

LO7

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

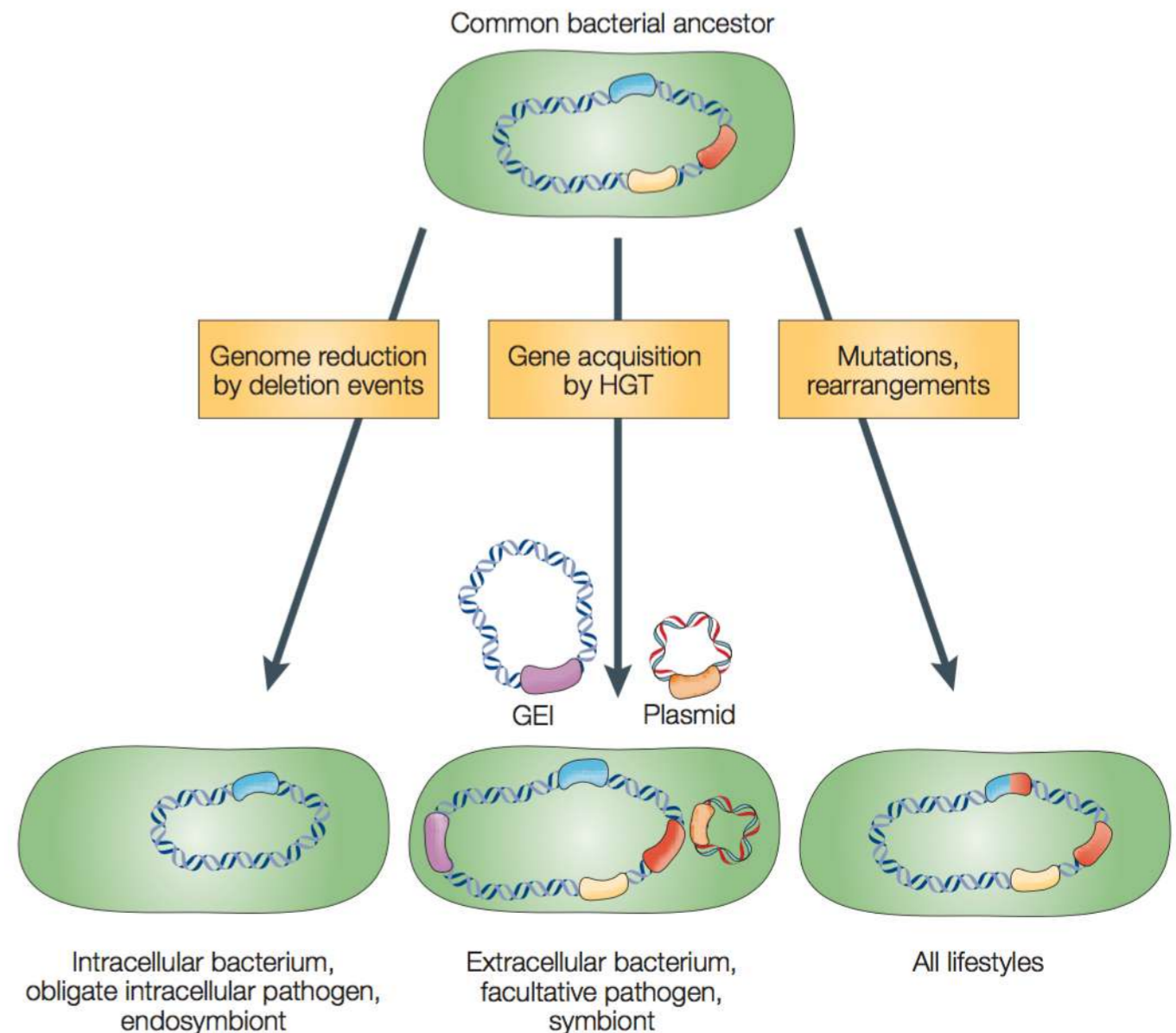
Evolution of bacterial variants by acquisition and loss of genetic information

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

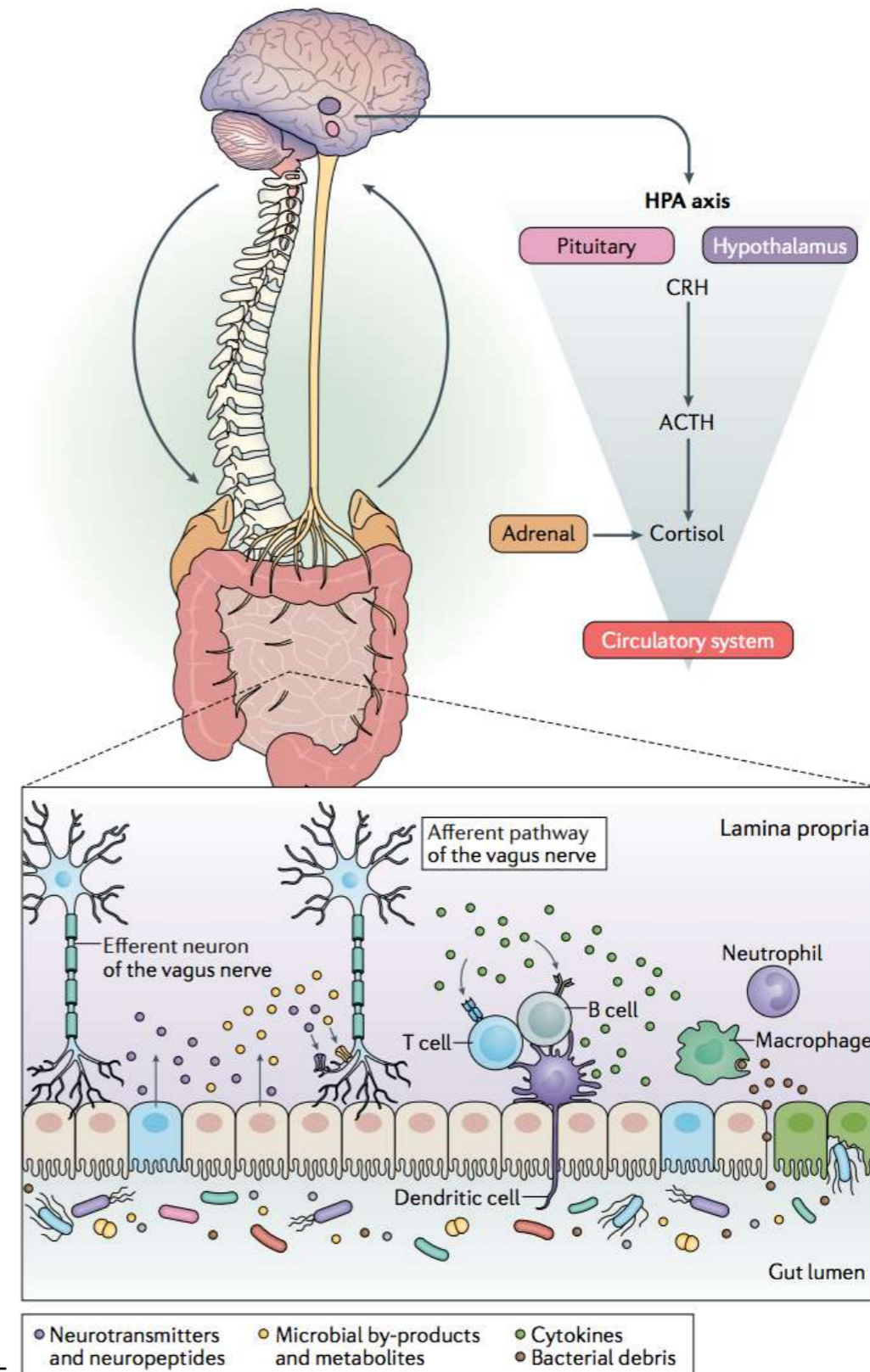
Gene acquisition by horizontal transfer between different species is common in extracellular bacteria (facultative pathogens, symbionts), which involves mobile genetic elements, such as plasmids, genomic islands (GEIs) and bacteriophages → **increases versatility and adaptability** of the recipient → 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



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’



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?

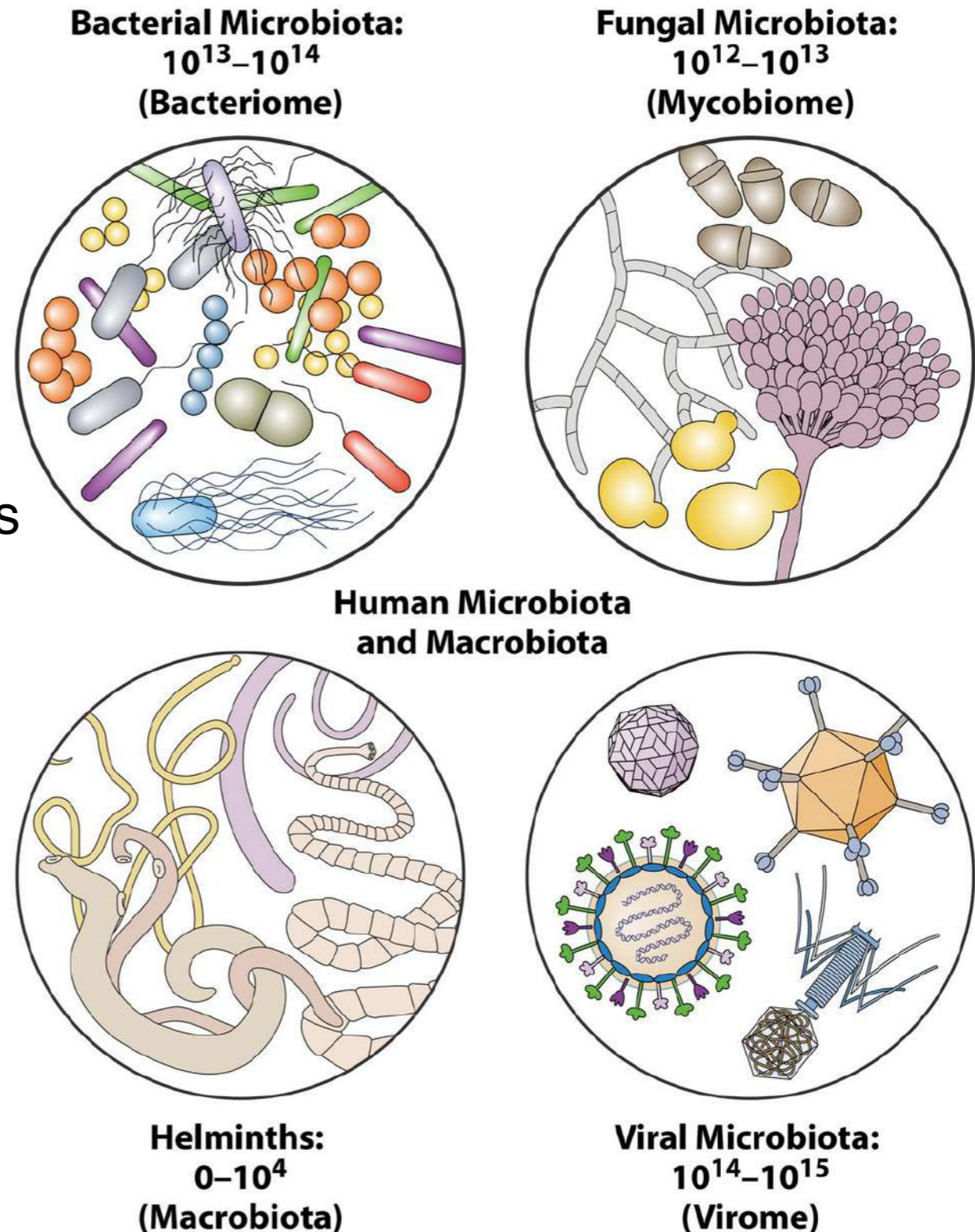
Healthy westernized humans

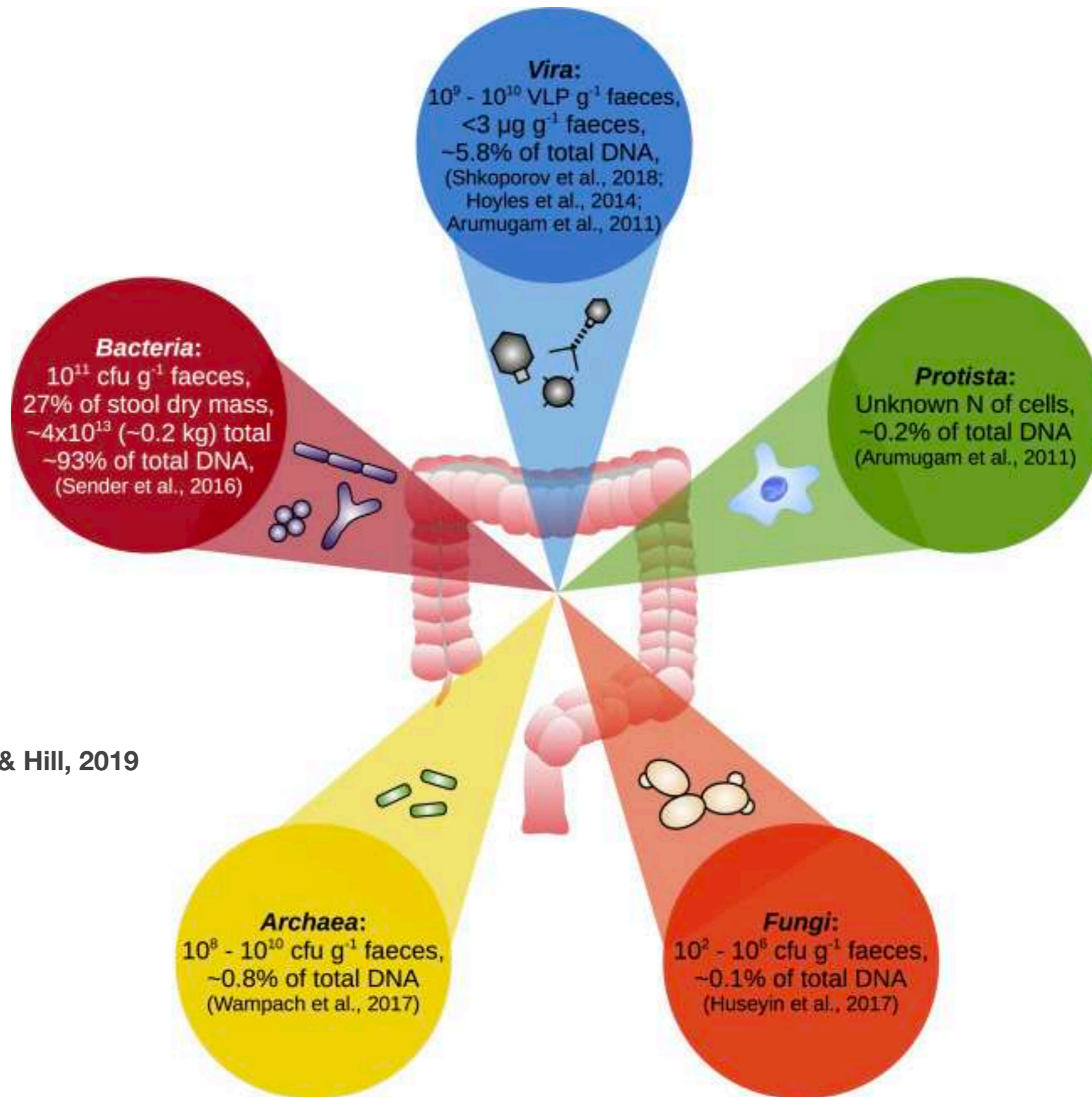
Obbligate symbionts

- 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

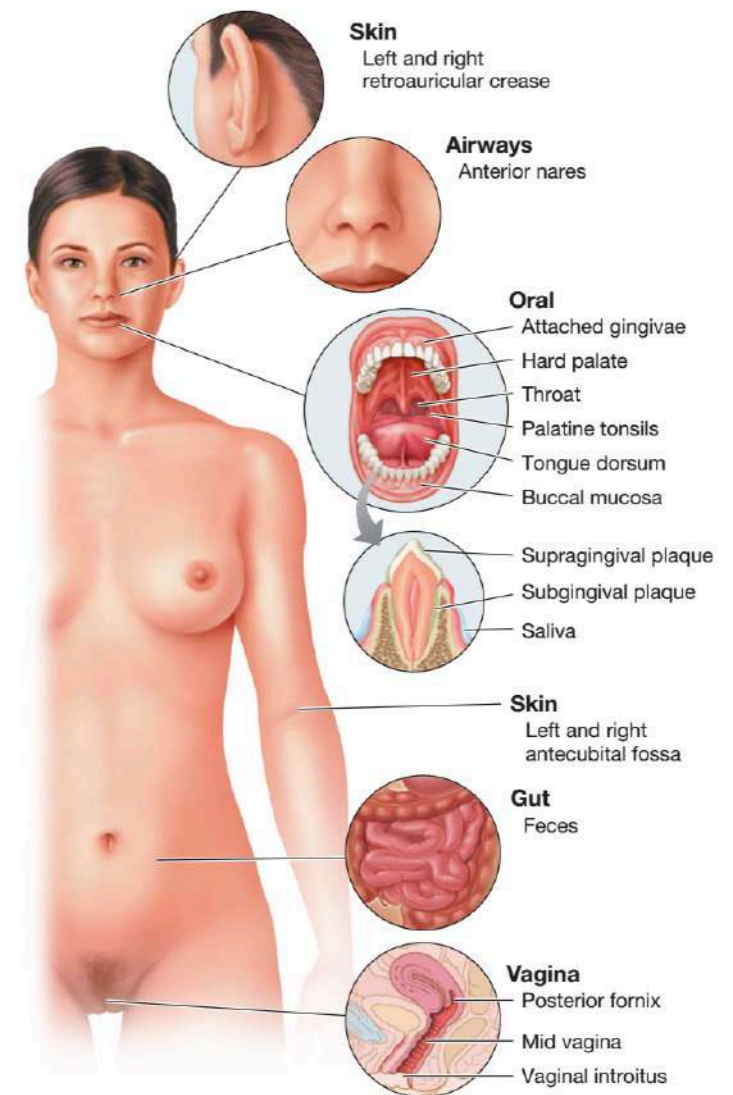




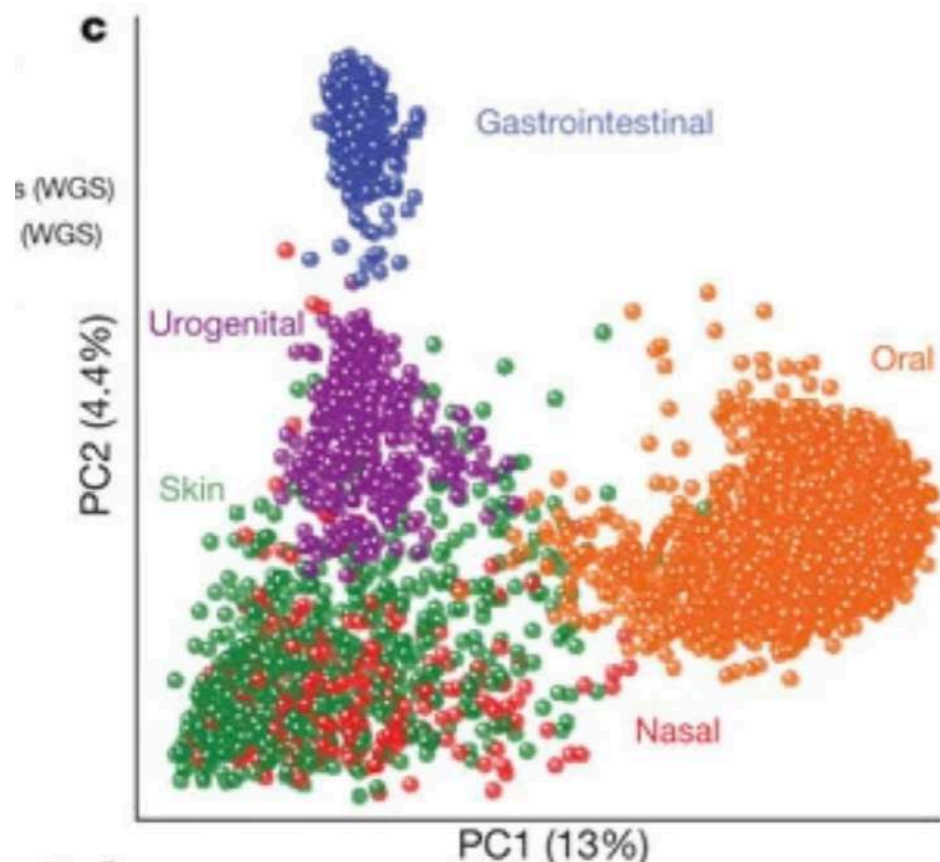
Shkoporov & Hill, 2019

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

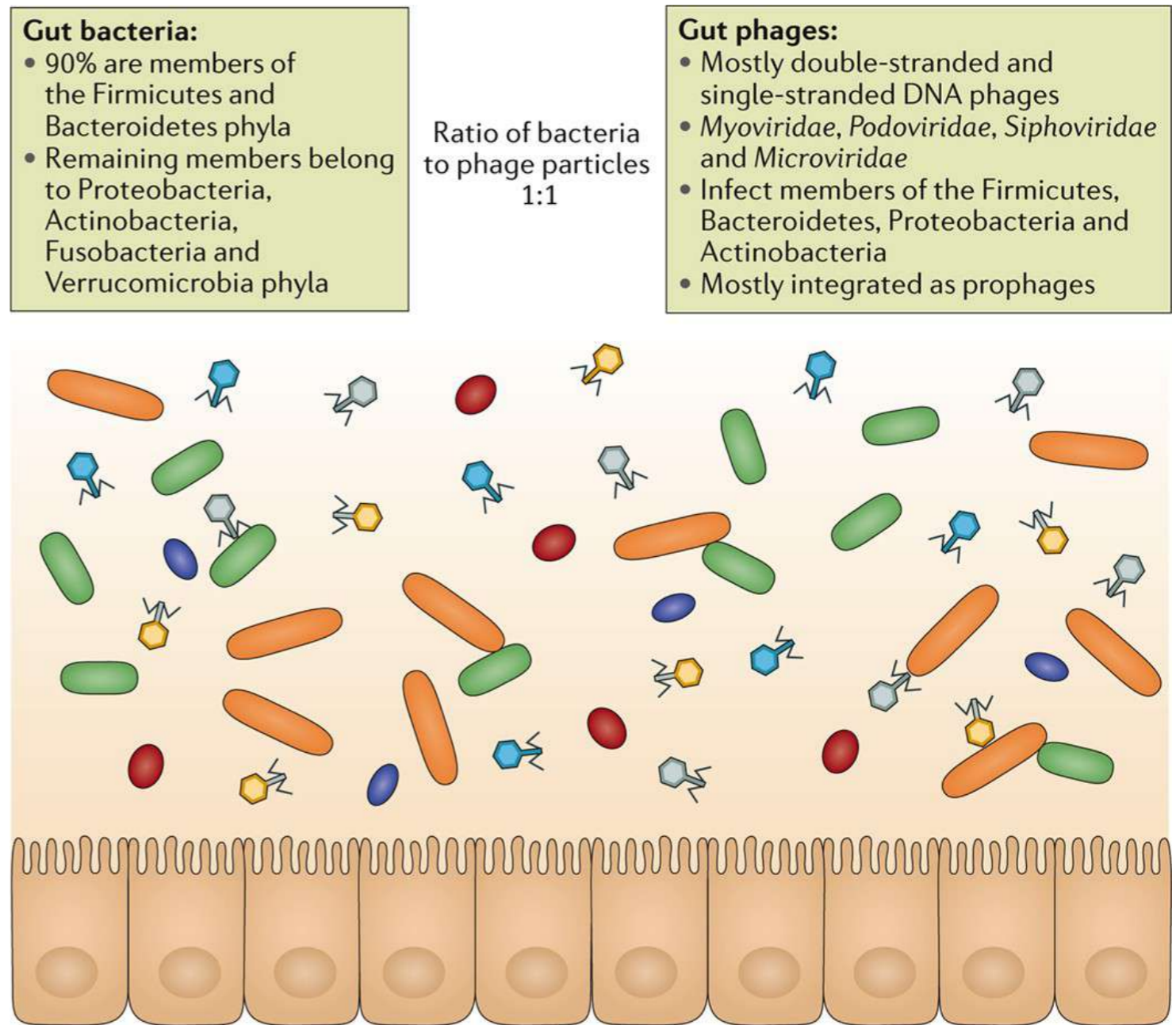


The Human Microbiome Project Consortium, 2012

What about viruses?

