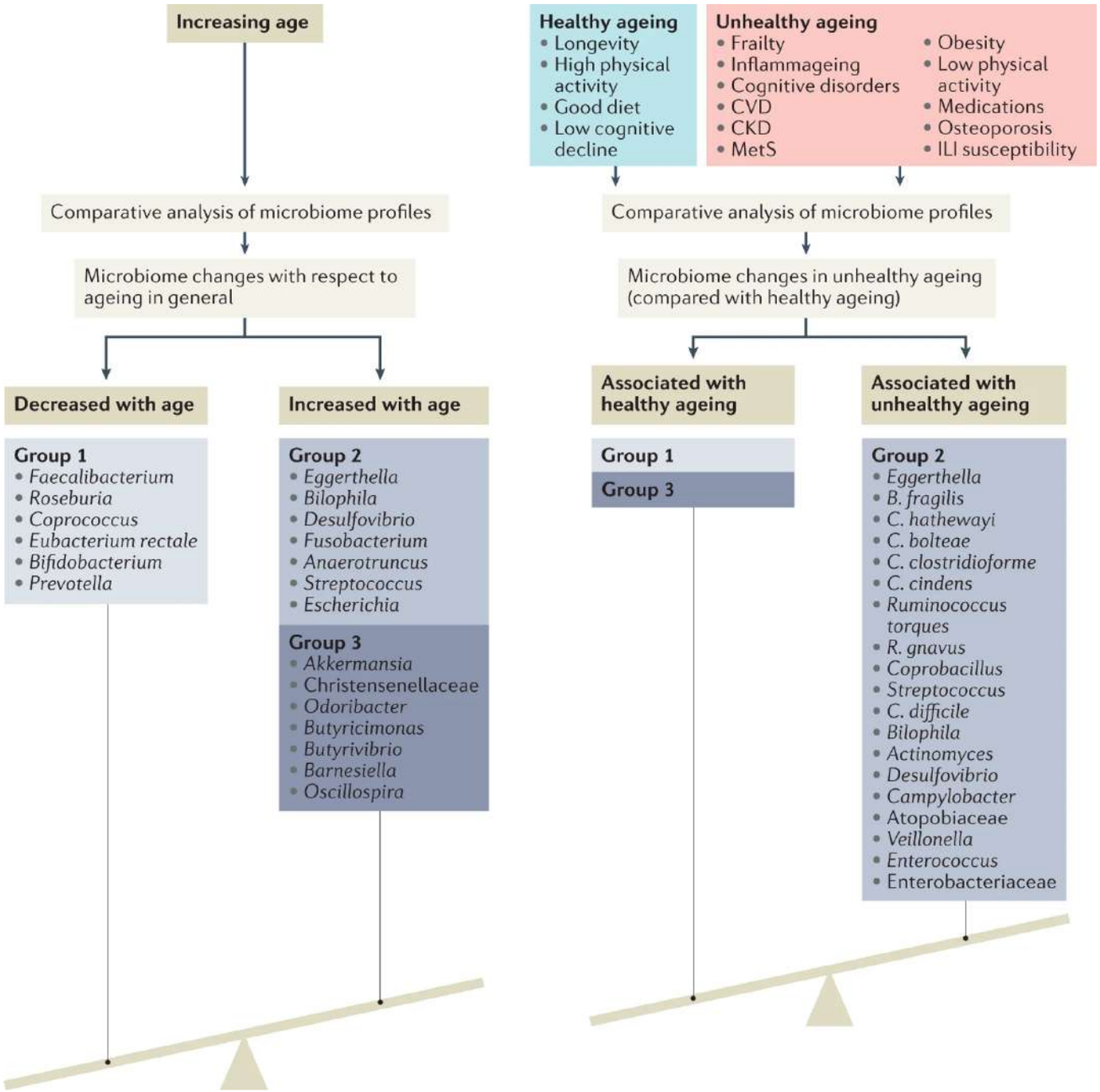
Animal responses to mVOCs

↑↓ Attraction
↑↓ Repulsion
↑ Food localization
↑ Selection of ovipositor or feeding sites
SFCA-induced:
↑ Energy
↑ Body weight
↓ SCFA-induced inflammation
Repulsion via specific neuron activation
Evaluation of food maturation level