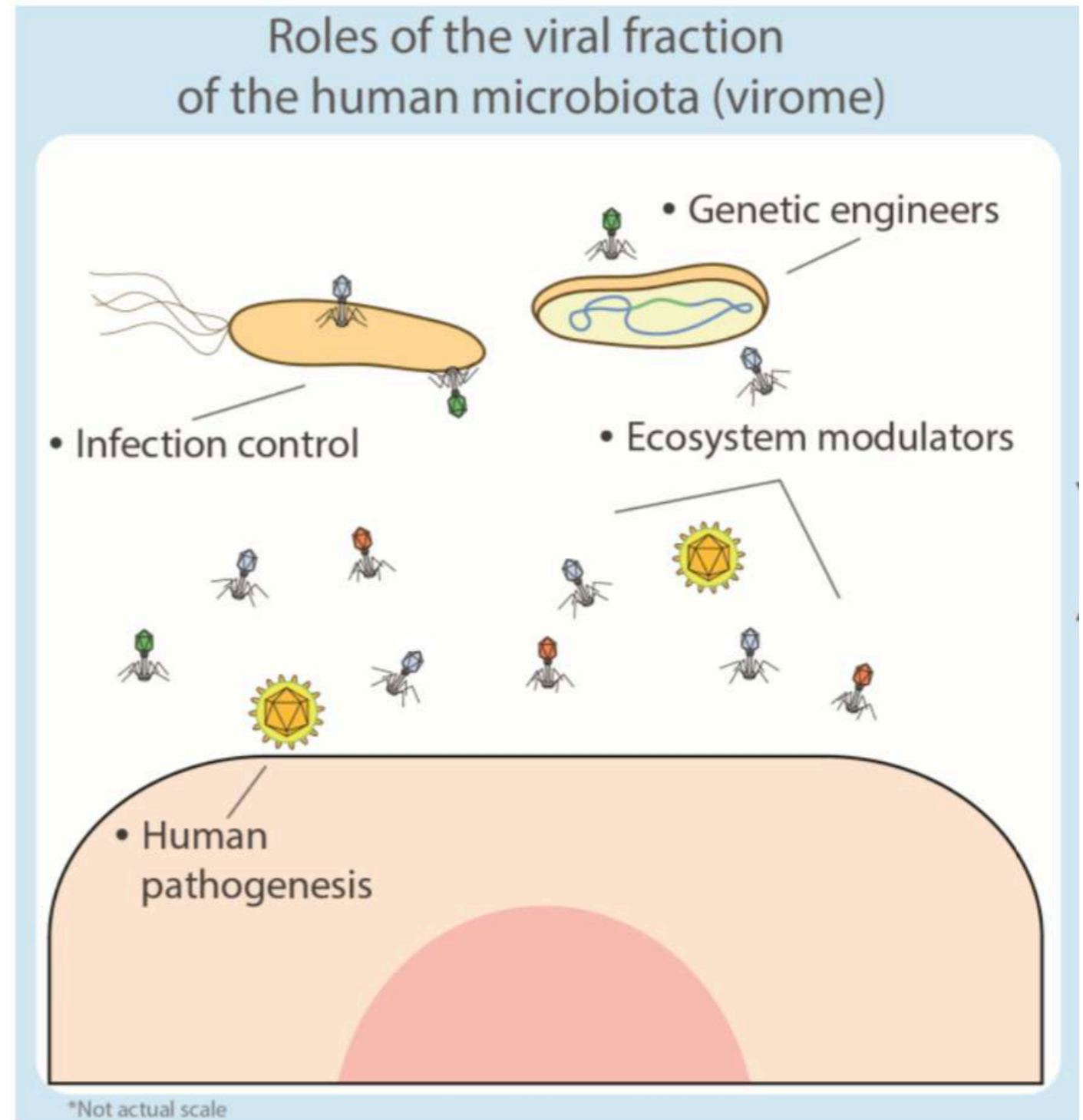
Human Virome

- 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



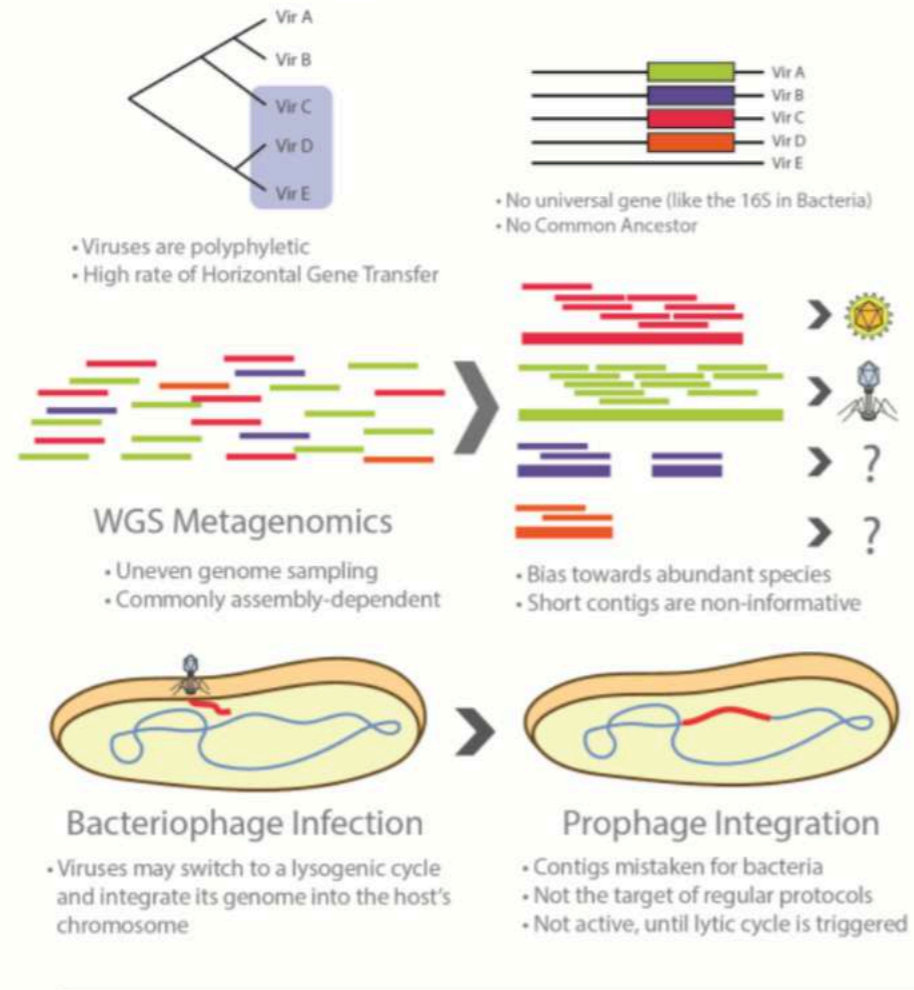
Virome role

- 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

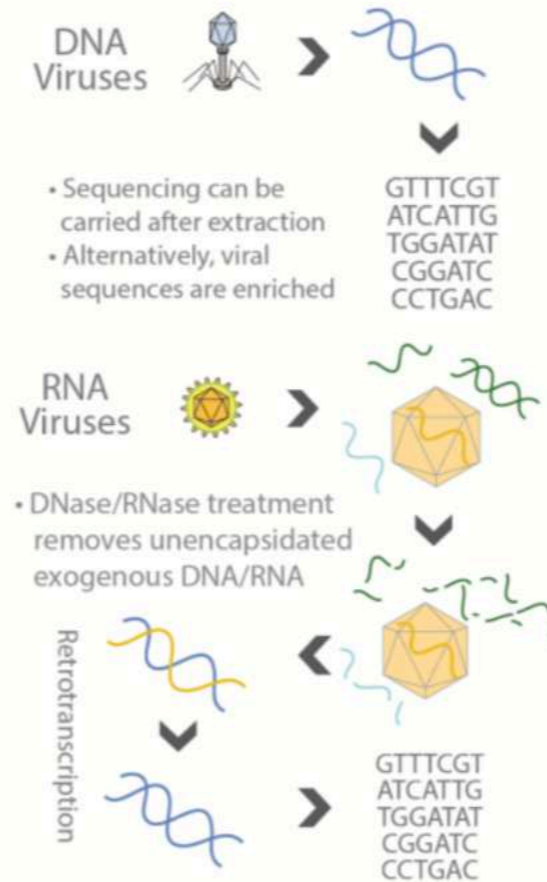


Virome challenges

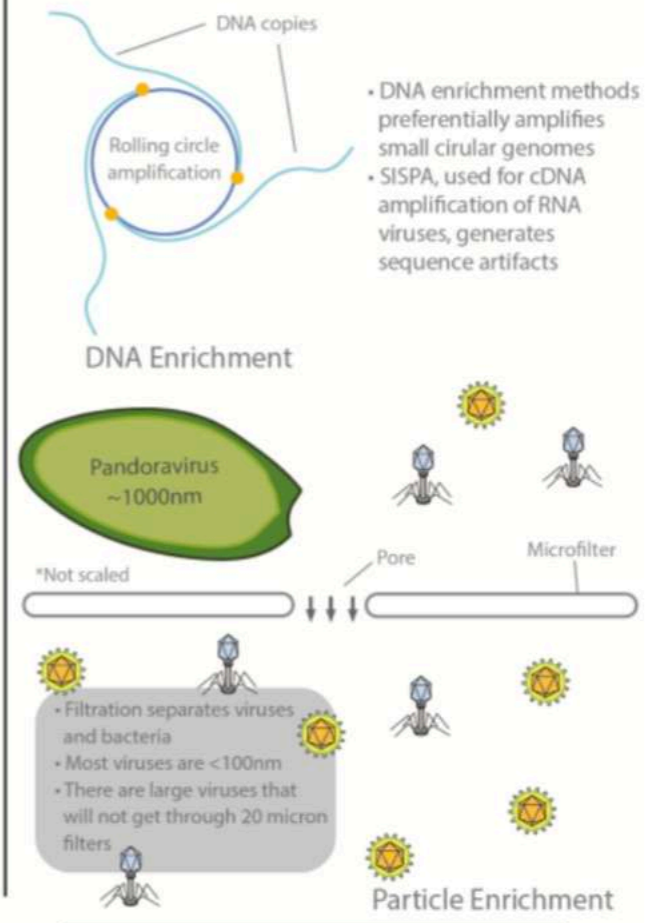
1) No universal gene exists, WGS required



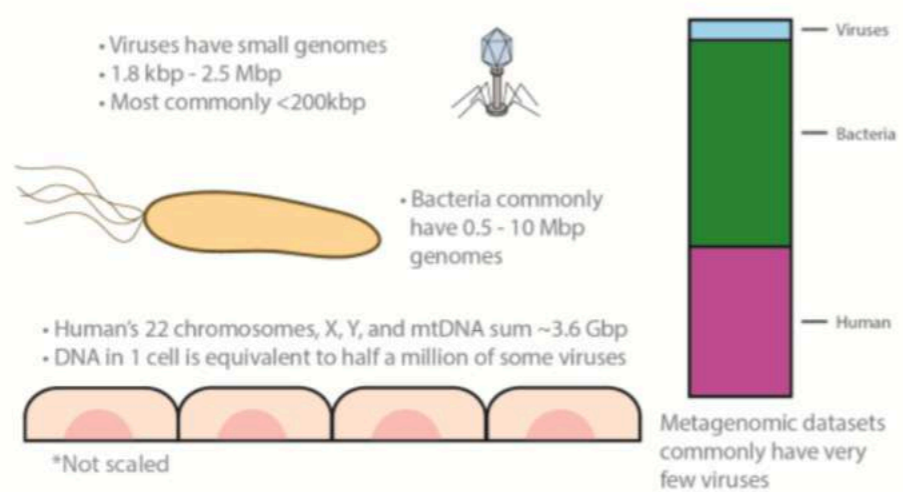
2) Viromics require DNA+RNA protocols



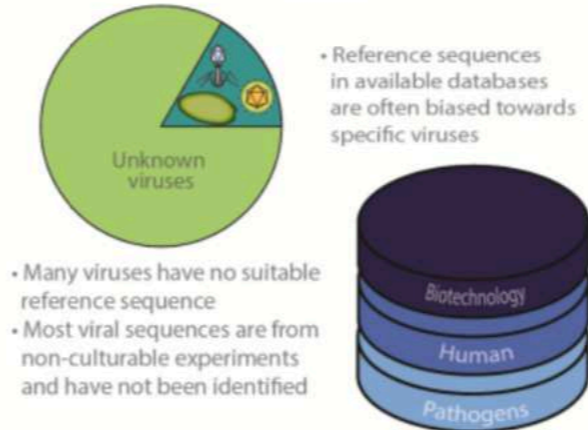
3) Experimental bias of enrichment methods



4) RNA/DNA from the host and bacteria



5) Uncharacterized viruses

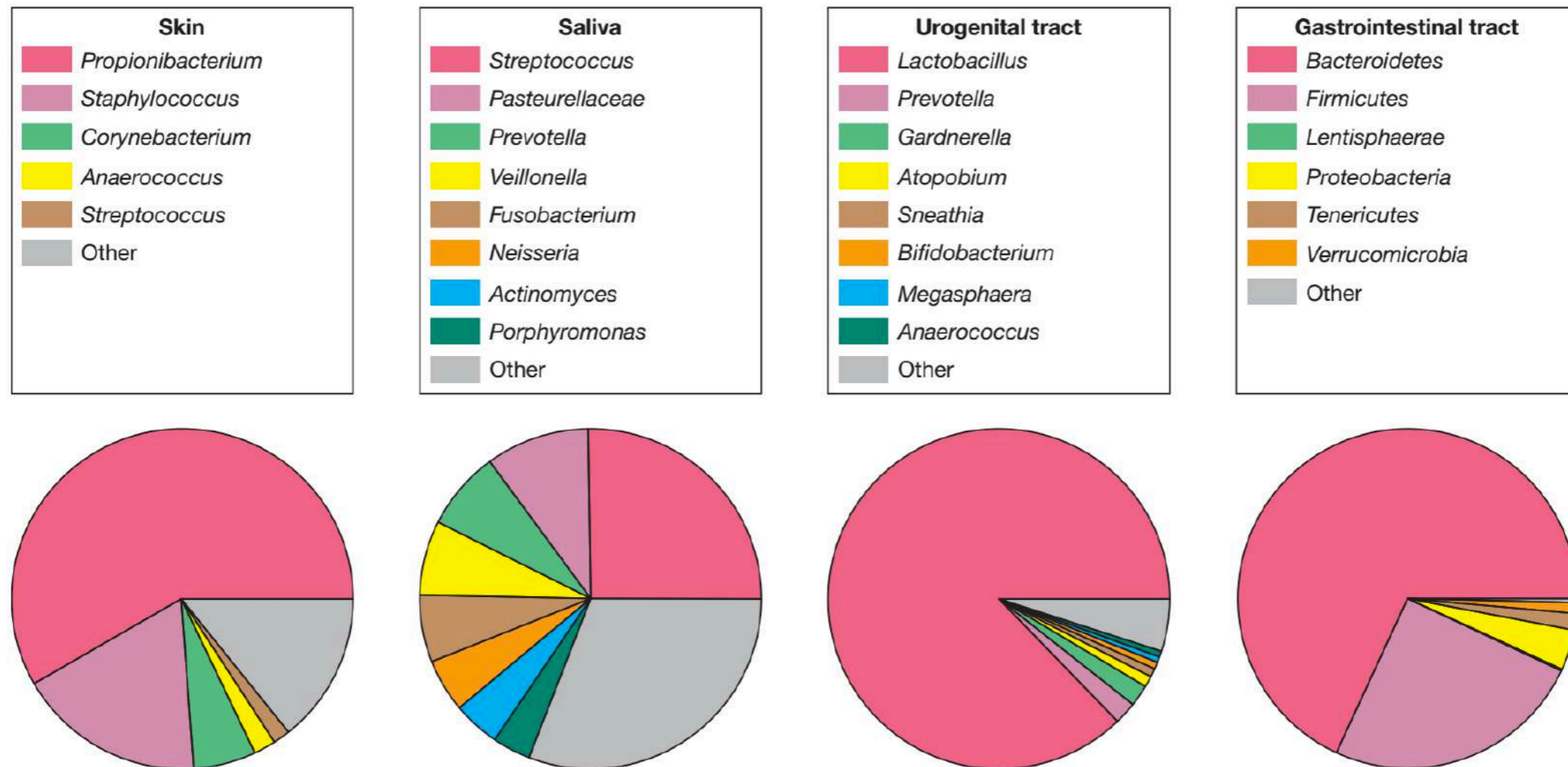


6) Complex Taxonomy



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

Human-microbes interactions

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

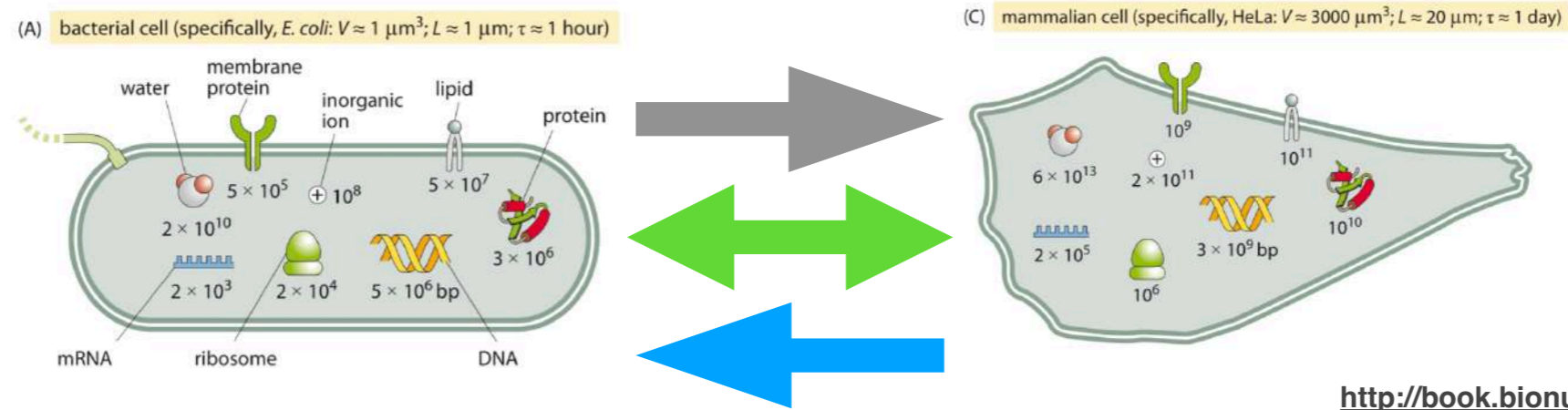
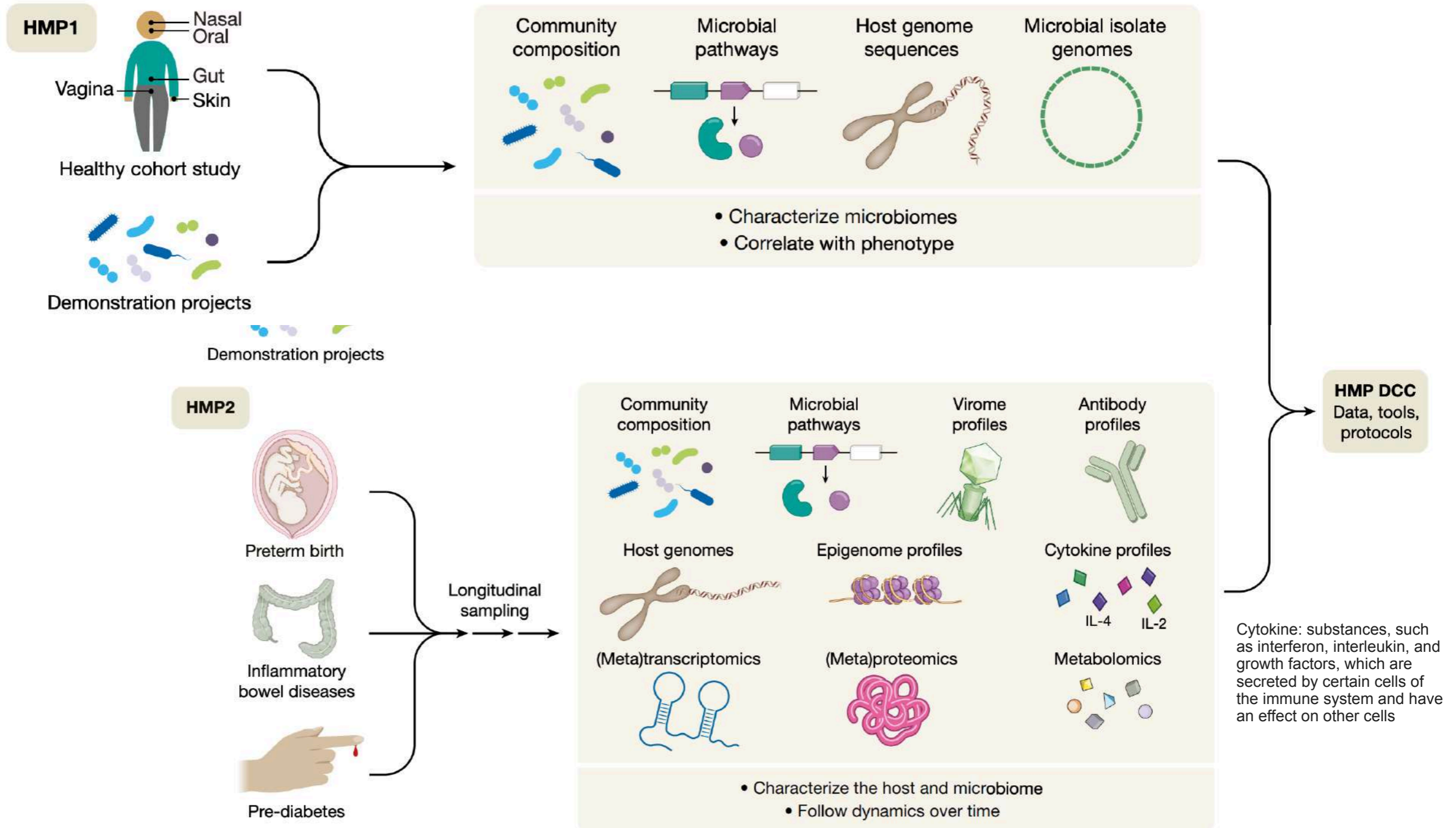


TABLE 24.1 Major human microbiome research programs

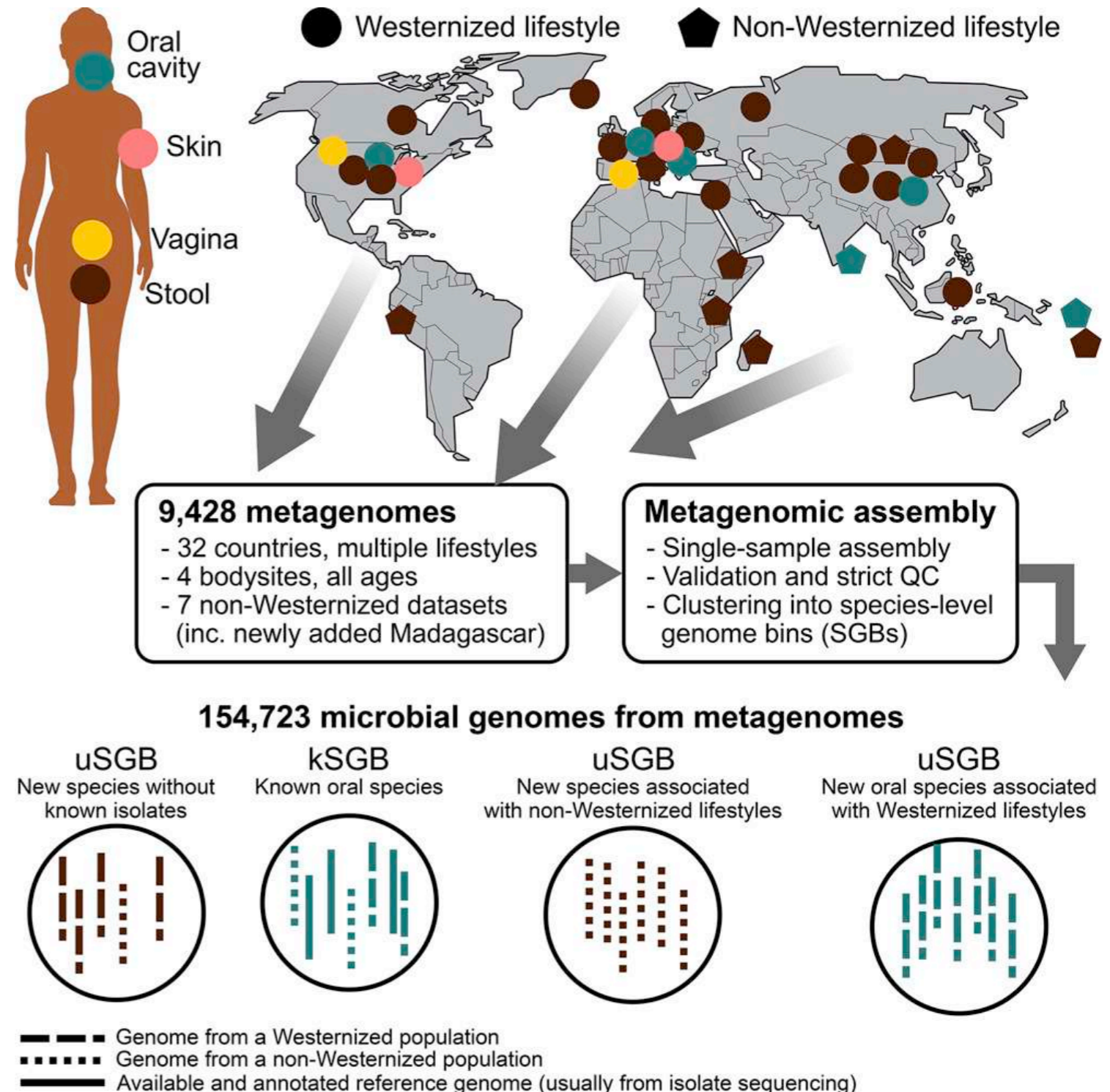
Research program	Participating countries	Programmatic objectives
MetaGenoPolis	France	Demonstrate the impact of the human gut microbiota on health and disease using metagenomics technology
International Human Microbiome Standards	European Commission	Optimize methods for the assessment of the effects 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

HMP 1 & HMP 2



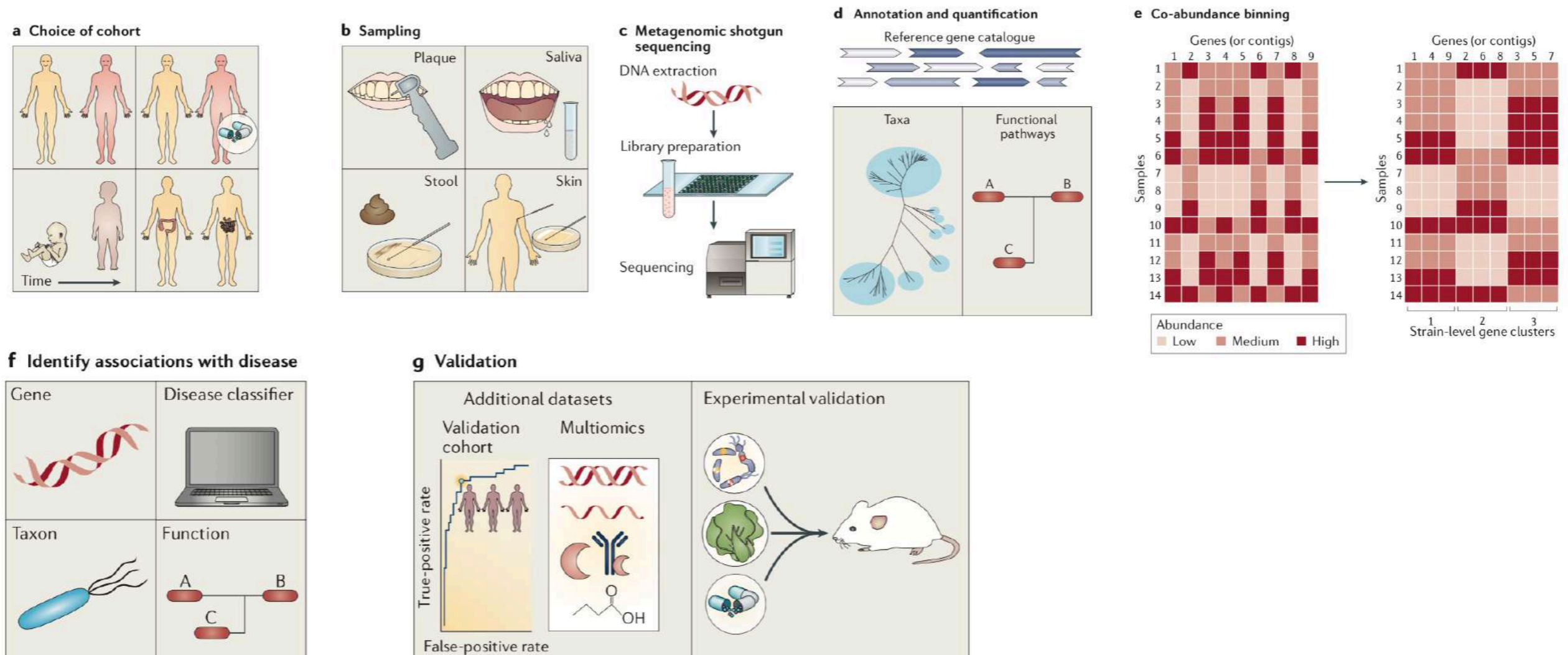
Exploring international microbiomes

- 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



Metagenome-wide association studies

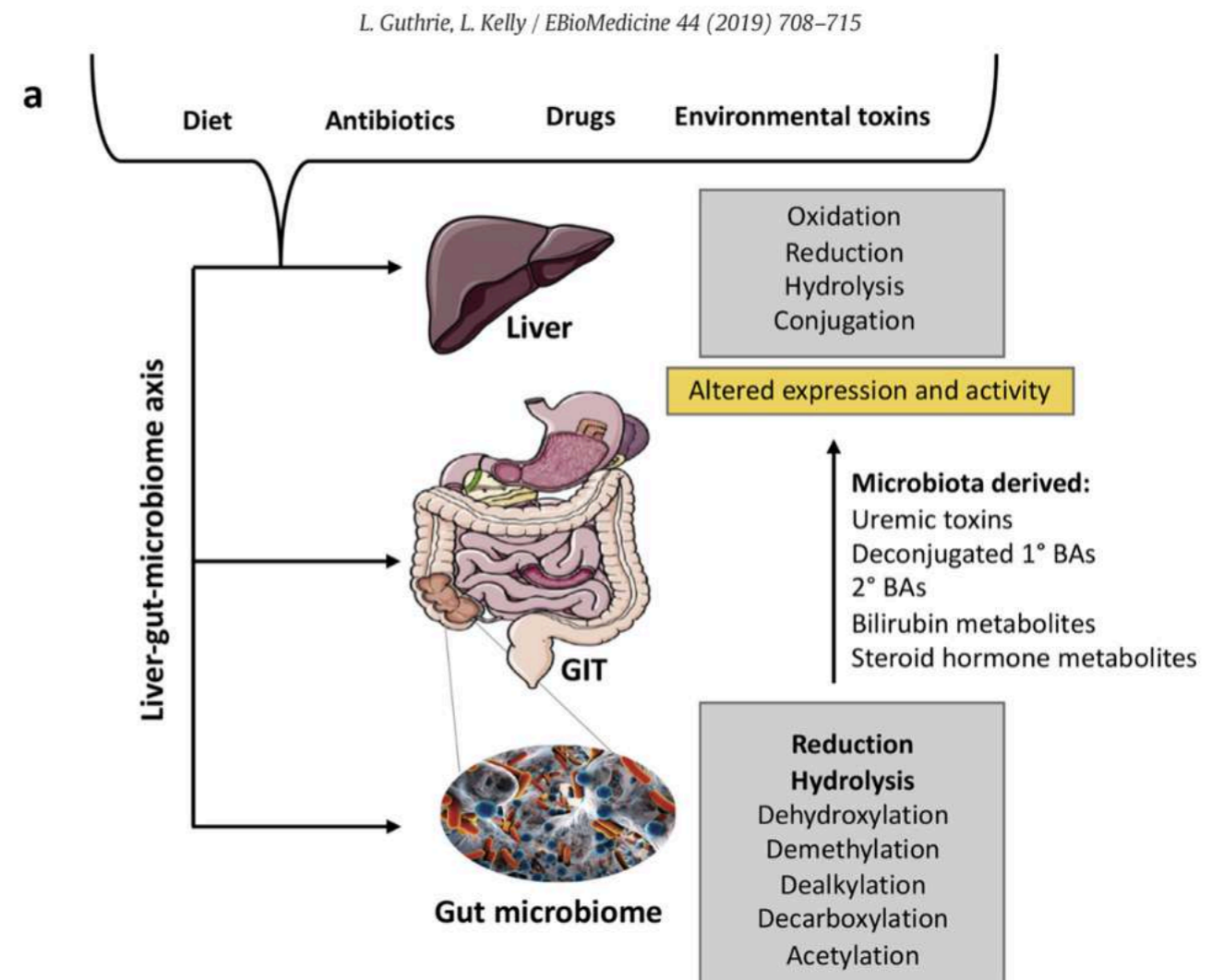
Wang & Jia, 2016



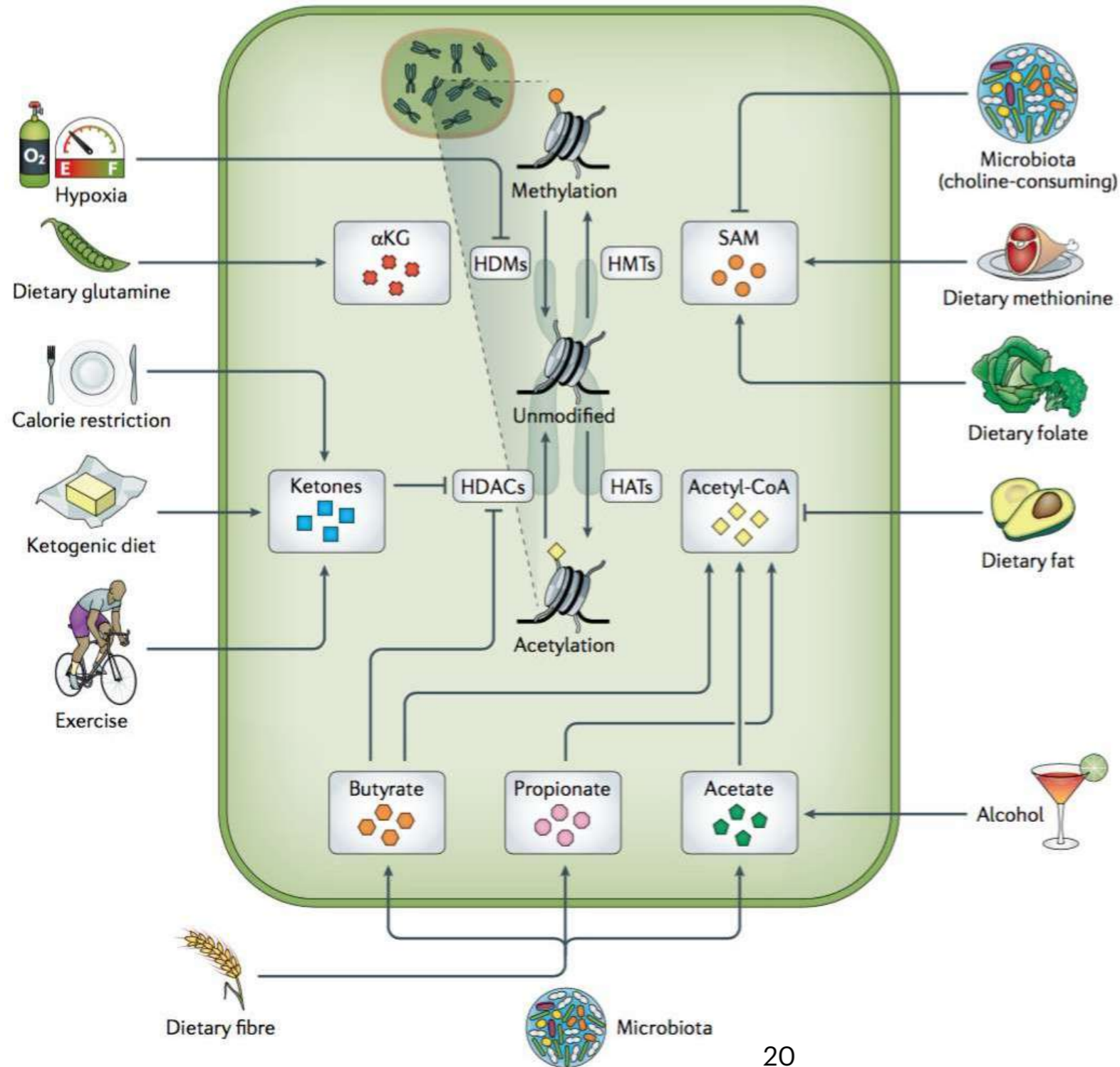
- Sufficient, extensive, sequence data
- High-resolution investigation of association human microbiome and several complex diseases, including type 2 diabetes, obesity, liver cirrhosis, colorectal cancer and rheumatoid arthritis
- Dysbiosis: Imbalance of the microbiota at a body site that is caused by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



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)

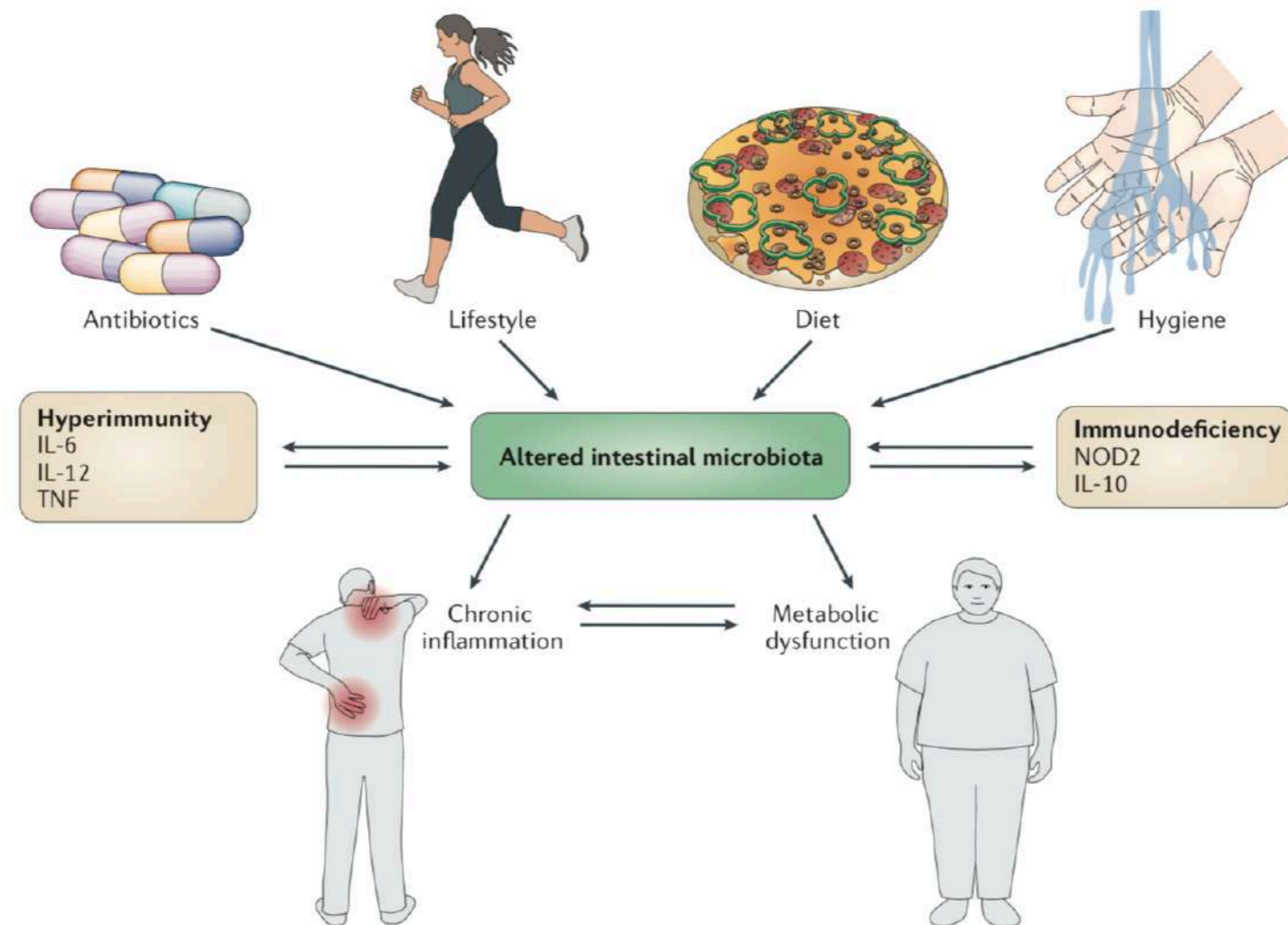
The activity of histone demethylases (**HDMs**) is supported by α -ketoglutarate (α KG), which can be derived from dietary glutamine, and is inhibited by the limited oxygen availability during hypoxia

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)

Box 1 | The epigenomes of eukaryotes and bacteria

- In eukaryotes, epigenetic modification of the genome involves DNA methylation³ and histone modification⁴. Bacteria lack histones, and epigenetic control relies on DNA methylation only⁶.
- In eukaryotes, de novo and maintenance forms of DNA methylation are performed by separate enzymes². Bacterial DNA methyltransferases have both de novo and maintenance activities³⁷.
- 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 replication³⁵. In bacteria, DNA demethylation is usually passive⁶⁶, and the relevance of active demethylation by DNA repair remains to be evaluated⁸².
- 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^{5,7,72,89,90,94,158}.
- The methylated base typically involved in the control of eukaryotic transcription is C⁵-methyl-cytosine³, whereas in bacteria it is often N⁶-methyl-adenine^{7,14}. However, direct control of bacterial transcription by C⁵-methyl-cytosine has been demonstrated recently¹²⁶. Transcriptional control by N⁴-methyl-cytosine may also exist¹³⁰.
- In multicellular eukaryotes, the DNA methylation pattern of the genome is reprogrammed during gametogenesis and during early embryonic development². 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 genes⁴¹ 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

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 ₂ S, 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

^aCapacity for amino acid biosynthesis inferred from the identification of biochemical pathways encoded in gut metagenomic sequences (see 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	<i>Ruminococcus gnavus</i>	Antibiotic
RiPP ^a (bacteriocin)	Ruminococcin C	<i>Ruminococcus gnavus</i>	Antibiotic
Amino acid metabolite	Indolepropionic acid	<i>Clostridium sporogenes</i>	Protective anti-oxidant
Amino acid metabolite	4-Ethylphenylsulfate	Undefined	Neuromodulatory
Amino acid metabolite	Tryptamine	<i>Ruminococcus gnavus</i>	Neurotransmitter
Volatile fatty acid	Propionic acid	<i>Bacteroides</i> spp.	Immunomodulatory ^b
Oligosaccharide	Polysaccharide A	<i>B. fragilis</i>	Immunomodulatory ^b

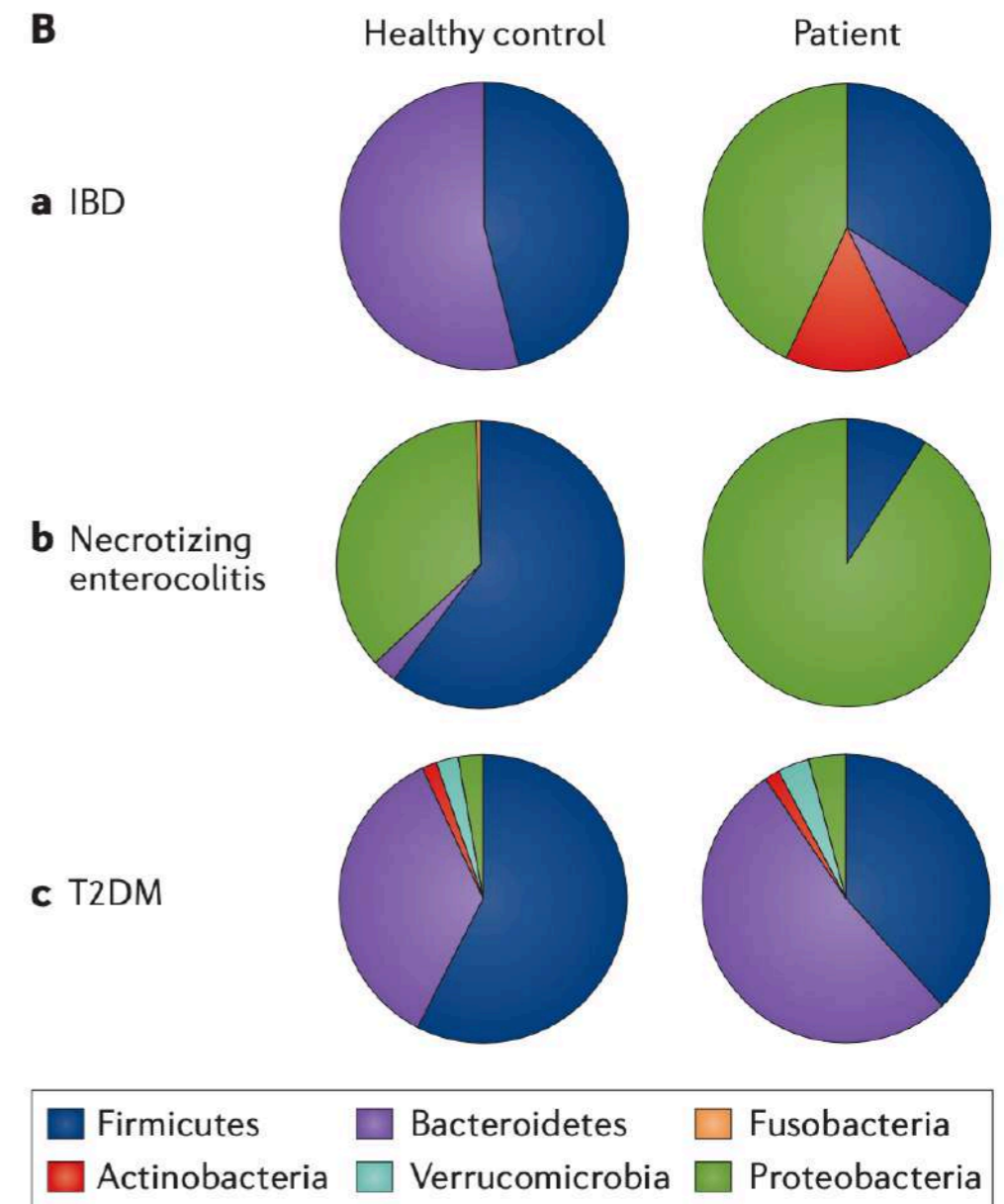
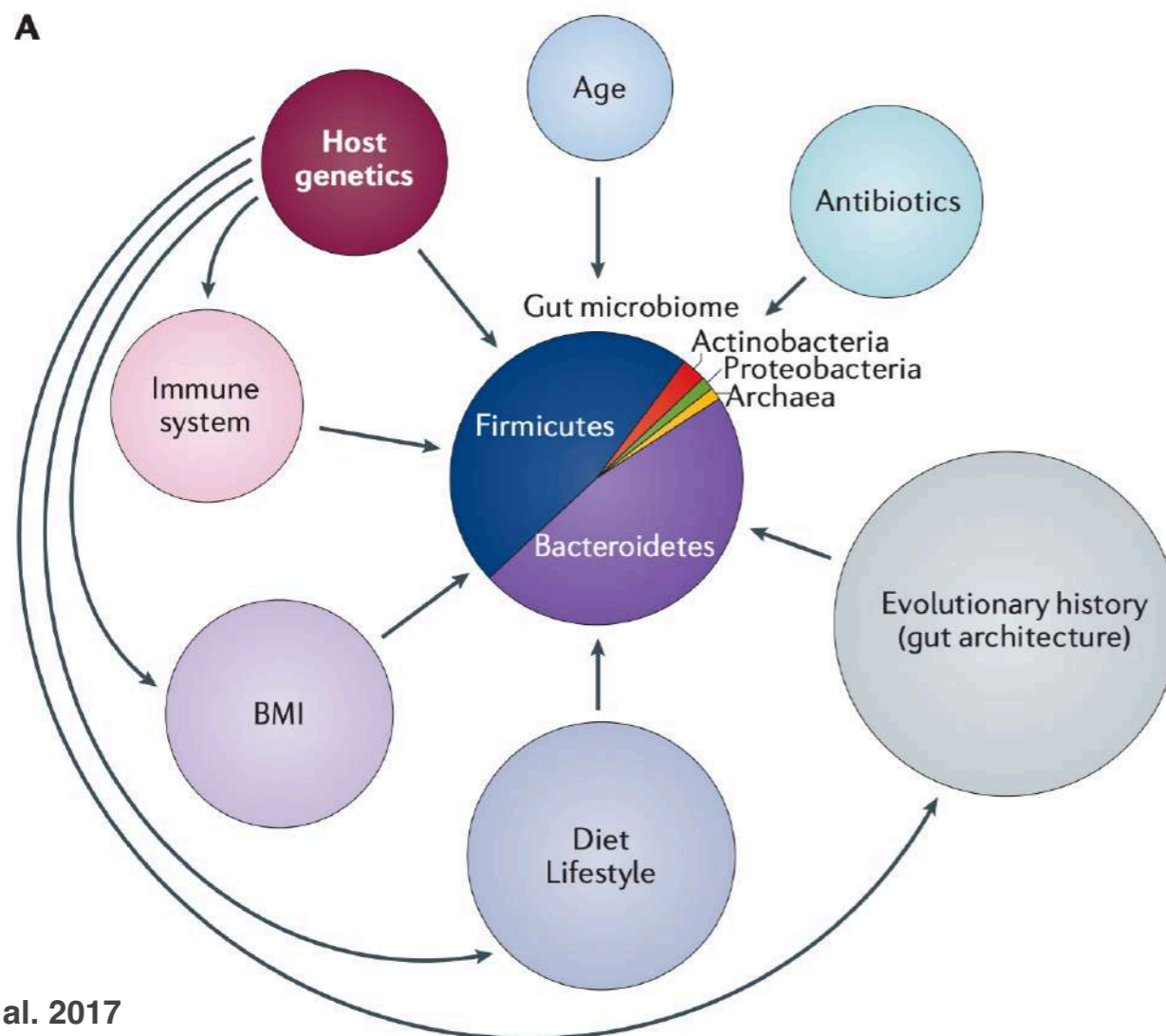
^aRibosomally synthesized and post-translationally modified peptides.

^bThese small molecules promote colonization by normal microbiota.

Gut as a second brain

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)