Weisskopf et al., 2021

The gut microbiome as a modulator of healthy aging

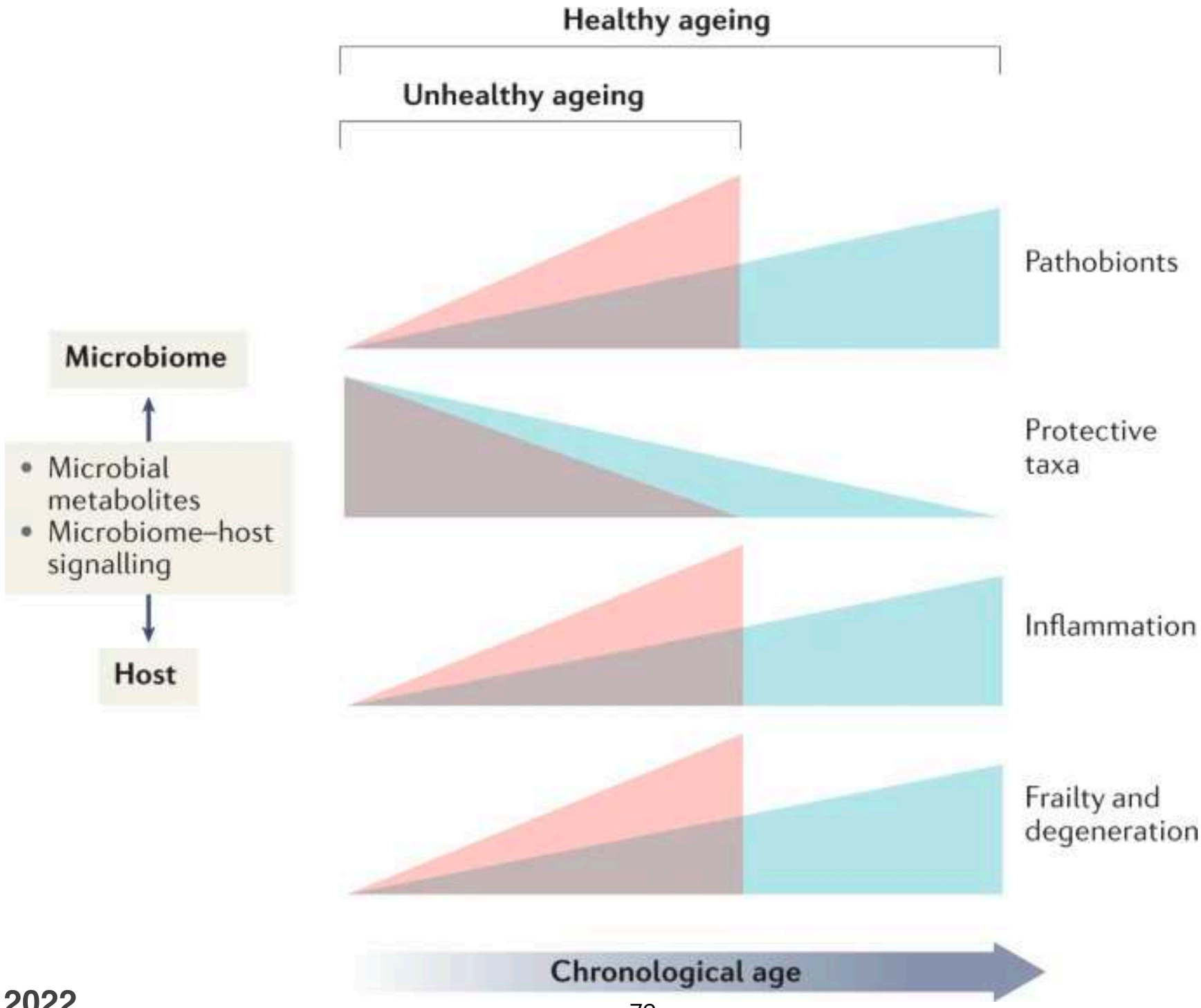


Gosh et al., 2022

- **Group 1 taxa decreased with age** and were associated with healthy aging
- **Group 2** consisted of the **pathobionts** that **increased with age** and were associated with unhealthy aging
- **Group 3 increased with age** but were observed to be **depleted in unhealthy aging**

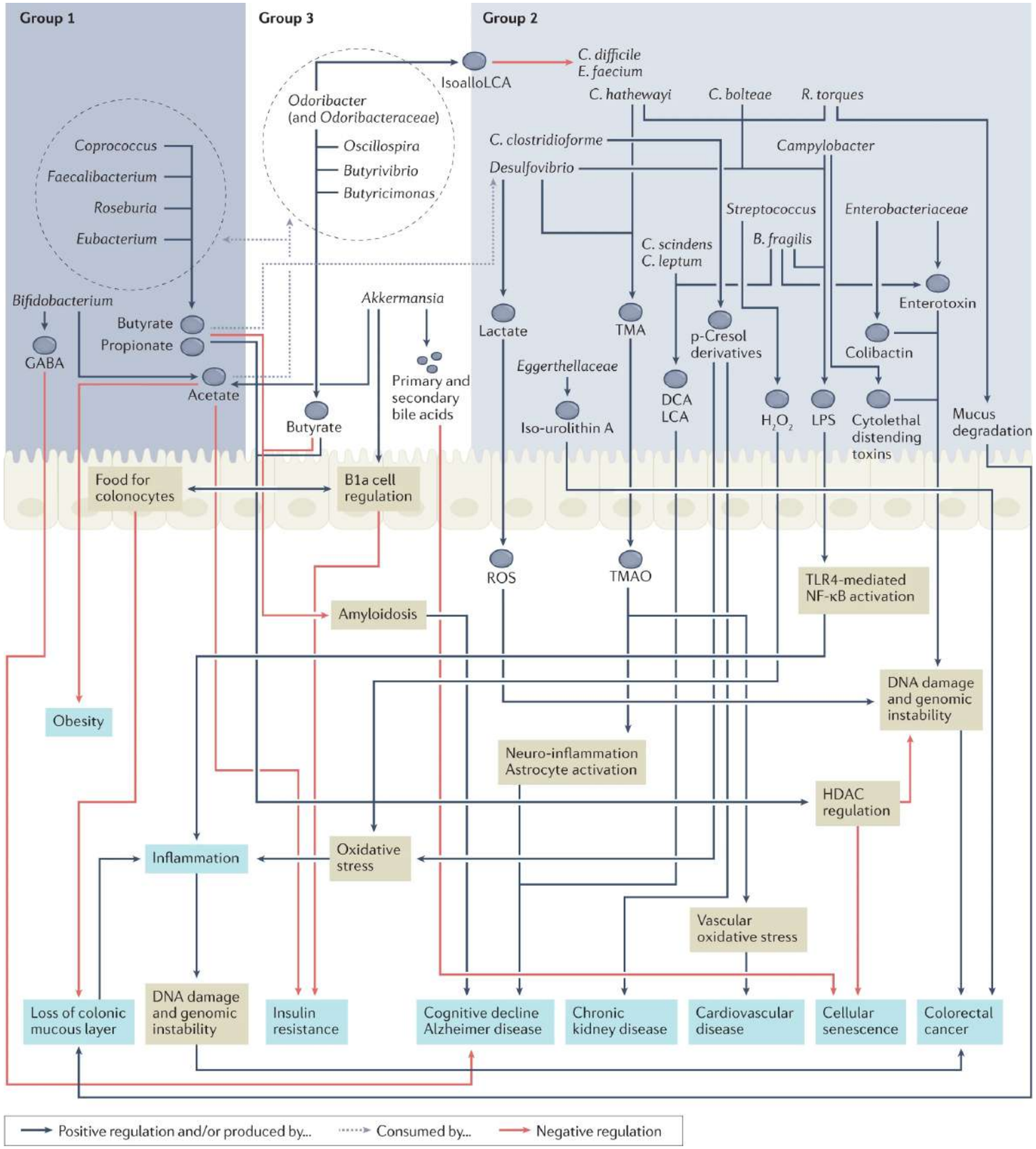
CKD, chronic kidney disease; CVD, cardiovascular disease; ILI, influenza-like illness; MetS, metabolic syndrome