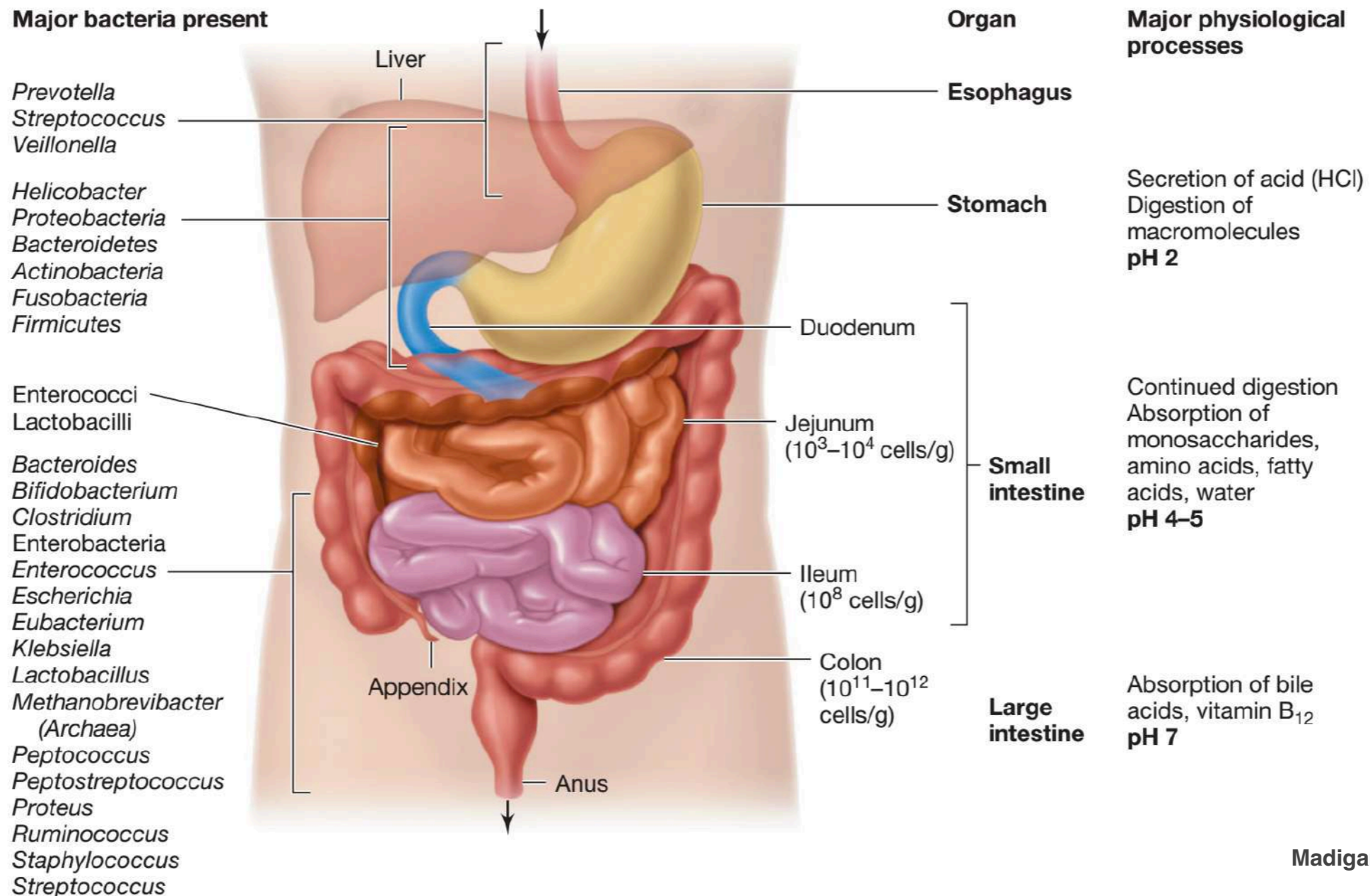
Gut-microbes association

Changing in space and time

Changing with age host

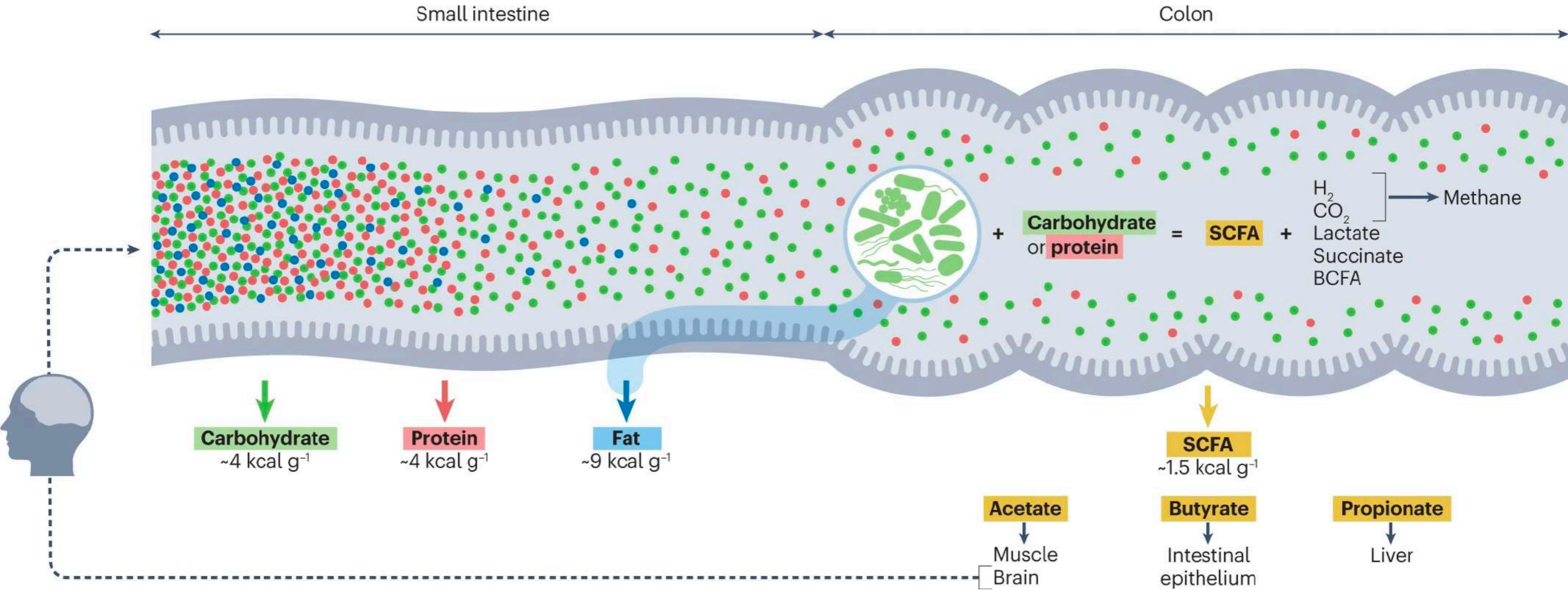
Changing with food ingested and drugs

Ever-changing microbial communities and abundance



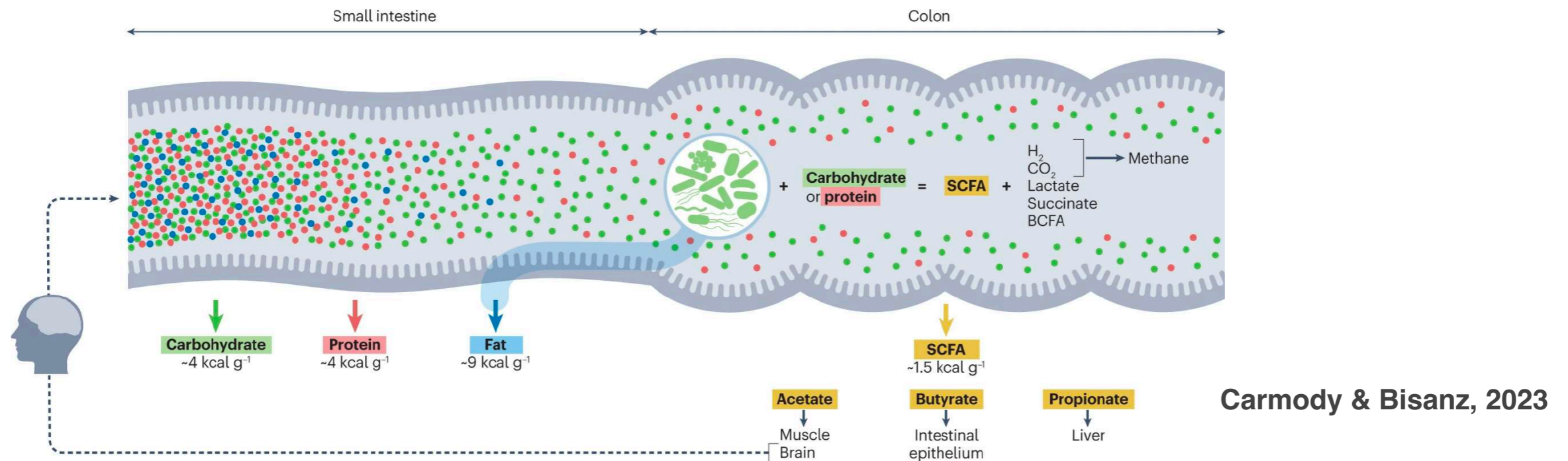
Madigan et al. 2018

Gut microbiome enhances dietary energy harvest



Carmody & Bisanz, 2023

Gut microbiome enhances dietary energy harvest



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

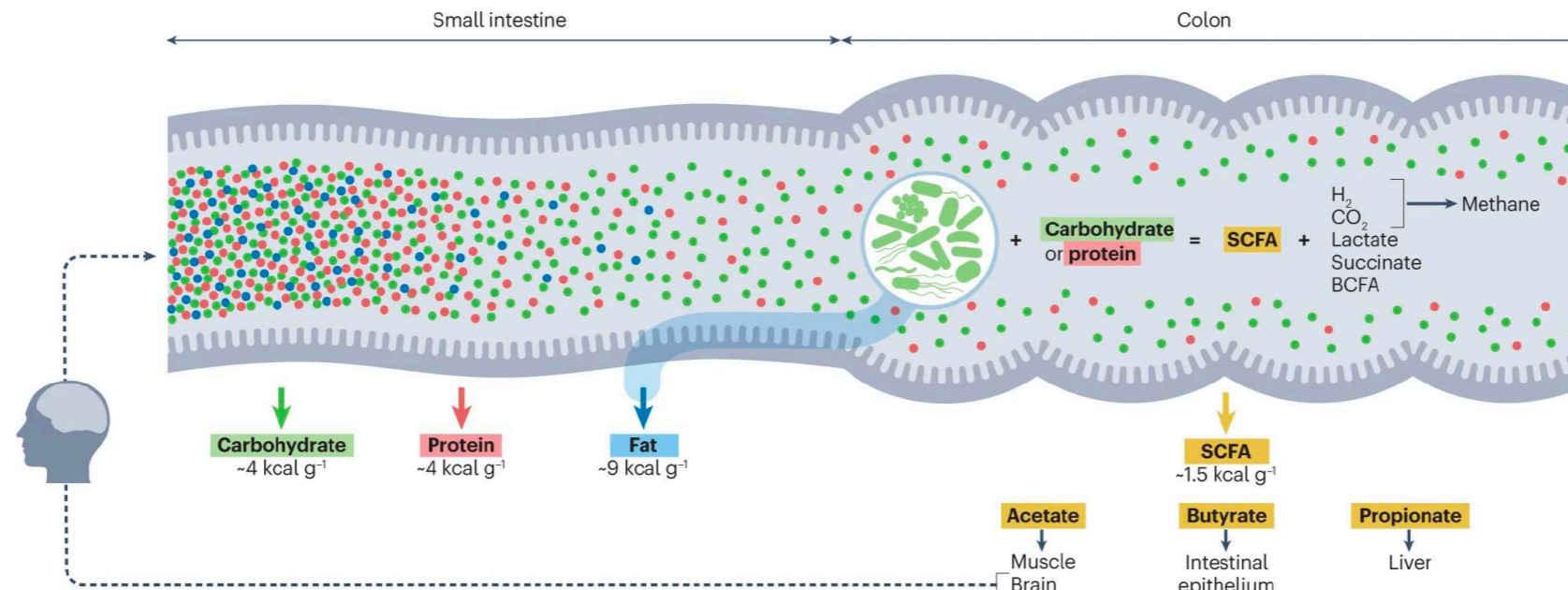
The fractions of carbohydrate and protein digested in the small intestine vary with macronutrient structural form (for example, higher for sugar versus fibre), meal composition (for example, higher for fibre-poor versus fibre-rich meals), thermal processing (for example, higher for cooked foods) and 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

Carmody & Bisanz, 2023



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

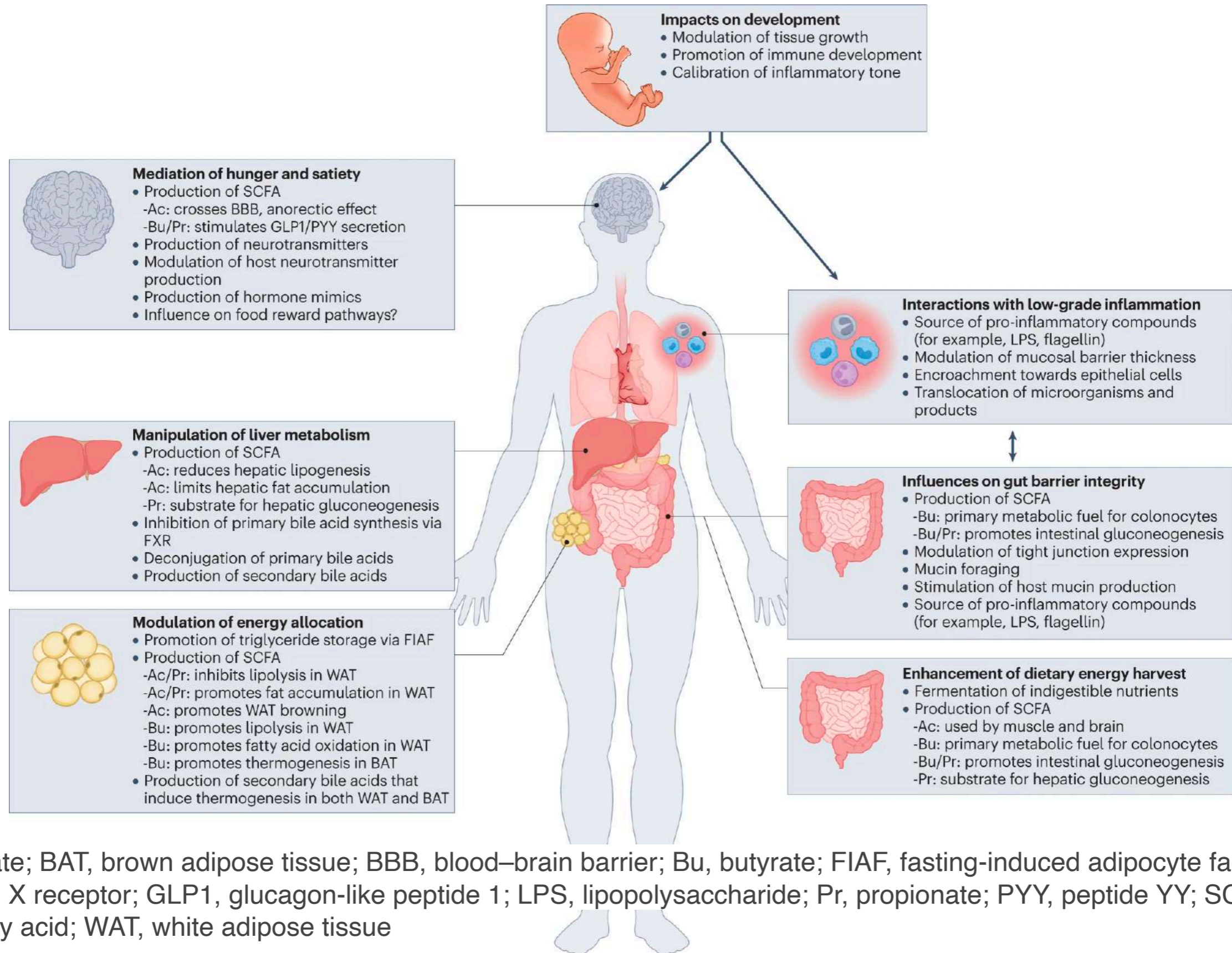
SCFAs account for ~5–10% of daily energy requirements in industrialized populations and almost certainly a >> fraction in populations with minimally processed and/or fibre-rich diets

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

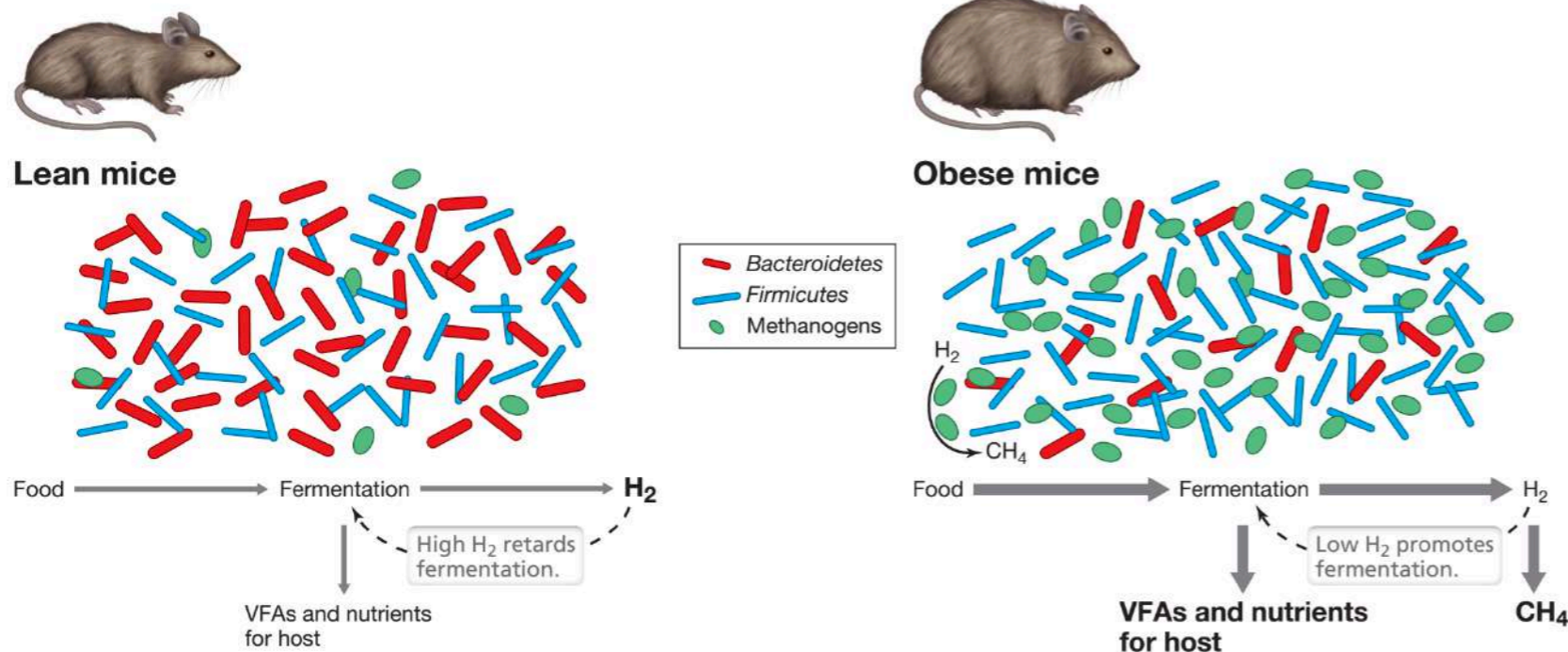
Carmody & Bisanz, 2023



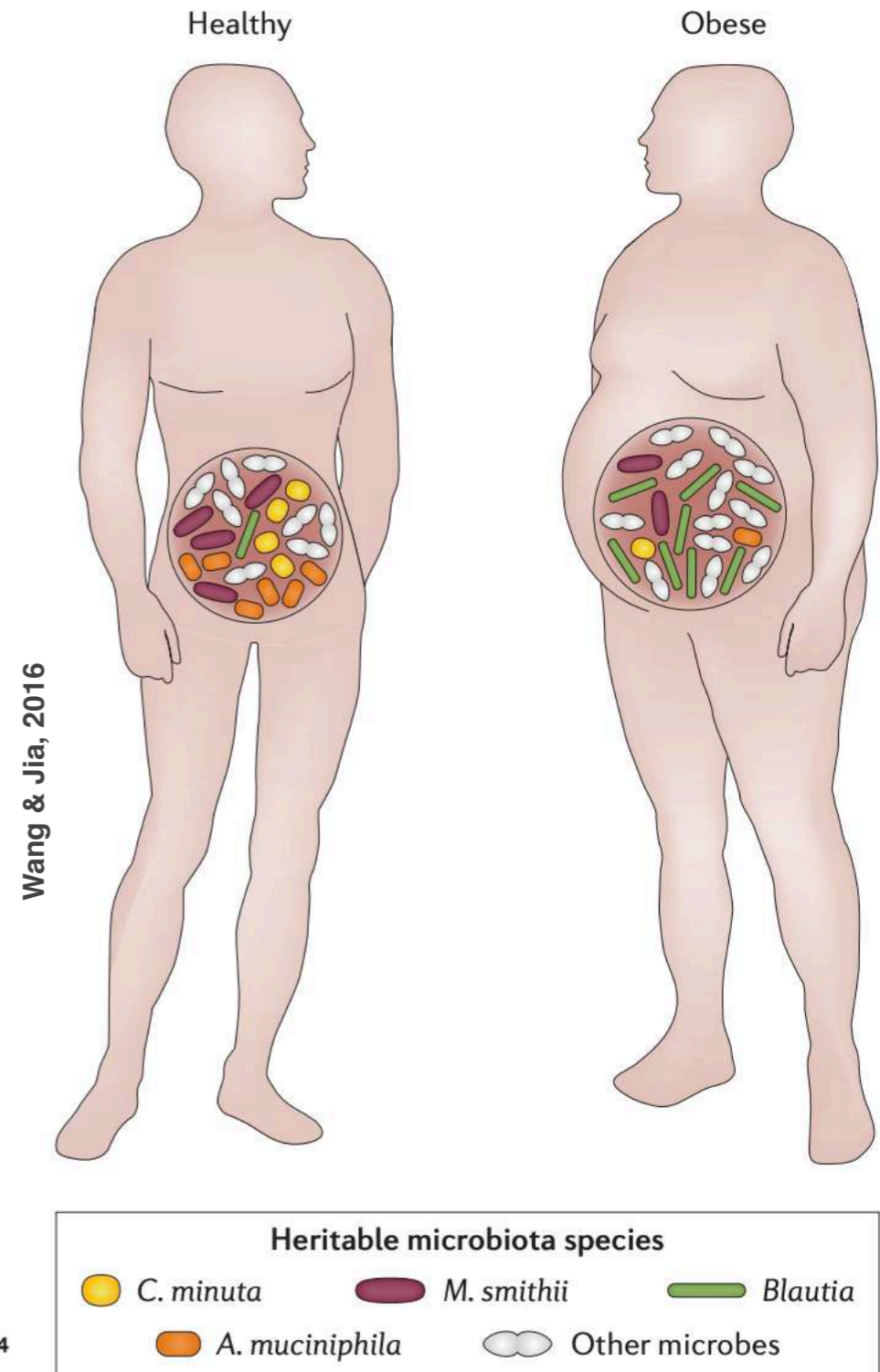
Ac, acetate; BAT, brown adipose tissue; BBB, blood–brain barrier; Bu, butyrate; FIAF, fasting-induced adipocyte factor; FXR, farnesoid X receptor; GLP1, glucagon-like peptide 1; LPS, lipopolysaccharide; Pr, propionate; PYY, peptide YY; SCFA, short-chain fatty acid; WAT, white adipose tissue

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

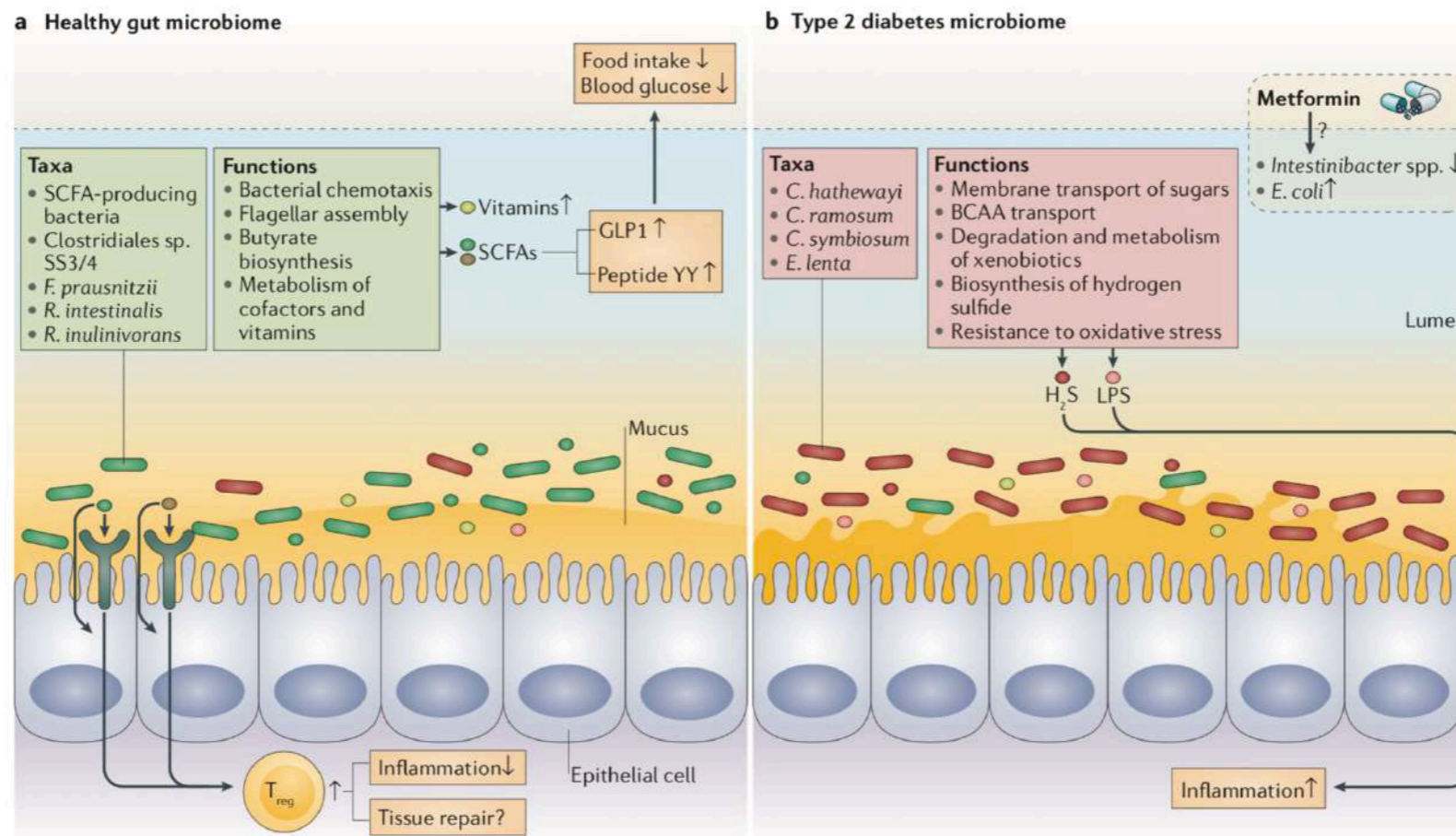


Madigan et al. 2018



Gut-microbiome- type 2 diabetes association

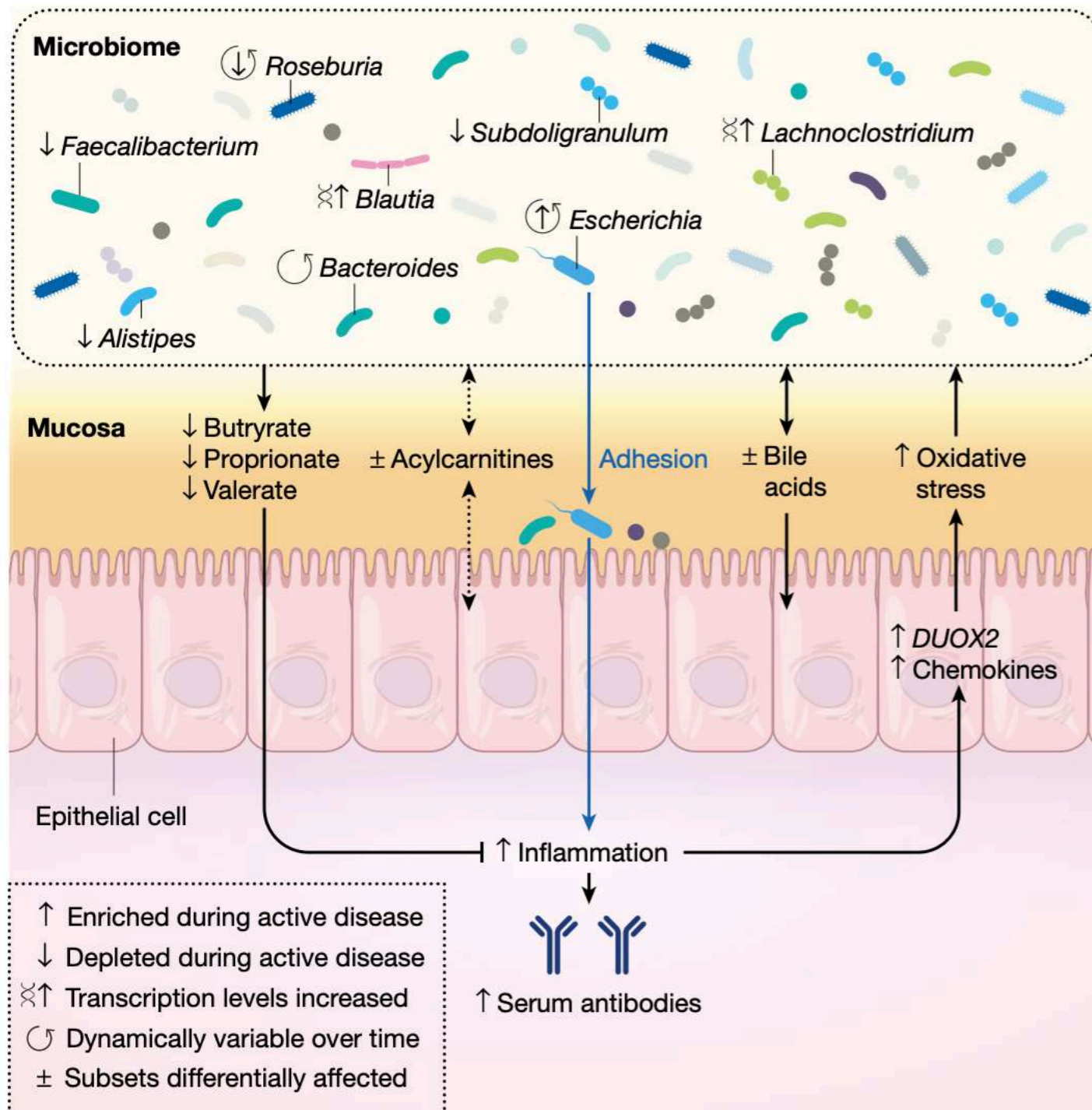
- **Healthy** individuals: gut microbiome enriched for taxa with increased capacity for **short-chain fatty acids (SCFAs)** production—> **intestinal integrity, energy homeostasis, signalling through host receptors to induce regulatory T cells, which restricts inflammation may even promote tissue repair**
- 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*