Microorganism–host signalling as a contributor to healthy or unhealthy ageing



Gosh et al., 2022

Functional implications of microbiome alterations on host physiology in aging



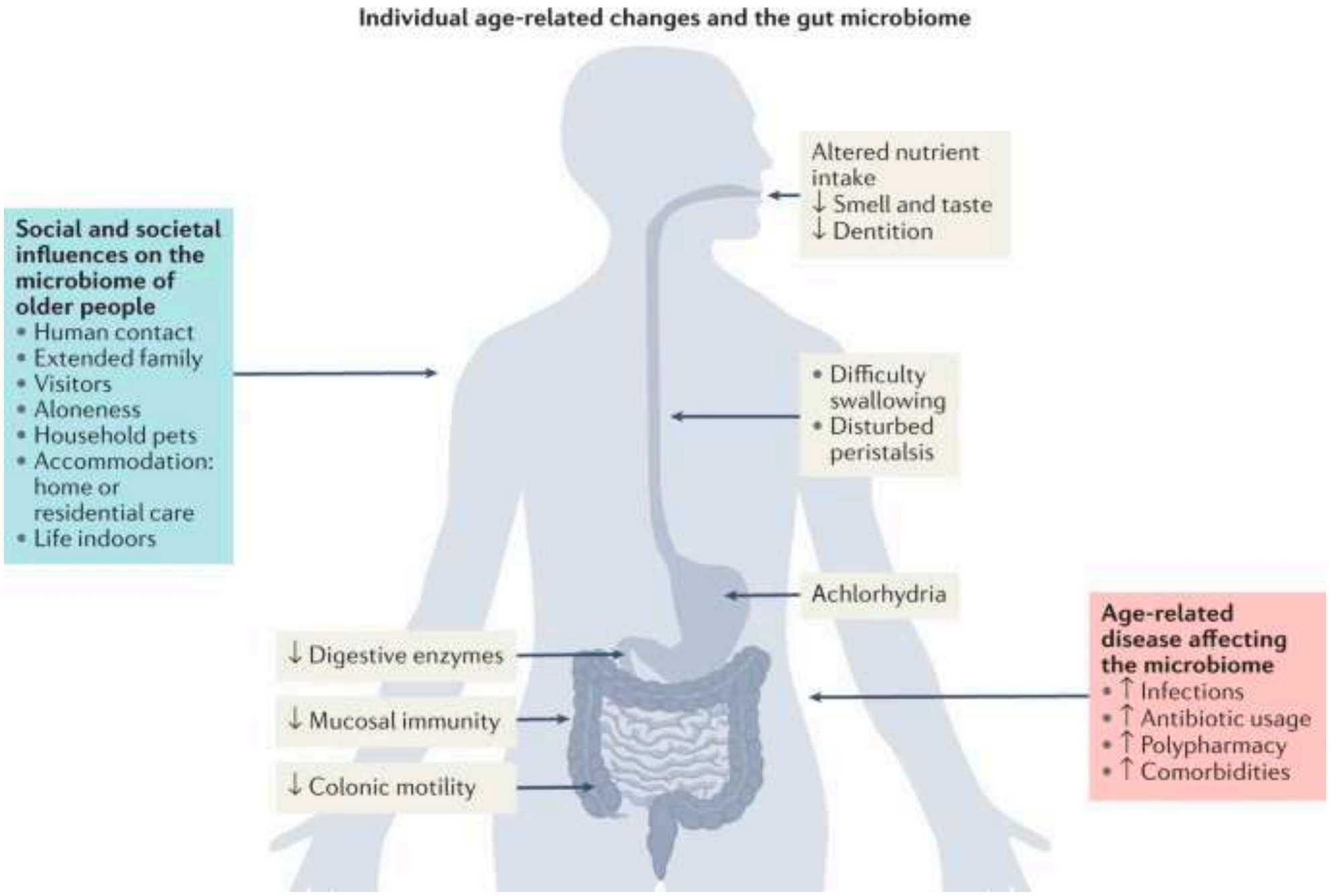
Metabolic capabilities of the three taxa groups are linked to unhealthy aging-linked decline in host physiology

Key metabolites or effectors produced by the three taxa groups and the effect each of these microbiome-derived entities has in either negatively or positively regulating various aging-linked diseases and disorders

DCA, deoxycholic acid; HDAC, histone deacetylase; IsoalloLCA, isoallolithocholic acid; LCA, lithocholic acid; LPS, lipopolysaccharide; p-Cresol, para-cresol; ROS, reactive oxygen species; TMA, trimethylamine; TMAO, TMAO, trimethylamine-N-oxide

Gosh et al., 2022

Physiological, social and disease-related influences on the microbiome of older people