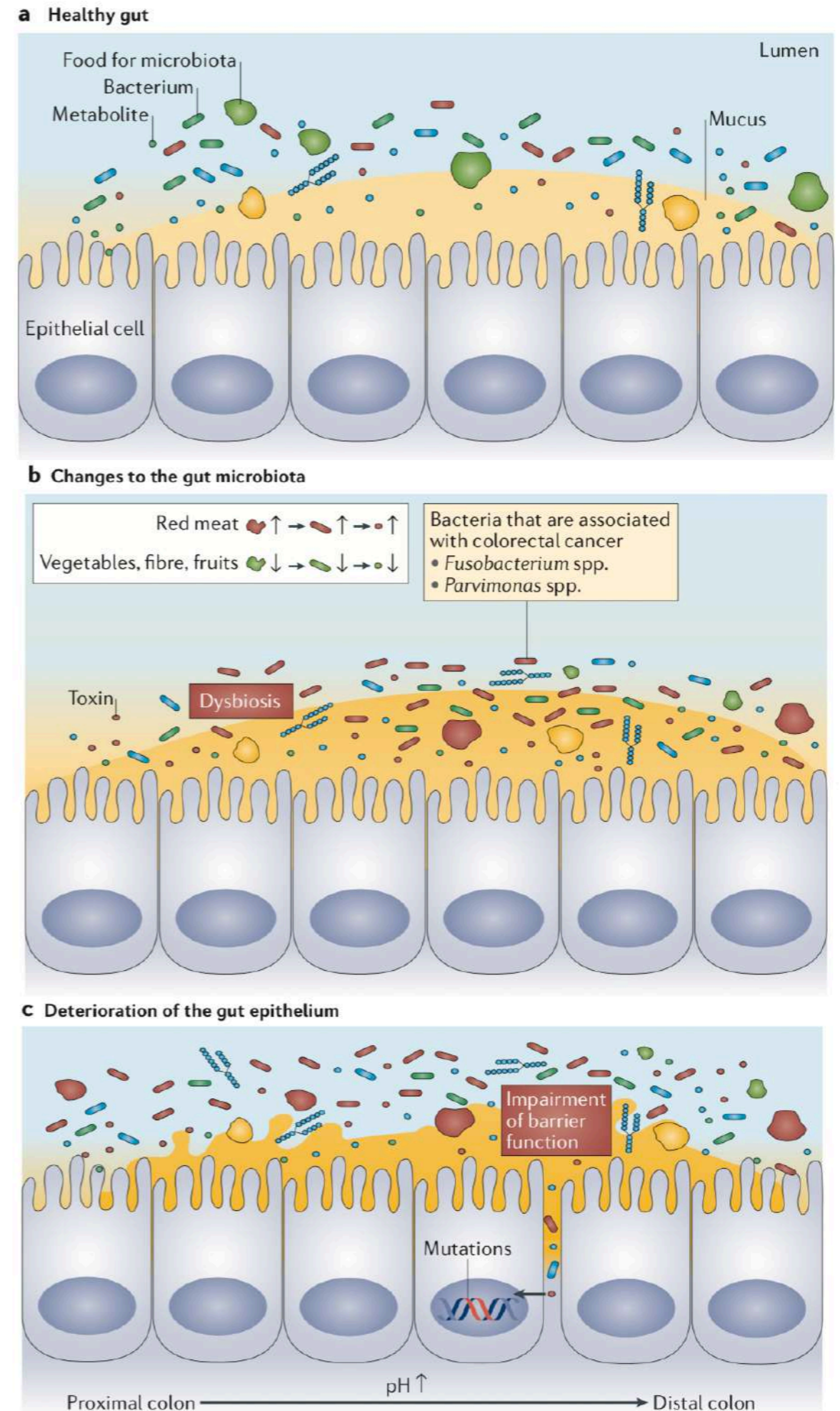
Host-microbiome dynamics in IBD



- 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

Dysbiosis in 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

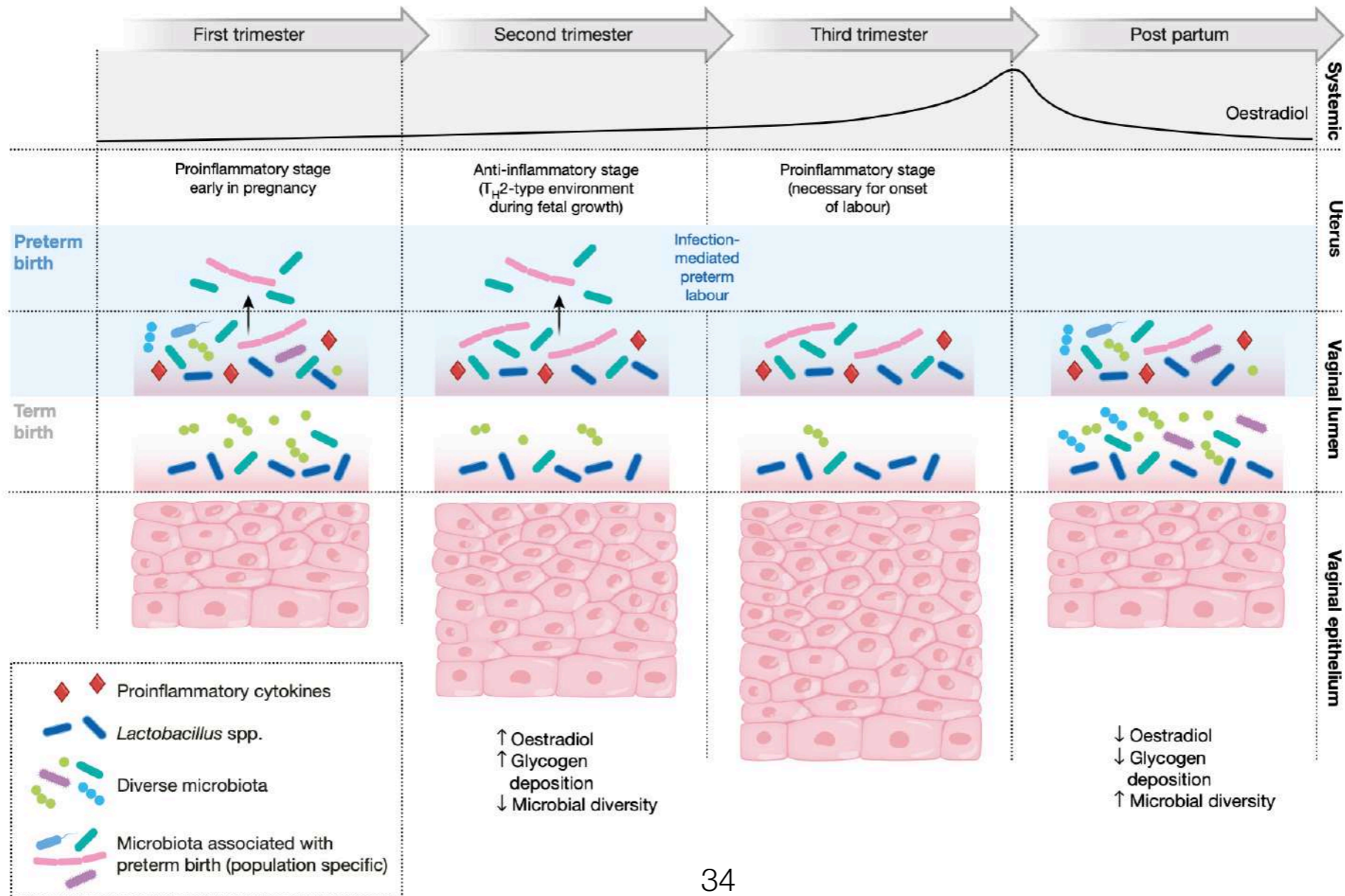


Vaginal microbiome in pregnancy and preterm birth

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**

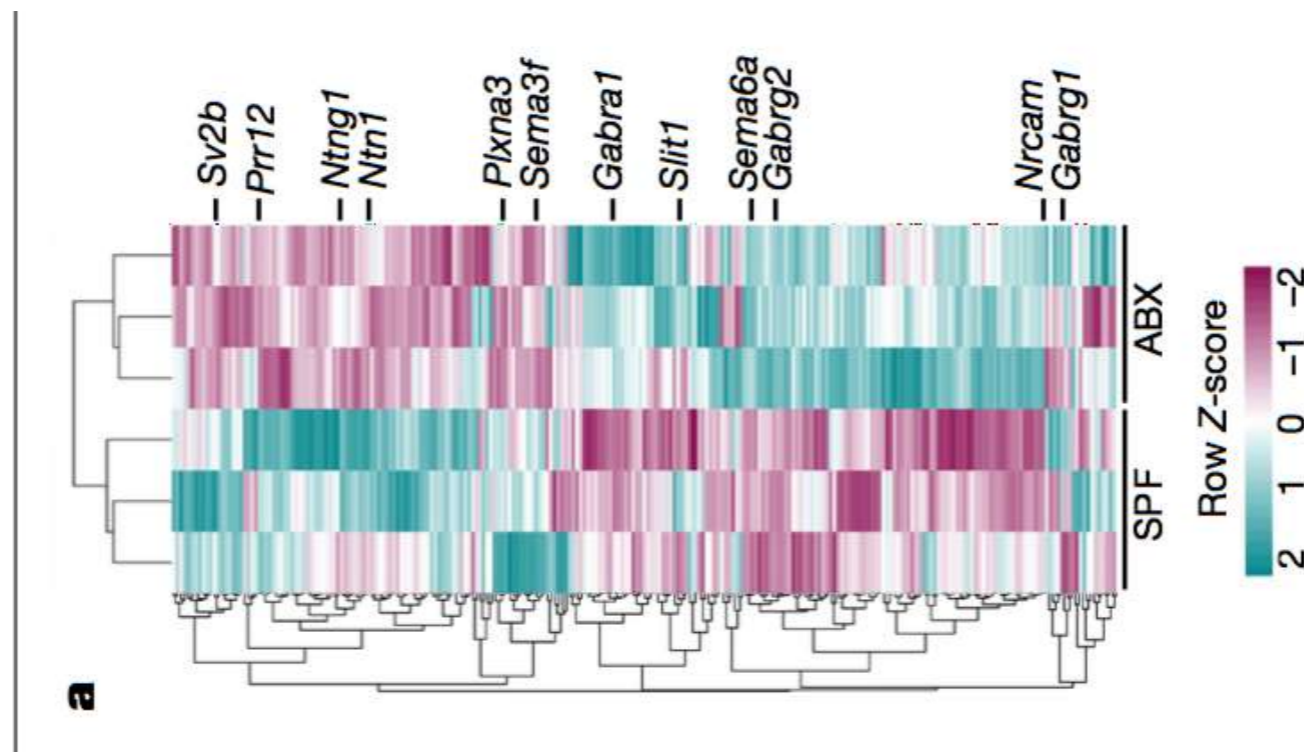
Specific changes in the microbiome of the vaginal lumen can be associated with preterm birth, possibly through mechanisms involving microorganisms traveling from the vagina to the uterus



The maternal microbiome modulates fetal neurodevelopment in mice

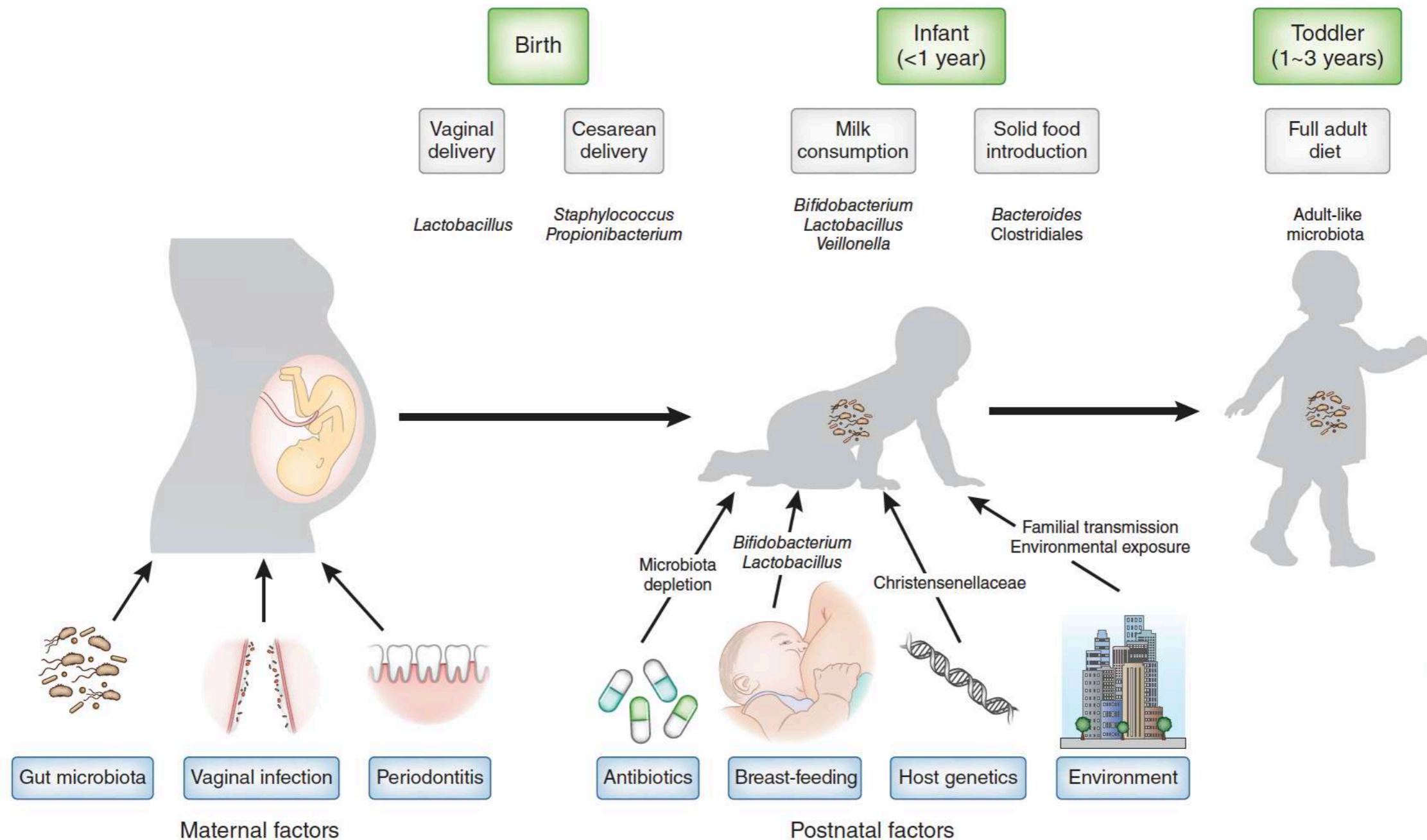
‘Dysbiosis’ of the maternal gut microbiome, in response to challenges such as infection, altered diet and stress during pregnancy, has been increasingly associated with abnormalities in brain function and behaviour of the offspring

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



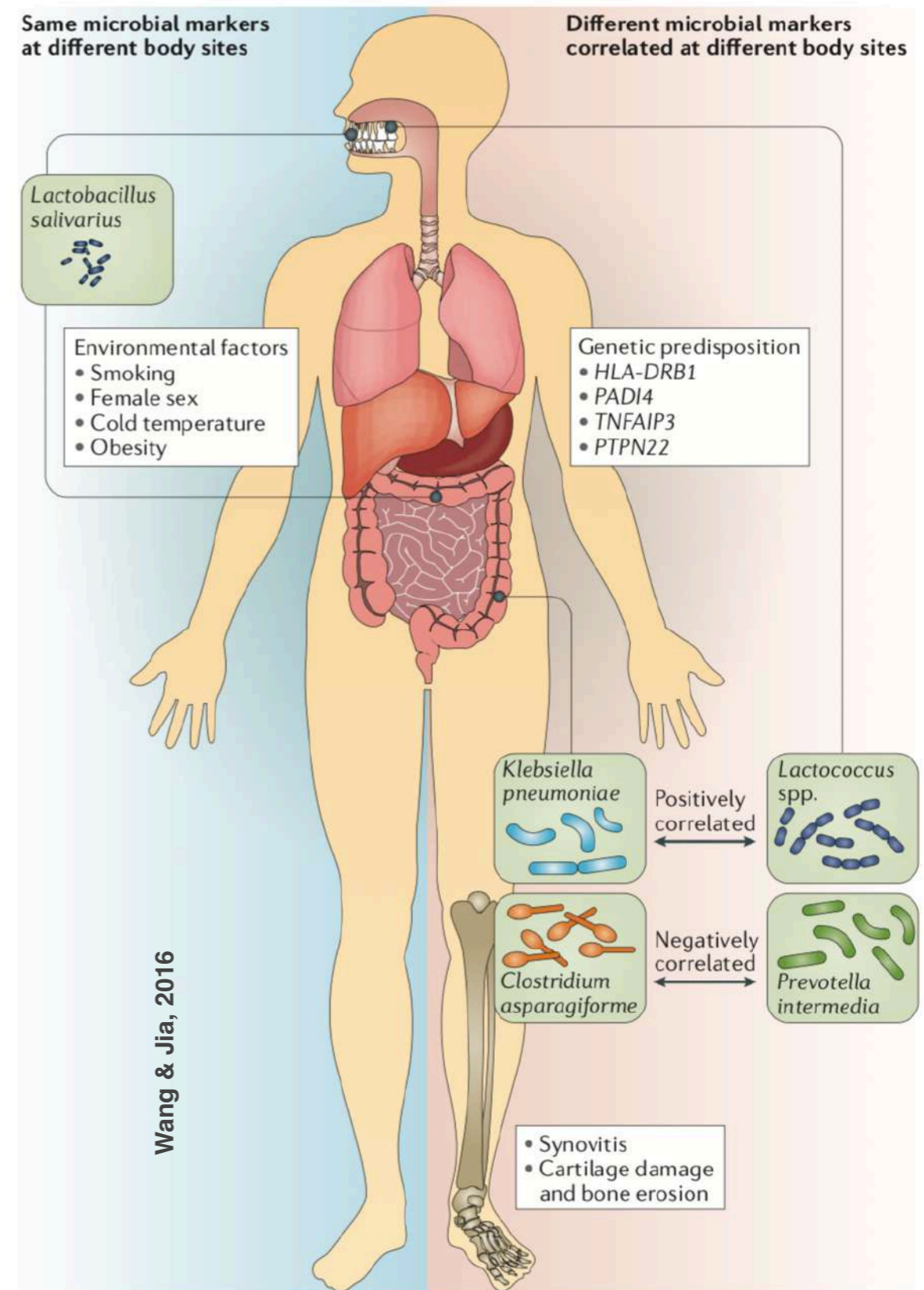
SPF: specific-pathogen-free

Factors shaping the neonatal microbiome



Microbial interplay within human ecosystems

- The **oral** and **gut** microbiomes of individuals with **rheumatoid arthritis**
- Microbiome might interact with both **genetic and environmental factors** that influence the risk of developing rheumatoid arthritis
- **Overlap** between **oral** and **gut** the microbiomes → enrichment of several bacterial species, including *Lactobacillus salivarius*, at both sites
- Sets of **bacterial species correlated** changes in abundance between the oral and gut microbiomes of individuals with rheumatoid arthritis

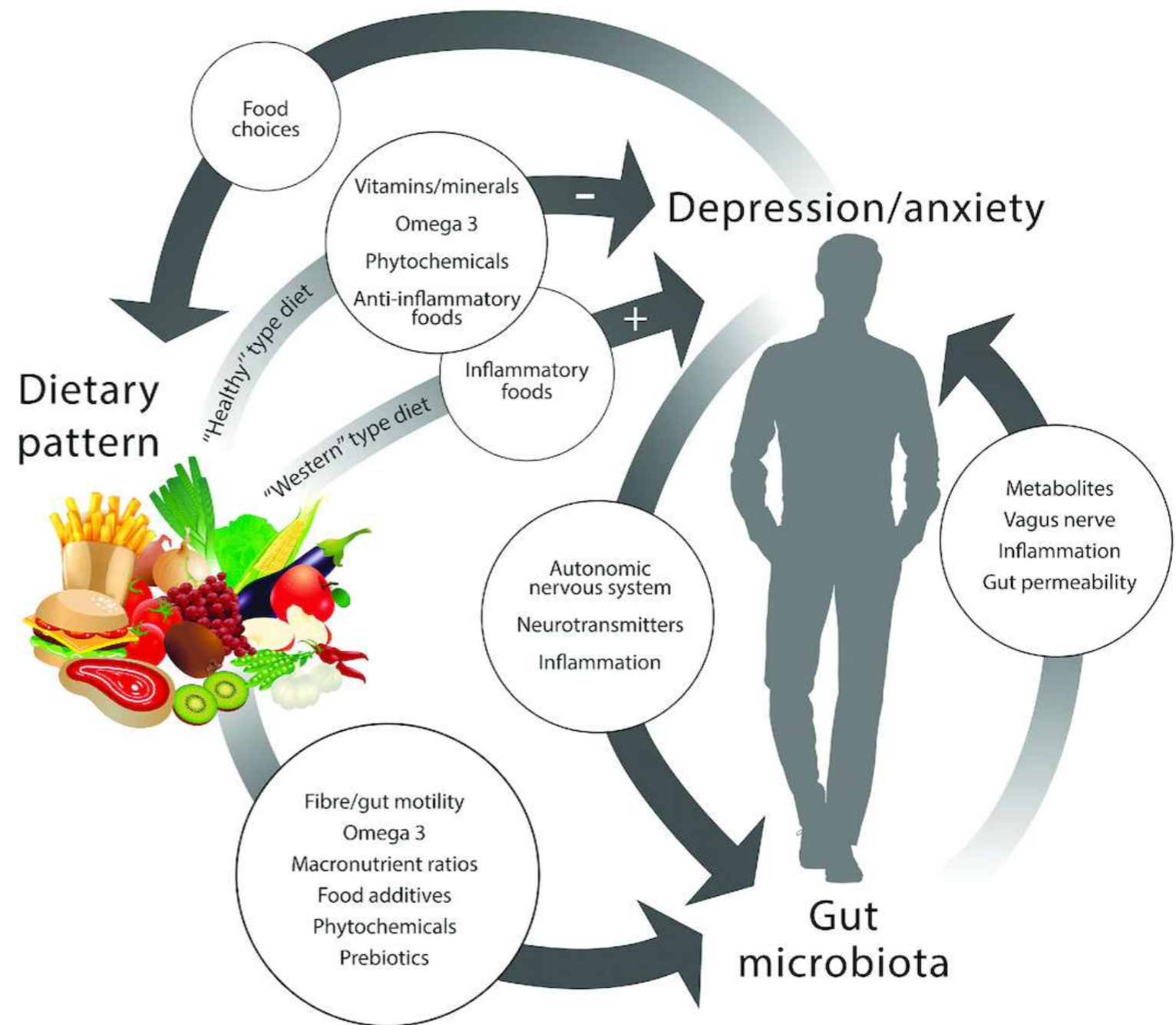


Representative studies linking human conditions to the microbiome

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 <i>Prevotella copri</i> and <i>Akkermansia muciniphila</i>	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, <i>Coriobacteriaceae</i> , <i>Faecalibacterium prausnitzii</i> ; higher abundance of <i>Actinomyces</i> , <i>Veillonella</i> , <i>Escherichia coli</i>	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	<i>Ruminococcus gnavus</i> and Lachnospiraceae are more abundant, <i>Barnesiella intestinihominis</i> and <i>Coprococcus catus</i> 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 <i>Fusobacterium nucleatum</i> 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

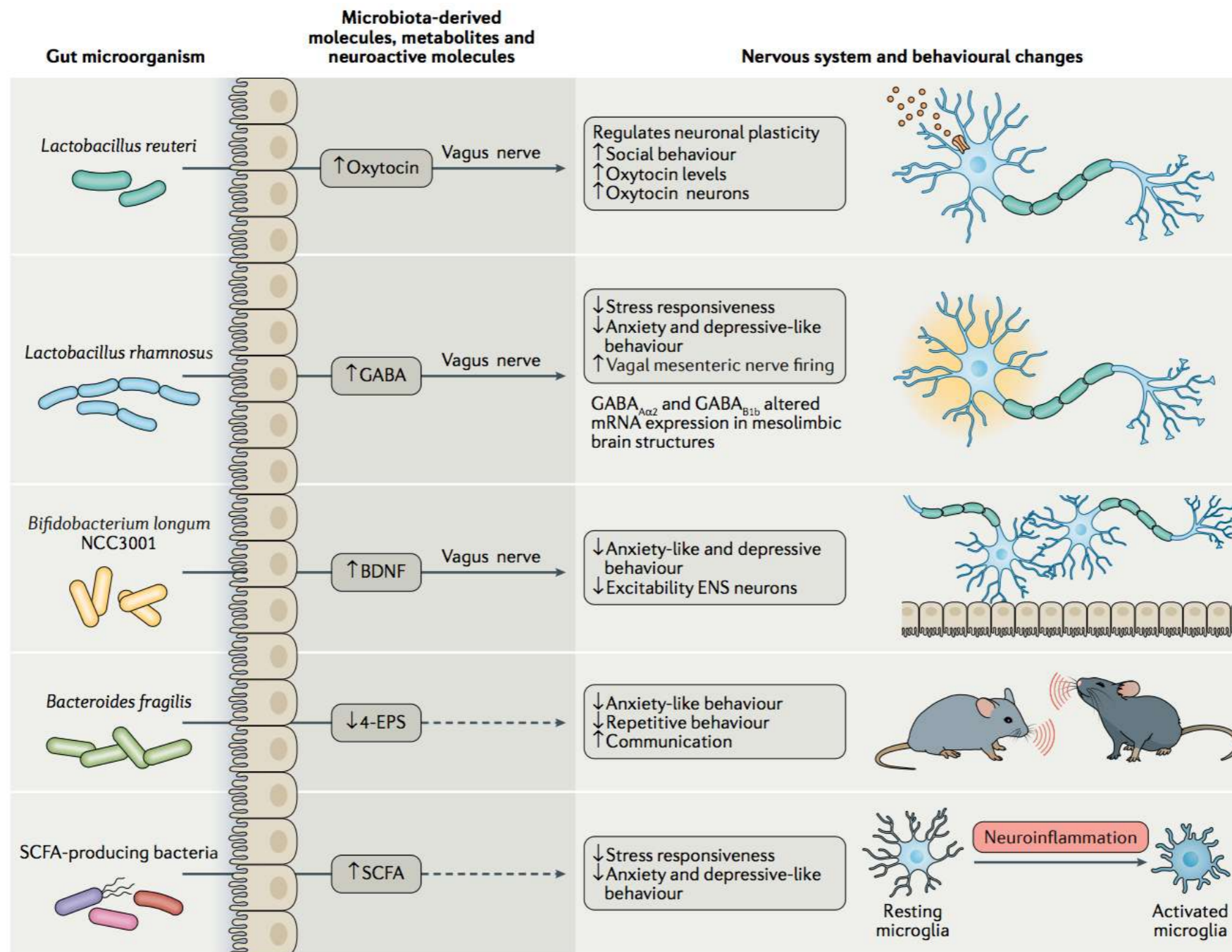
Gut-Brain Axis

- “**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**



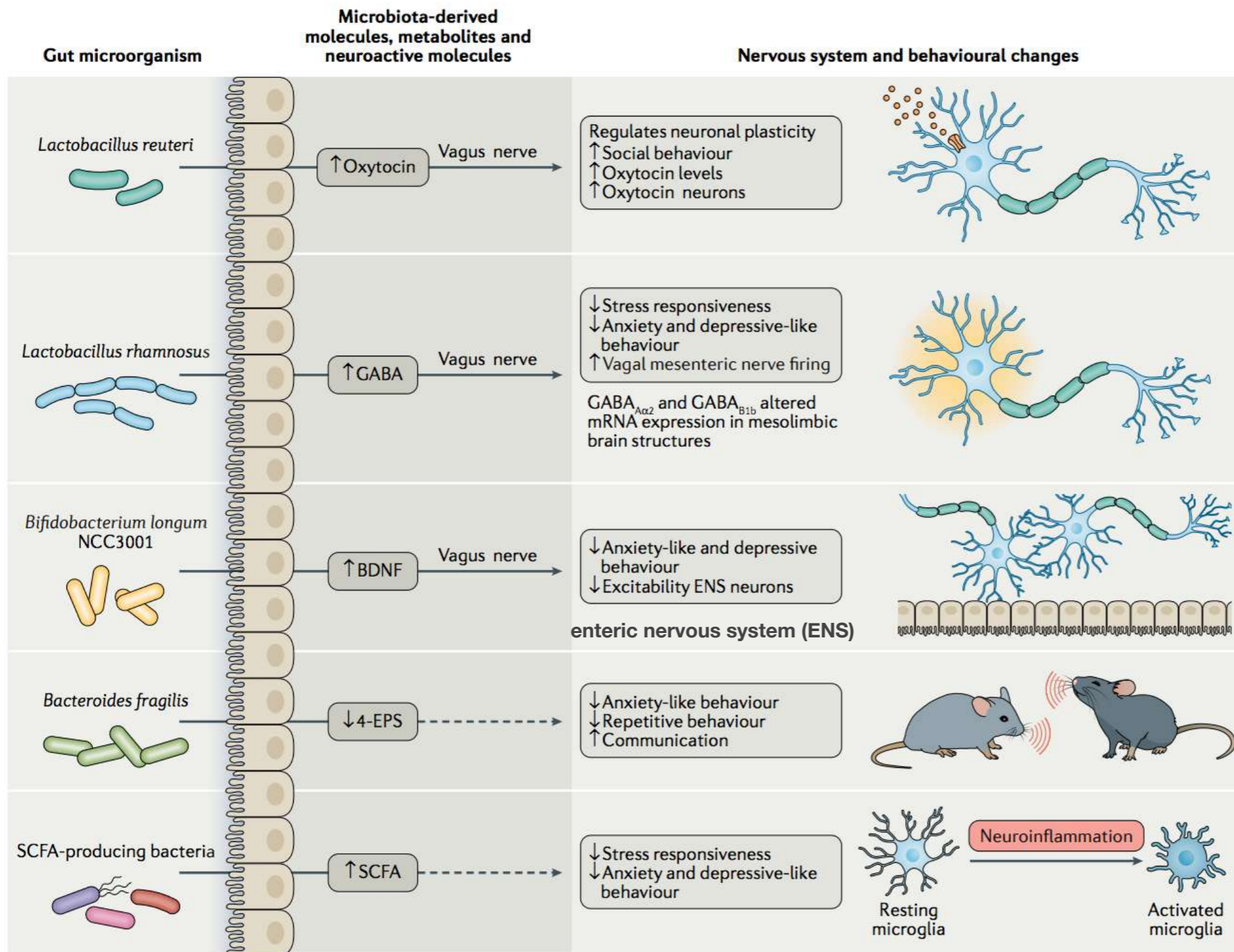
Microbiota and microbial-derived molecules modulate host behaviour and nervous system function

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)

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 microbiota¹

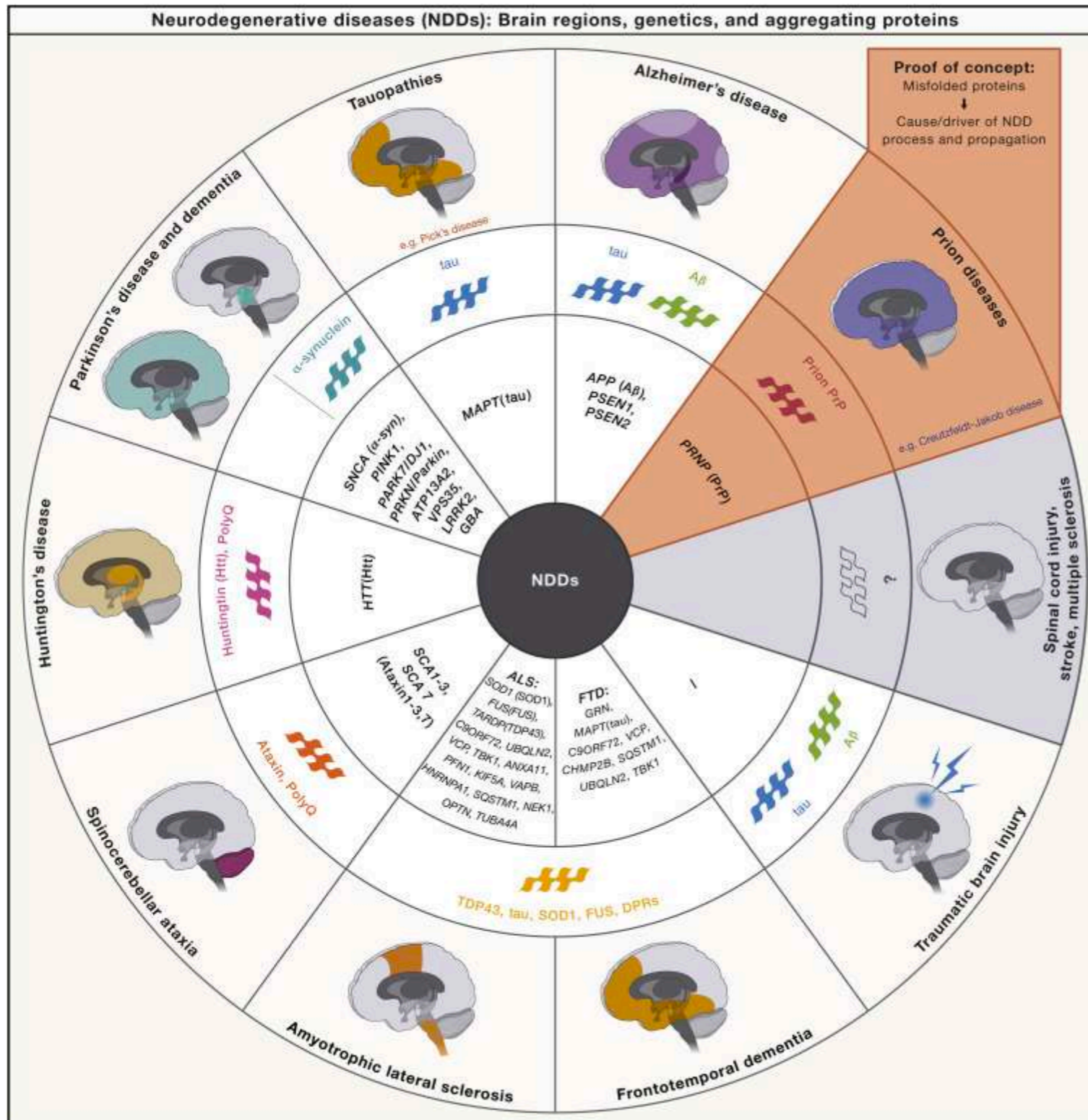
Dietary component	Effect	Summary	Subject	Ref.
Phytochemicals Cocoa polyphenols	Affected mood	In an RCT in adults, 500 mg supplement for 30 d increased self-rated calmness and contentedness compared with placebo.	Human	Pase et al. (183)
	Altered microbial growth	A 6-wk diet with 10% cocoa in rats caused a decrease in <i>Bacteroides</i> , <i>Clostridium</i> , and <i>Staphylococcus</i> 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 <i>Bifidobacteria</i> , <i>Lactobacilli</i> , and butyrate was found.	In vitro	Fogliano et al. (185)
Blueberry extract (anthocyanins)	Altered immune function	A 6-wk diet with 10% cocoa in rats caused an altered toll-like receptor pattern and increased gastrointestinal immunoglobulin A secretion.	Animal	Massot-Cladera et al. (184)
	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)
	Altered host metabolites	A 5% blueberry drink given to rats for 8 wk protected against cognitive impairment during chronic mild stress.	Animal	Guo et al. (187)
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 <i>Lactobacillus rhamnosus</i> and also <i>Lactobacillus</i> 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 <i>Bifidobacterium</i> spp., <i>Lactobacillus Enterococcus</i> spp., <i>Clostridium coccooides</i> - <i>Eubacterium rectale</i> , and a decrease in <i>Bacteroides</i> spp., <i>Clostridium histolyticum</i> group, <i>Escherichia coli</i> , and <i>Desulfovibrio</i> 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 <i>Bifidobacterium</i> spp. and <i>Clostridium difficile</i> and increased <i>B. fragilis</i> .	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 <i>Lactobacillus</i> spp., and increased <i>Escherichia coli</i> . 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 <i>Fat-1</i> transgenic mice, which endogenously produce ω -3 fatty acids.	Animal	Kaliannan et al. (176)
	Increased endogenous antimicrobial defenses	<i>Fat-1</i> 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	<i>Fat-1</i> 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 <i>Bifidobacterium</i> , <i>Roseburia</i> , and <i>Lactobacillus</i> .	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 <i>Firmicutes</i> to <i>Bacteroidetes</i> in the offspring, along with altered behavior and immune function. 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.	Animal	Robertson et al. (178)

Dietary component	Effect	Summary	Subject	Ref.
High fat, particularly saturated fat	Altered microbiota composition	A high-fat diet in mice decreased <i>Ruminococcaceae</i> and increased <i>Rikenellaceae</i> compared with a carbohydrate diet.	Animal	Daniel et al. (199)
		Increase in <i>Firmicutes</i> , particularly the family <i>Erysipelotrichaceae</i> , and decrease in <i>Bacteroidetes</i> 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 <i>Firmicutes</i> , particularly the <i>Erysipelotrichi</i> class, <i>Bacilli</i> , and decreased <i>Bacteroidetes</i> .	Animal	Turnbaugh et al. (201)
		BALB/c mice fed a high-fat diet showed alterations in the gut microbiota including an increase in <i>Firmicutes</i> , particularly in the families <i>Ruminococcaceae</i> and <i>Lachnospiraceae</i> , a decrease in the <i>Bacteroidetes</i> phylum, and a resulting decrease in the ratio of <i>Bacteroidetes</i> to <i>Firmicutes</i> .	Animal	Pyndt Jørgensen et al. (202)
High-fat, high-sugar diet	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)
	Altered microbiota composition	A Western-style diet in humanized mice resulted in increased <i>Erysipelotrichi</i> class (mainly <i>Clostridium innocuum</i> , <i>Eubacterium dolichum</i> , and <i>Catenibacterium mitsuokai</i> genera) and <i>Bacilli</i> class (mainly <i>Enterococcus</i> 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 <i>Clostridium</i> spp. from the phylum <i>Firmicutes</i> .	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 nitroso 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, <i>Firmicutes</i> phylum and <i>Oscillospira</i> , <i>Coprococcus</i> , and <i>rc4_4</i> genera were reduced, as well as reduced <i>Dorea</i> with P80, and reduced <i>Bacteroides</i> , <i>Burkholderia</i> , <i>Clostridium</i> , and <i>Veillonella</i> with CMC. In females, <i>Bacteroides</i> , <i>Sphingomonadales</i> , <i>Sphingomonas</i> , and <i>Ruminococcus</i> were reduced, and there was an increase in <i>Anaeroplasma</i> with P80, and the <i>Proteobacteria</i> phylum and <i>Clostridium</i> and <i>Burkholderia</i> 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.		

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

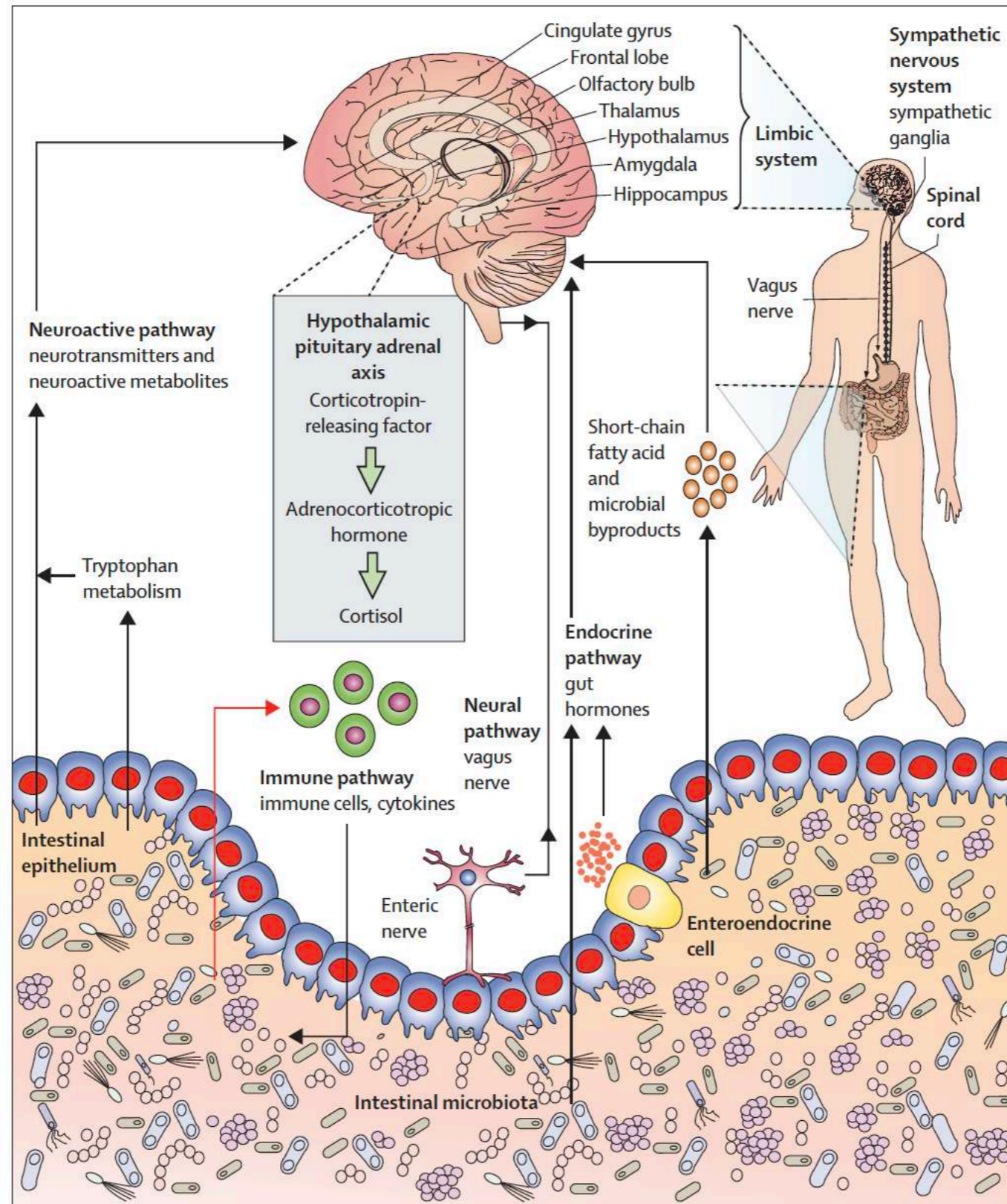
Neurodegenerative disease



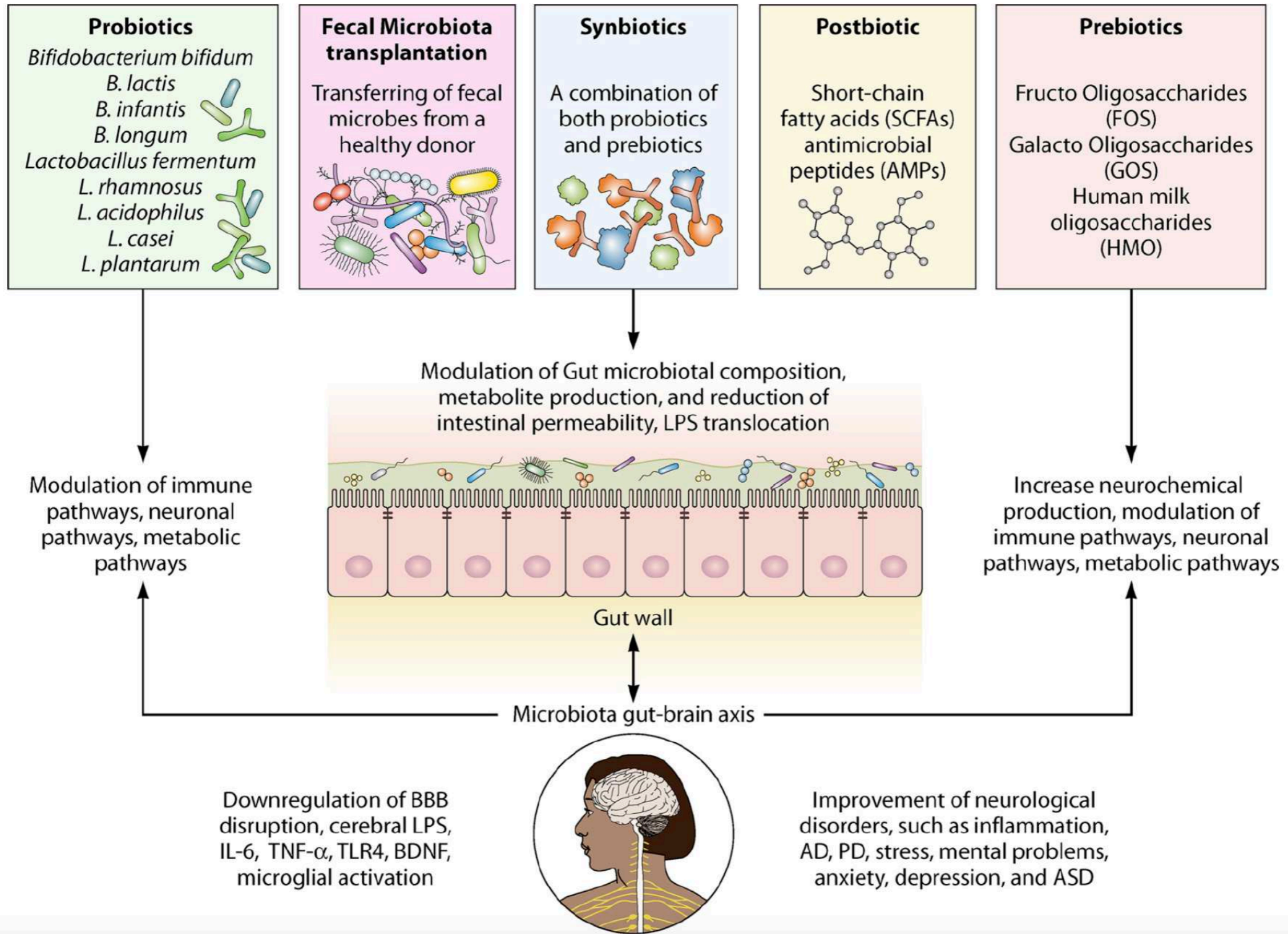
Neurodegenerative diseases (NDDs) are a heterogeneous group of neurological disorders adversely affecting the lives of millions of people worldwide and entail the progressive loss of neurons in the central nervous system (CNS) or peripheral nervous system (PNS)

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

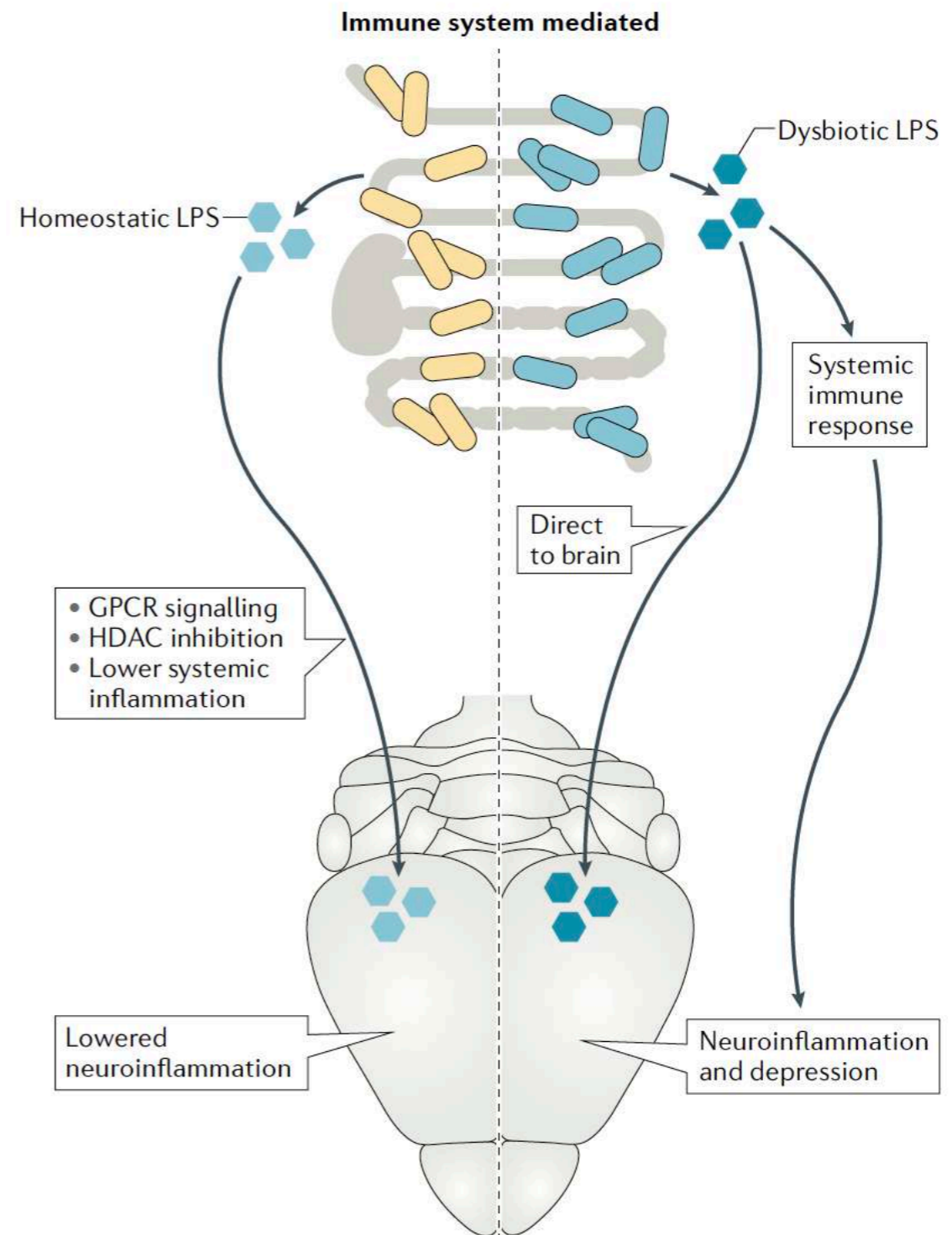
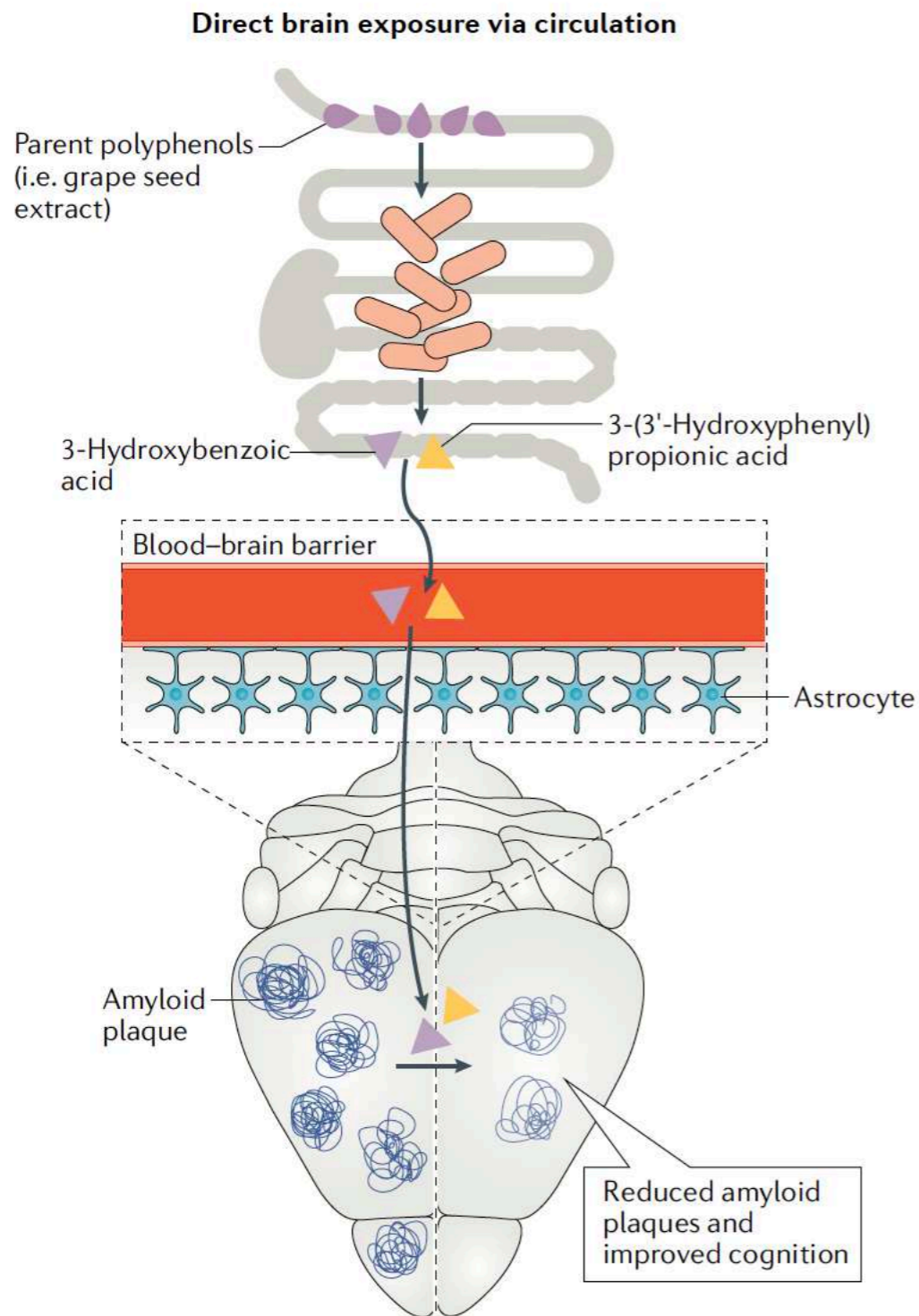
Pathways of communication between the microbiota and the brain