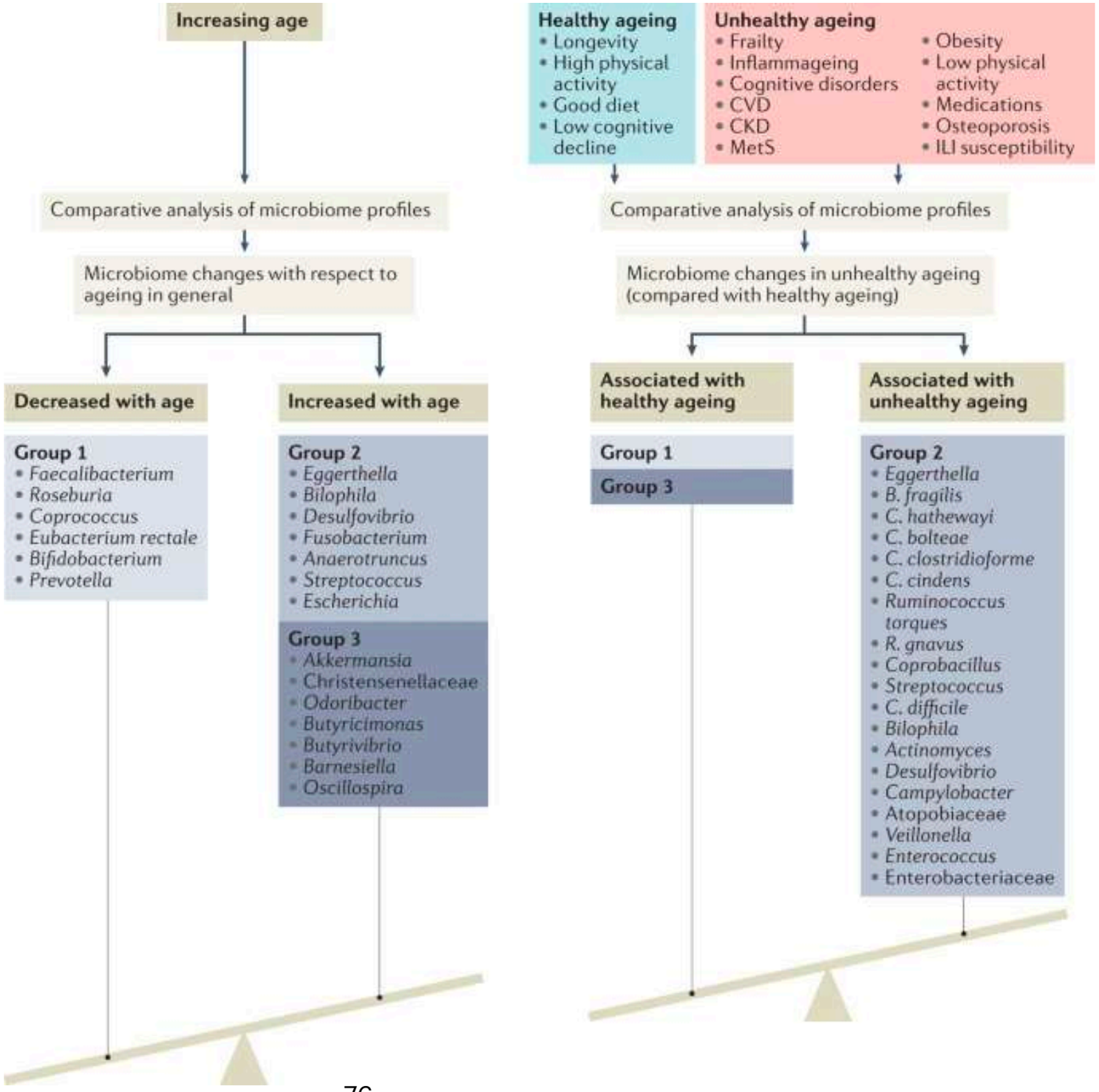


Gosh et al., 2022

Microbiome alterations in ageing (and unhealthy ageing)