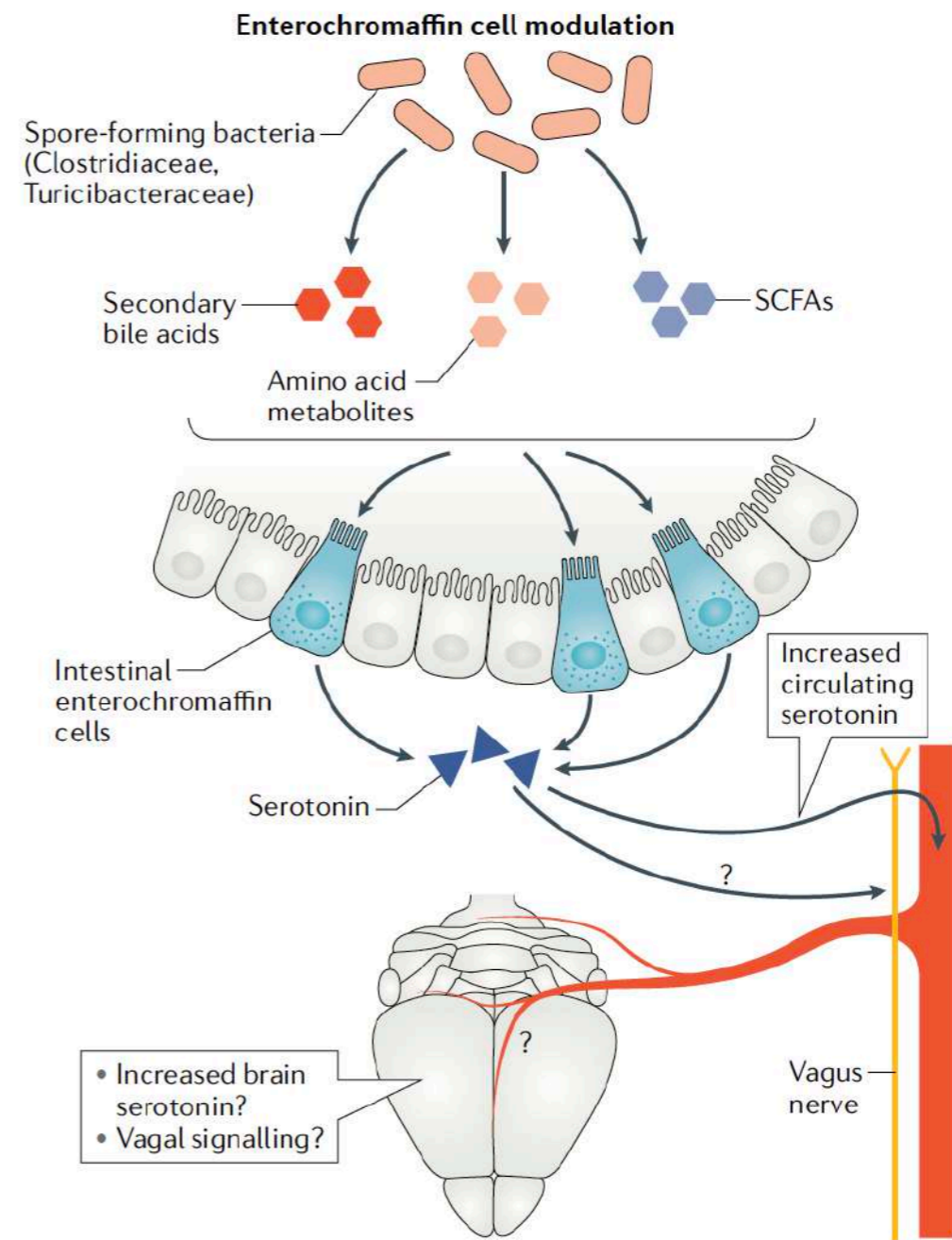
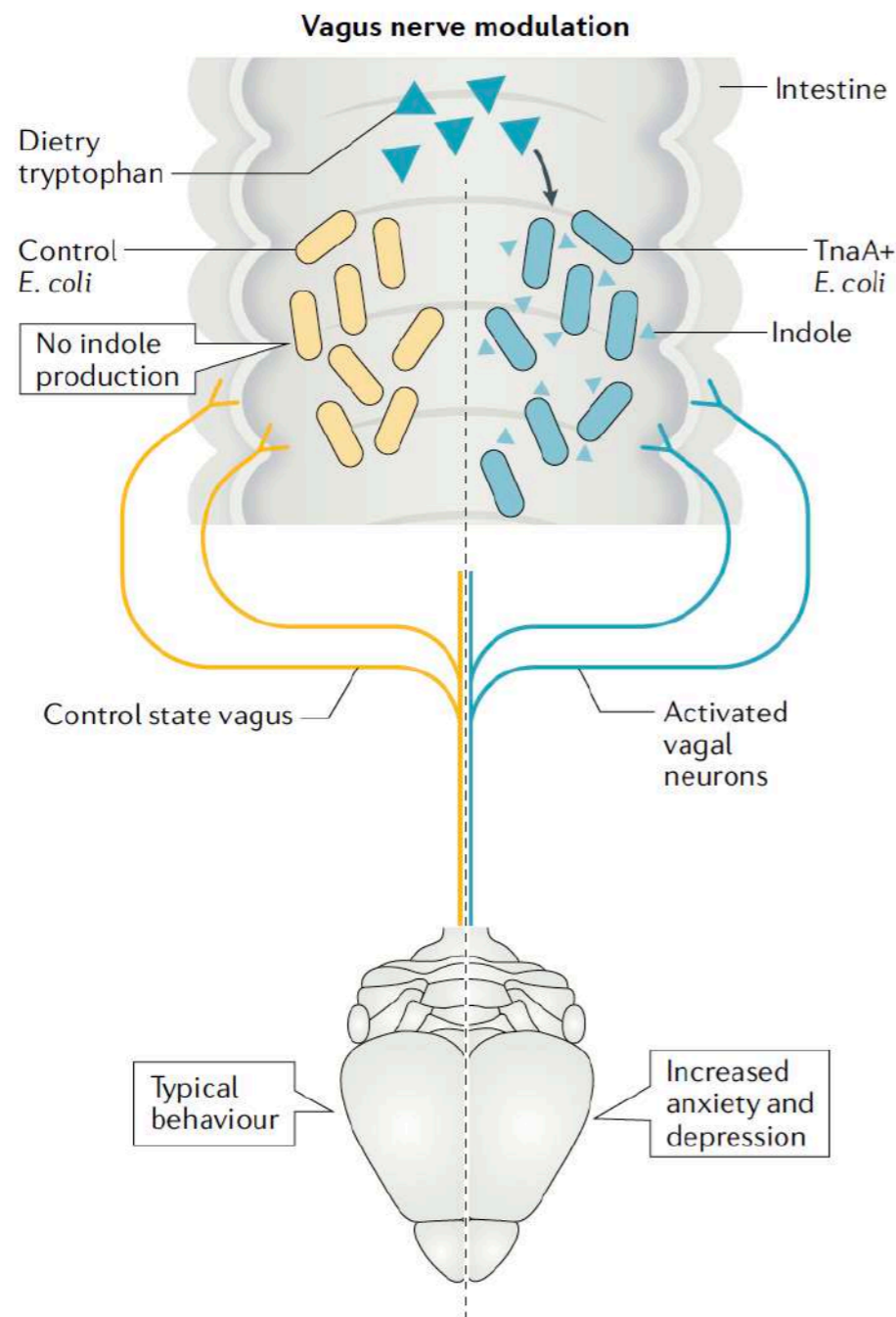
Modulation of gut microbiota by therapeutic microbial interventions



Mechanistic examples of the routes of gut–brain communication



Mechanistic examples of the routes of gut-brain communication



Gut microbial molecules in behavioural and neurodegenerative conditions

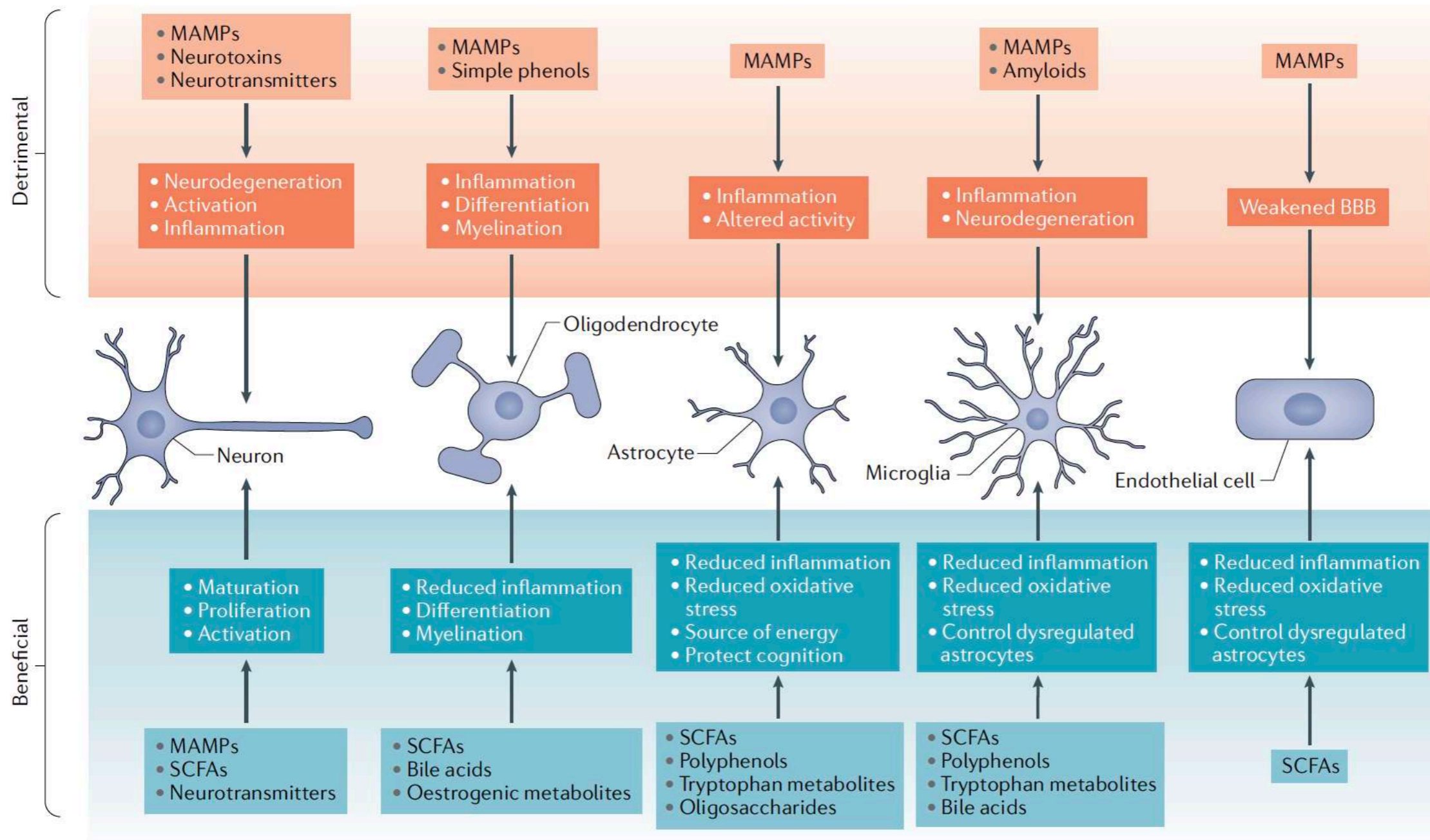
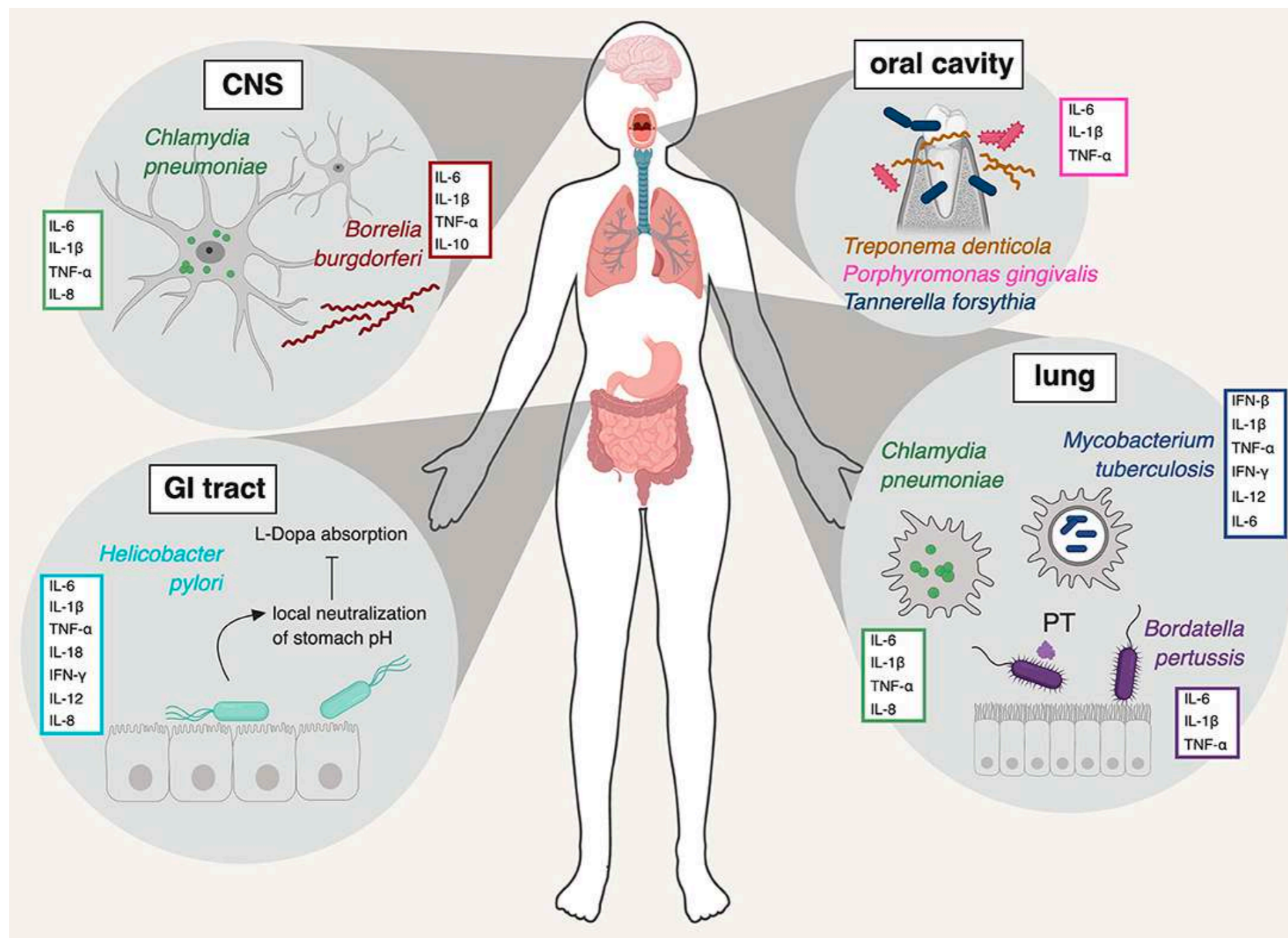


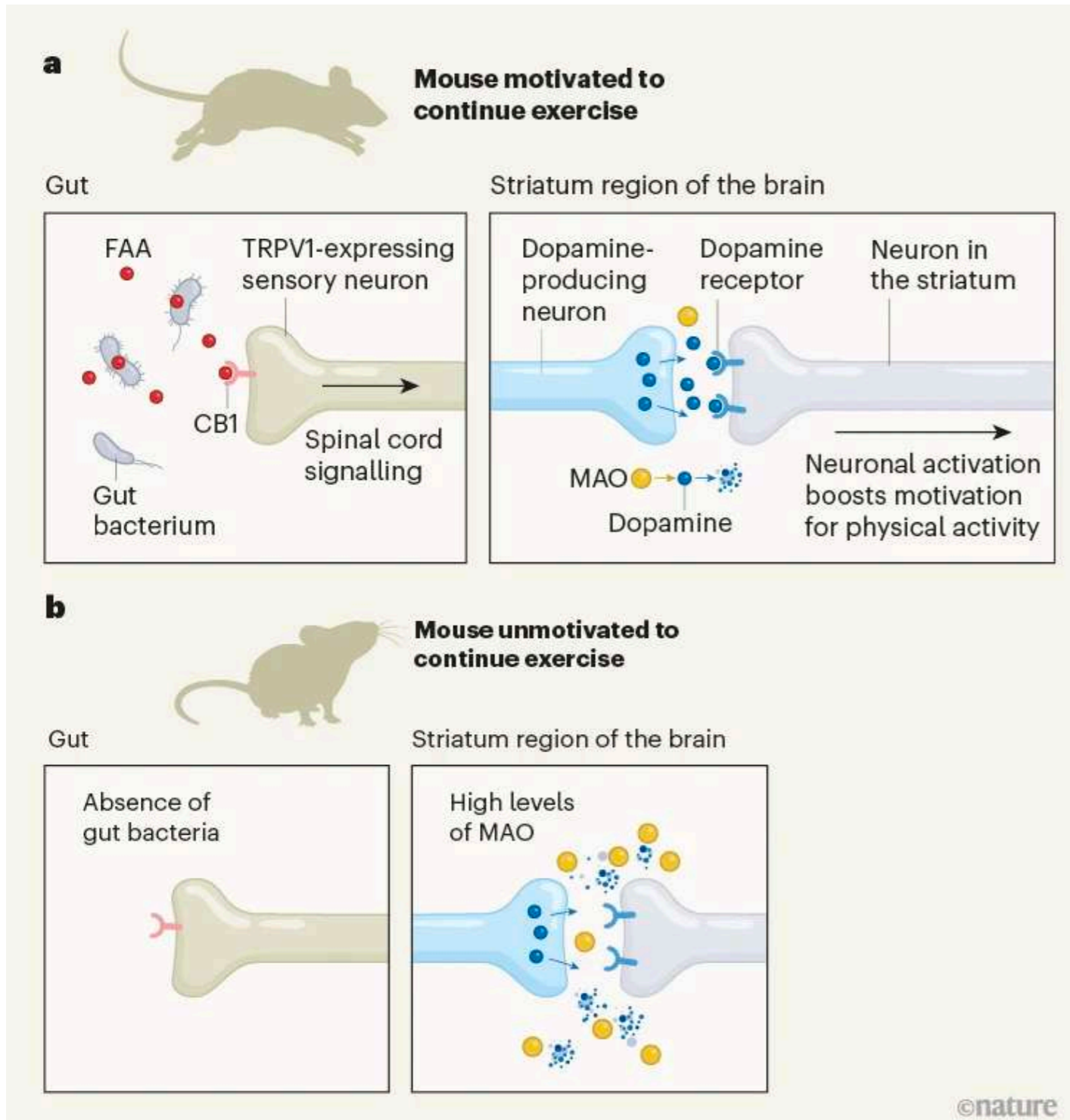
Fig. 4 | **Brain cell-specific effects of microbial metabolites.** Some microbial metabolites have known cellular targets in the brain. The beneficial and detrimental effects of these interactions are summarized. BBB, blood–brain barrier; MAMPs, microorganism-associated molecular patterns; SCFAs, short-chain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

Different bacterial species that have been implicated in neuroinflammation

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



Gut microbes shape athletic motivation

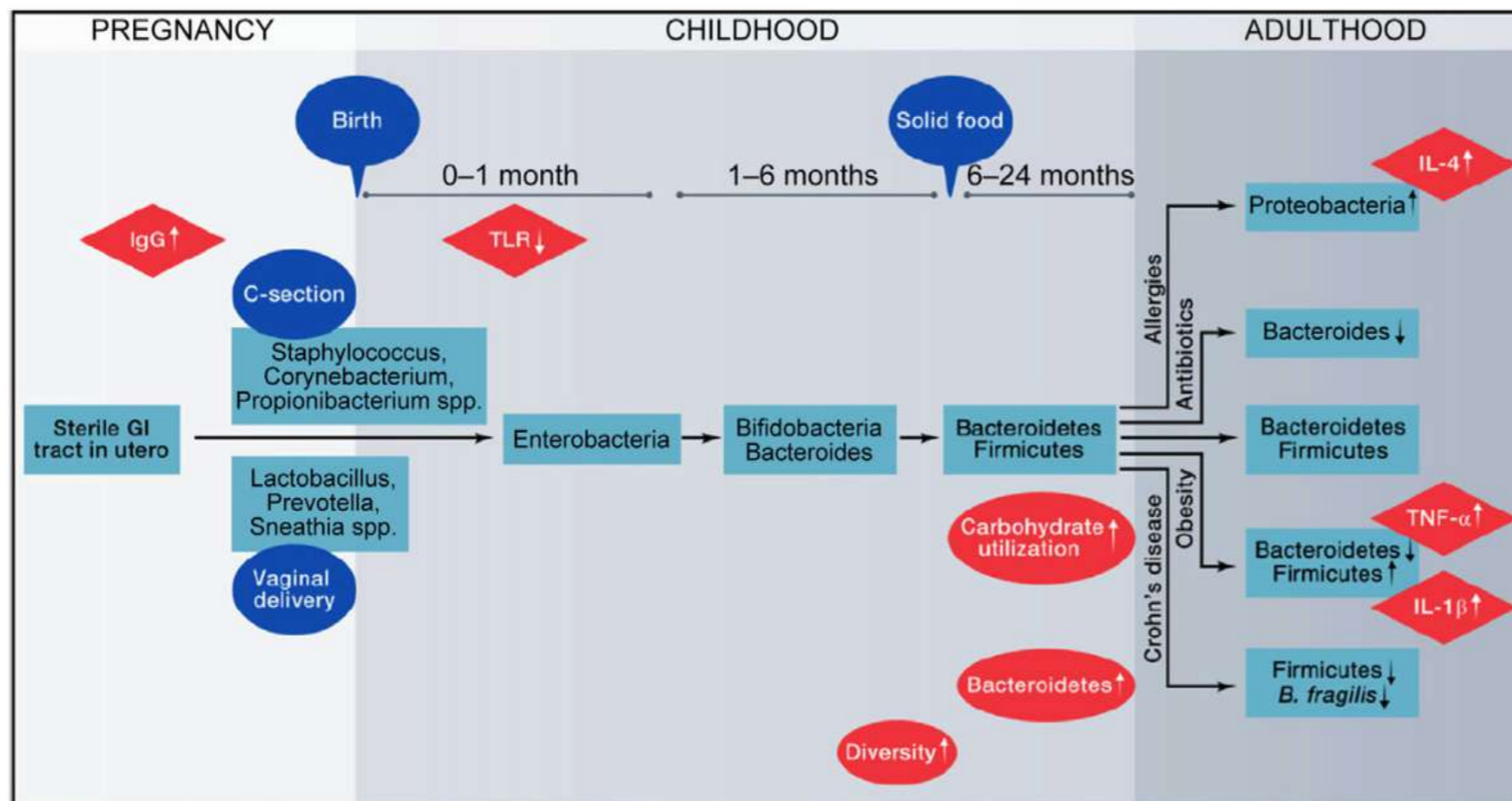


- Certain gut **bacteria** in mice **produce** molecules called **fatty acid amides (FAA)**, which **bind** to the **cannabinoid 1 receptor (CB1)** and thereby **activate sensory neurons** in the gut that express the protein TRPV1
- These neurons connect to the brain through the **spinal cord**
- Activation 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

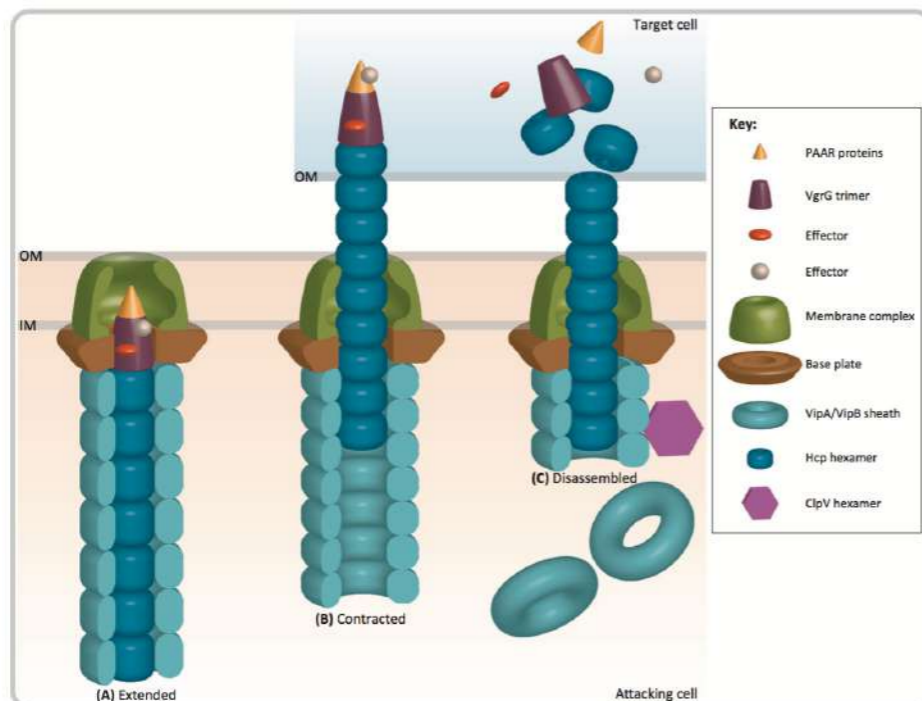
Host colonization

- 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

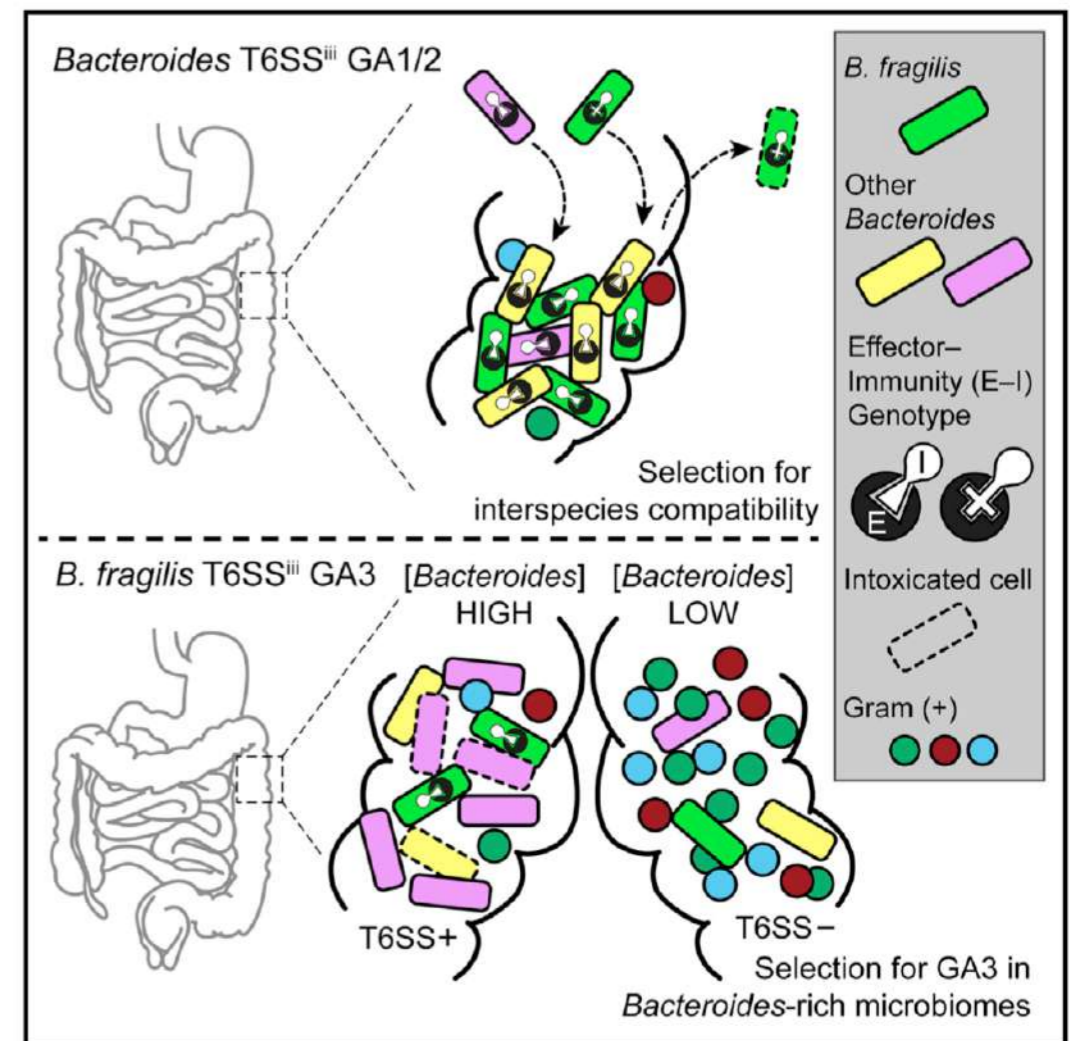


Intense microbial competition in human colonization phase

- 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



Fecal transplant

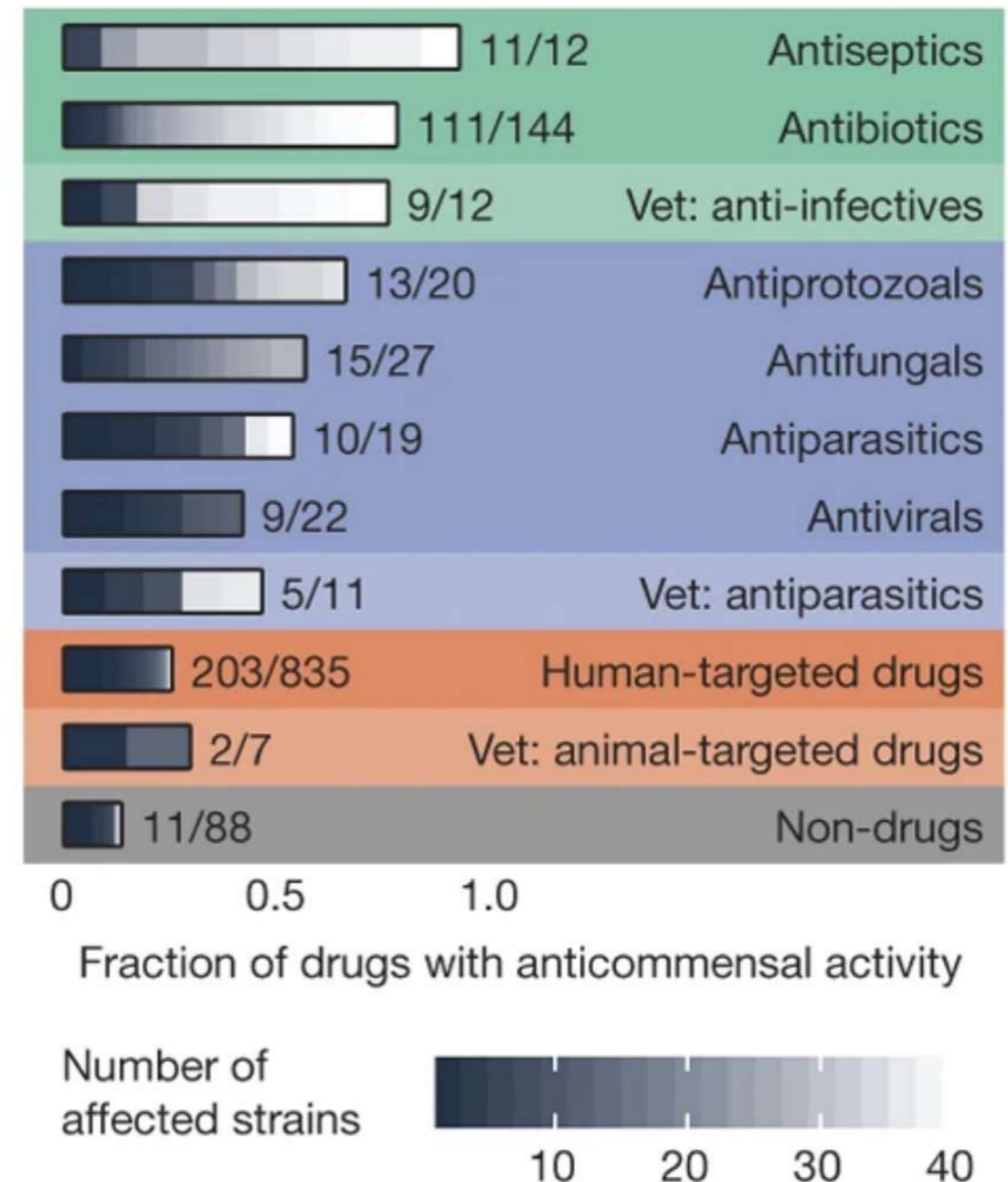
- Finding that thousands of bacterial species, viruses and fungi live in people, and are an integral part of human biology, has challenged medicine's view of microorganisms solely as agents of infectious disease
- The discovery that dietary fibre stimulates the particular groups of bacteria that produce 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