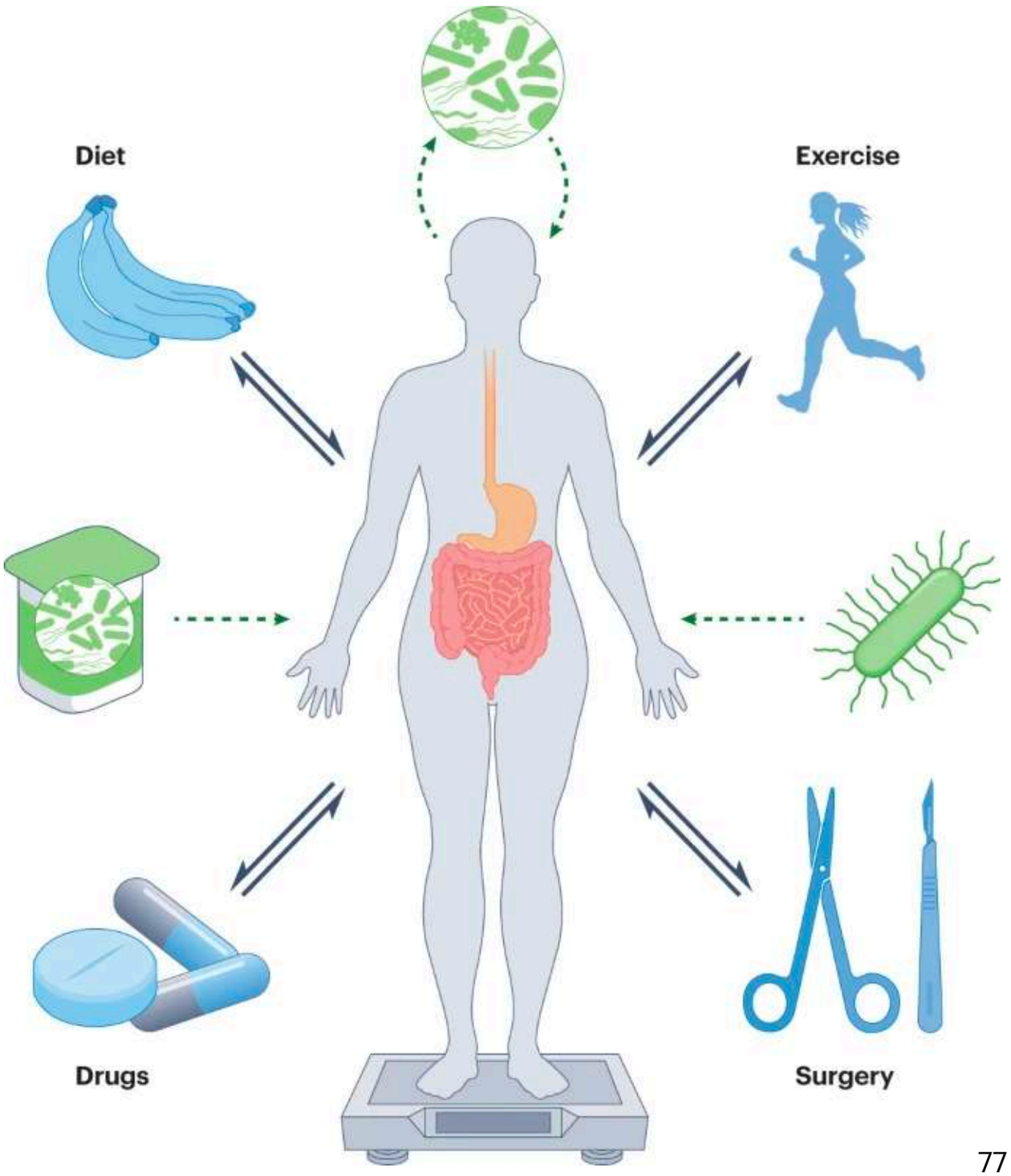
Pathobionts can cause or promote disease only when **specific genetic or environmental conditions are altered in the host**

Conditions under which pathobionts exhibit virulence **include impaired host immune defenses and altered microbiota composition**



Gosh et al., 2022

Reciprocal influences between the gut microbiome and key lifestyle and clinical approaches for weight management



Common weight-modulating interventions (blue) such as diet, exercise, drugs and surgery impact gut microbial structure and function, and these changes in the gut microbiome in turn alter intervention efficacy

Gut microbial contributions to weight management are targeted by **emerging microbiome-directed therapies (green), including foods engineered to support the engraftment or growth of beneficial microorganisms, autologous faecal microbiota transplantation after weight loss and next-generation probiotics**

Carmody & Bisanz, 2023