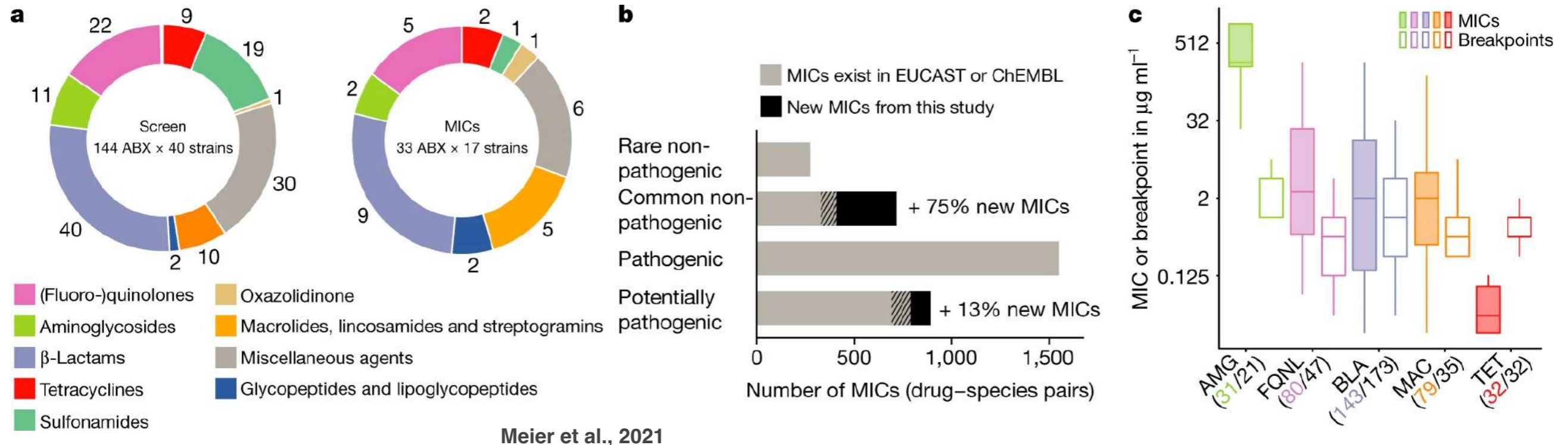
1,197 pharmaceuticals marketed drugs against 40 representative gut bacterial strains, and found that 24% of the drugs with human targets, including members of all therapeutic classes, inhibited the growth of at least one strain *in vitro*

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 μ M drug



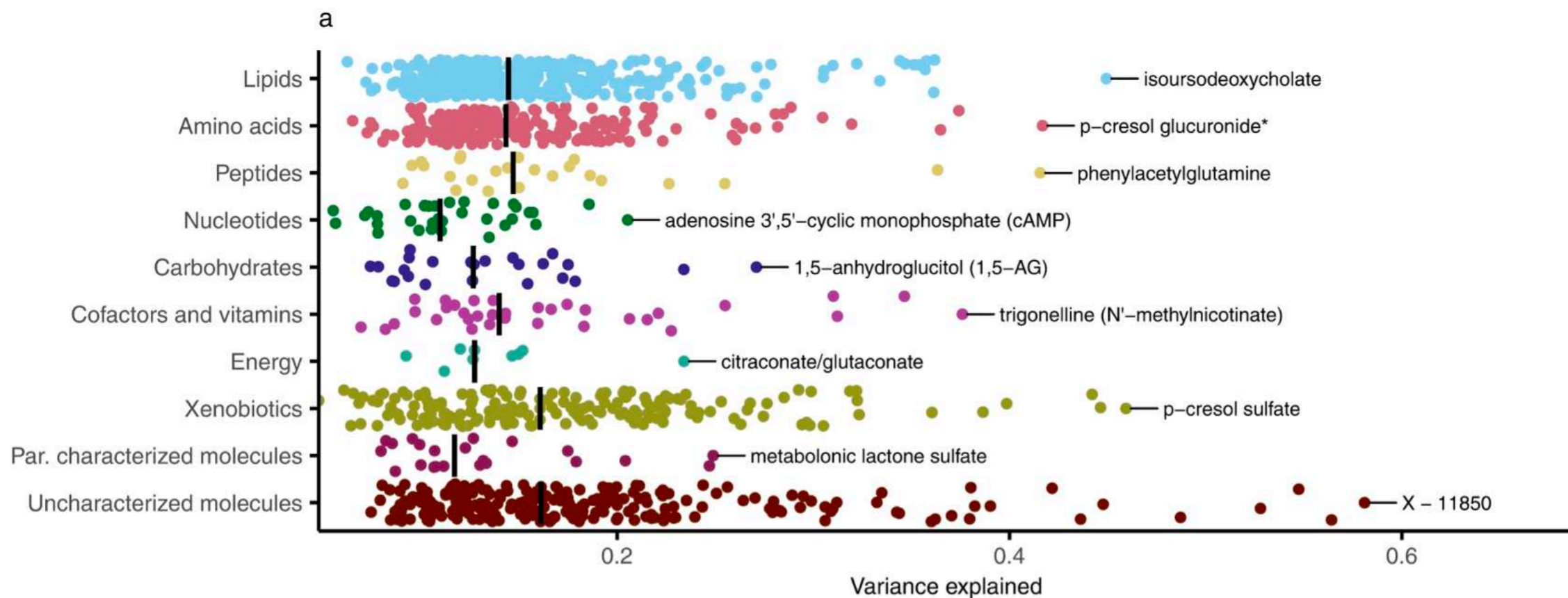
Activity spectrum of antibiotic classes on human gut commensals



- 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

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

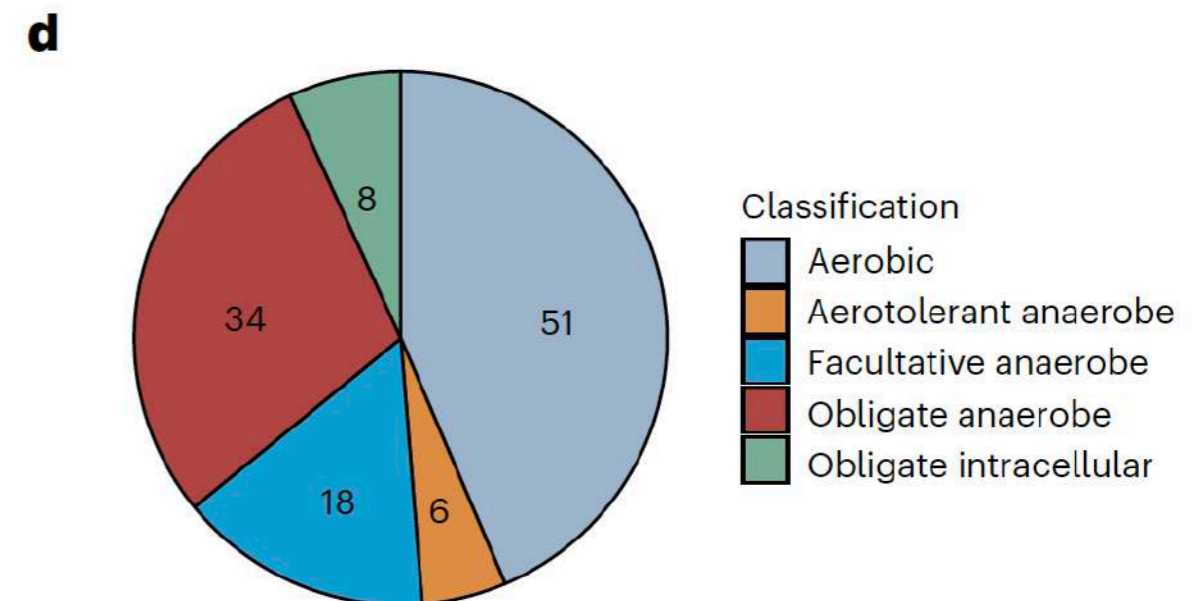
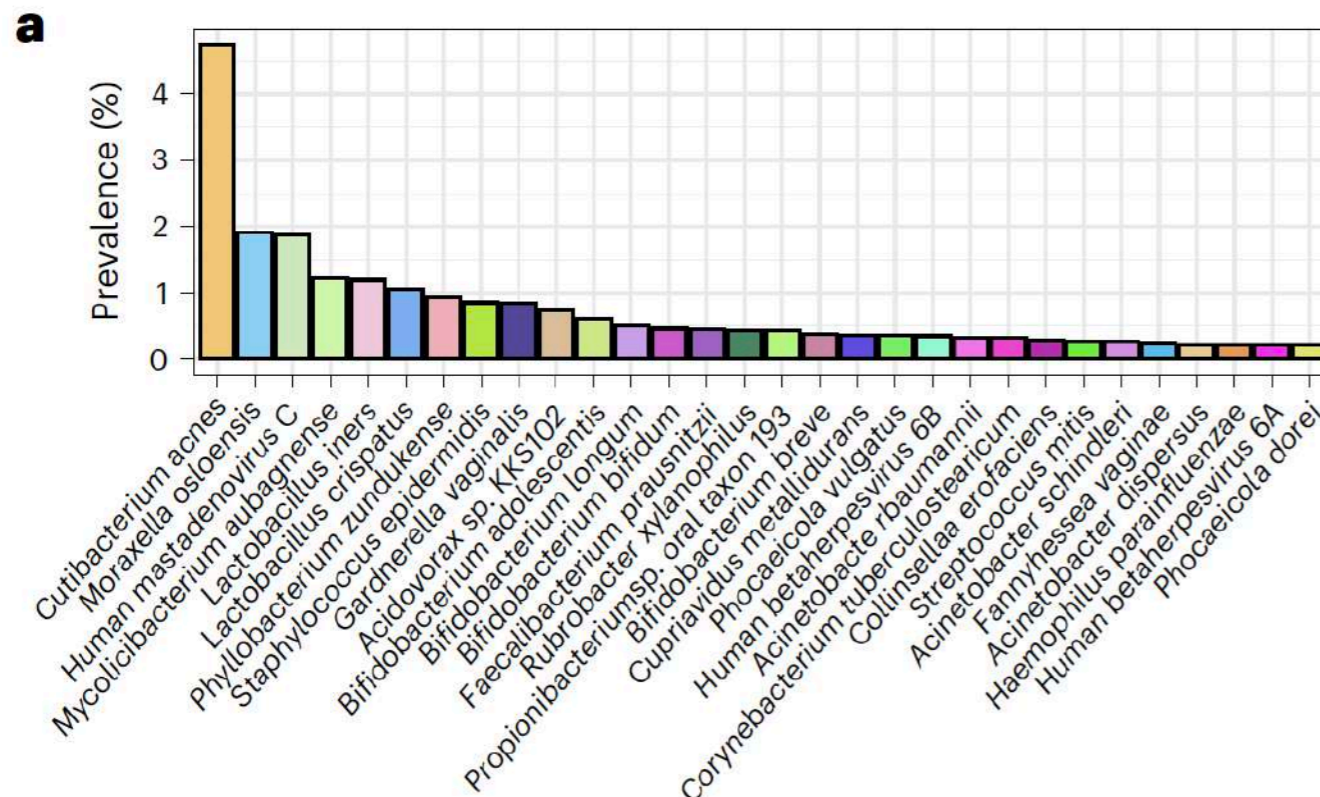


Microbes in human blood

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

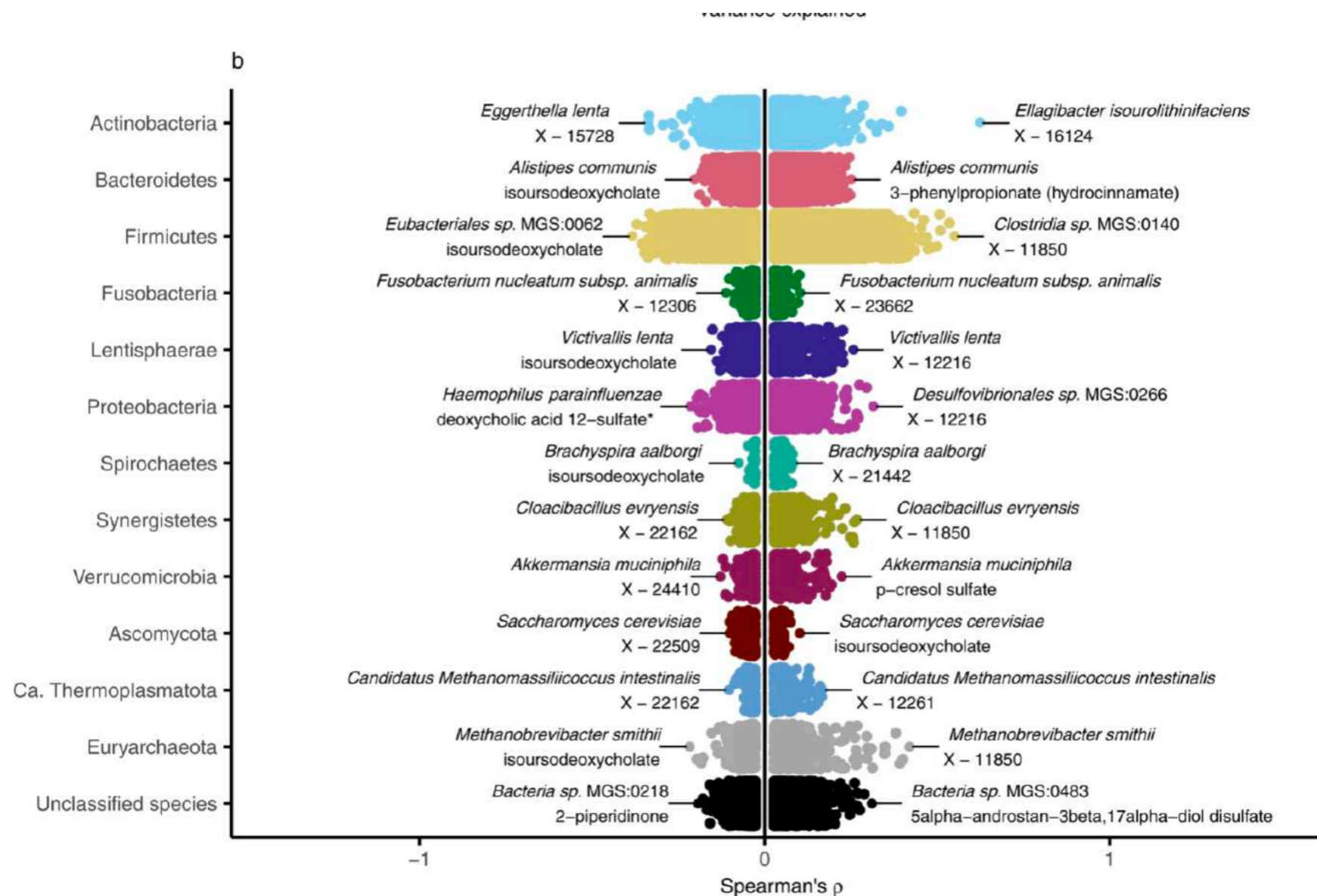
Commensals associated with the gut (n = 40), mouth (n = 32) and genitourinary tract (n = 18), and were distinct from pathogens detected in hospital blood cultures

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



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



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

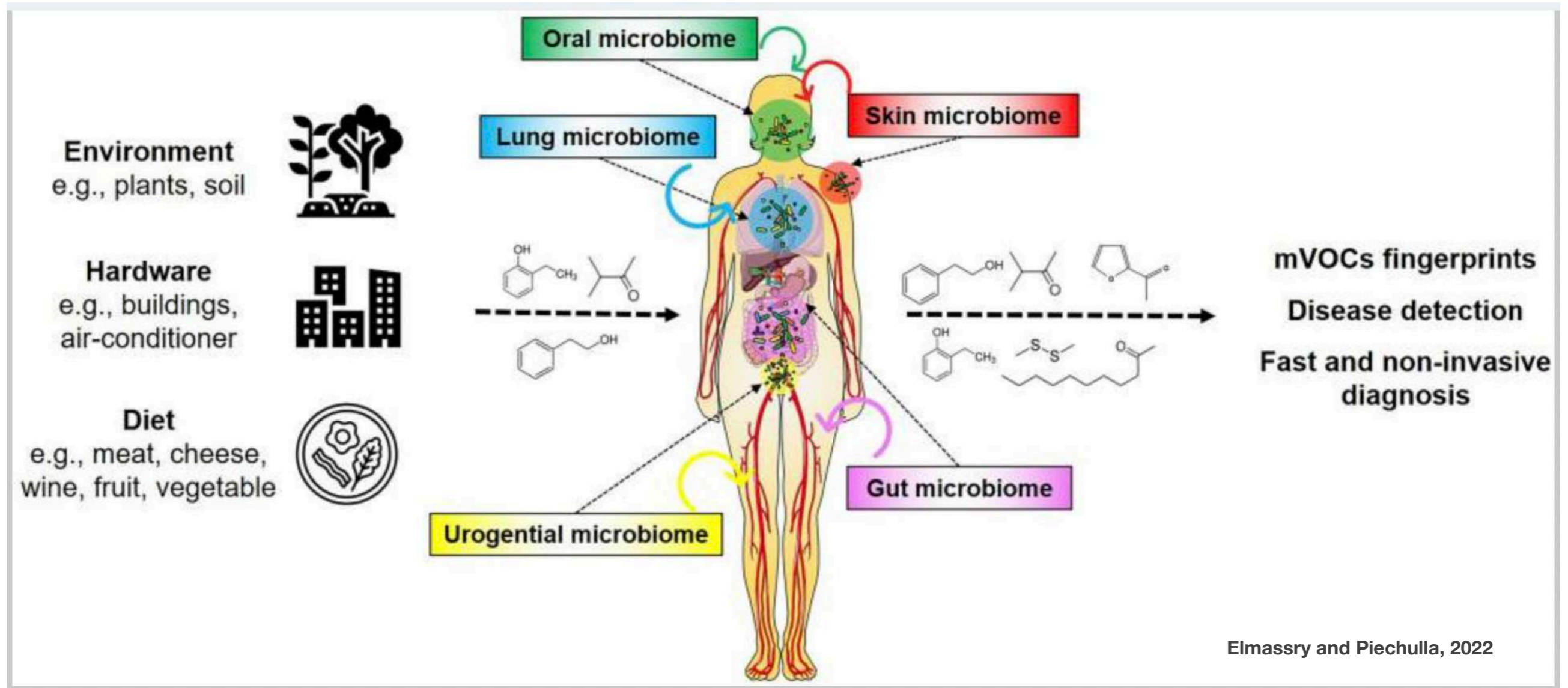
Microorganisms (bacteria, archaea, fungi and protists) use chemical signals as a primary source of information —> quorum sensing

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



Elmassry and Piechulla, 2022

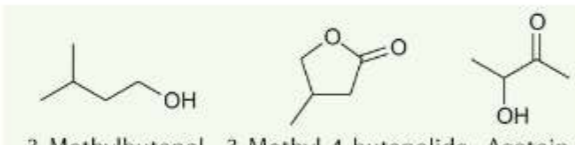
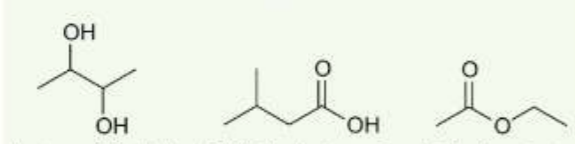
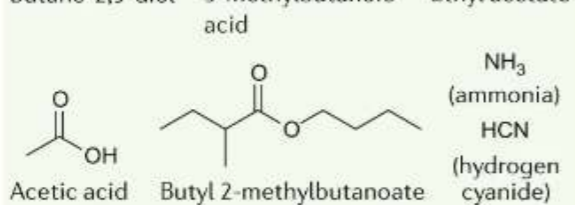

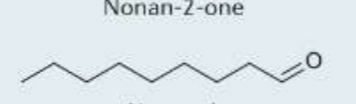
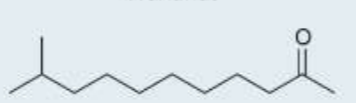
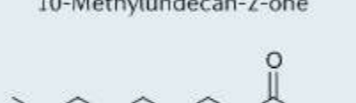
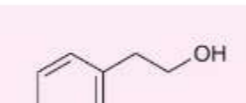
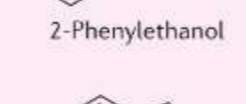
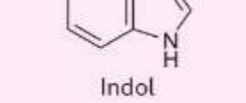
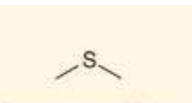
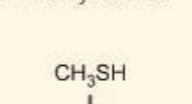
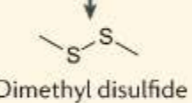
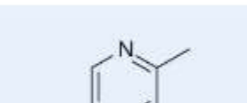
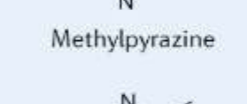
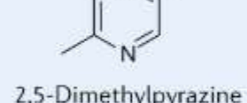
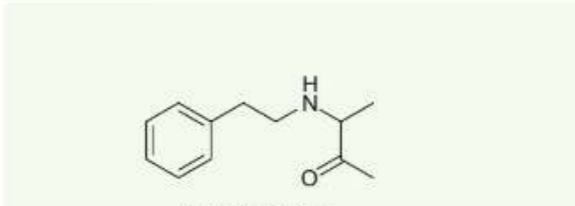
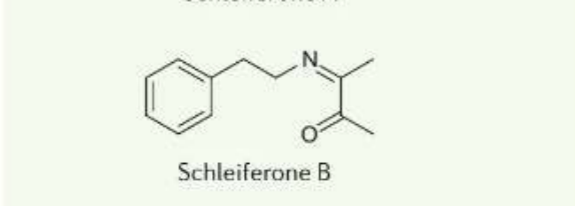
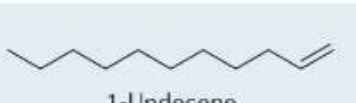
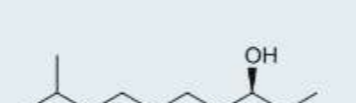

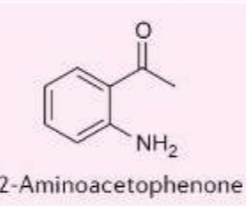

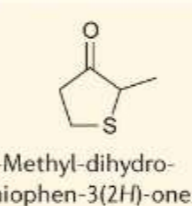
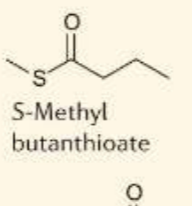
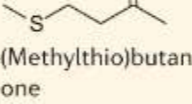
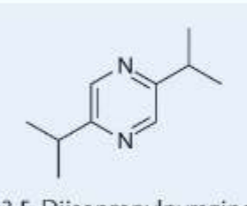
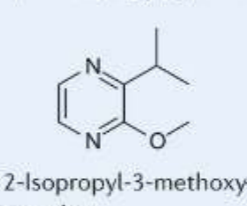
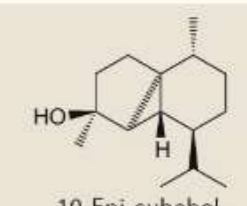
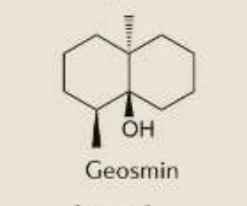

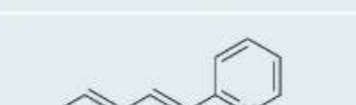
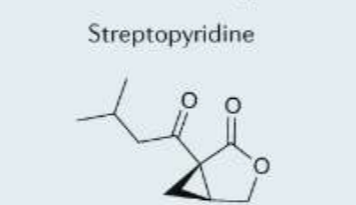
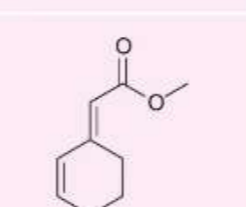
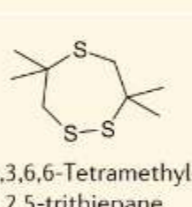
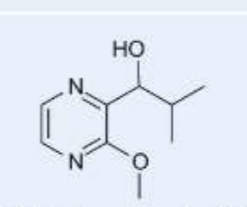
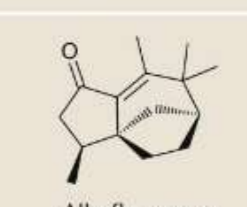

- mVOCs and the human holobiont
- Microorganisms appear universal in the environment
- Microbes produce many compounds, including volatiles
- Volatiles influence and affect humans
- mVOCs released from the human microbiomes are potential biomarkers for non-invasive diagnosis.

Pathogen	Infection	Volatiles	Specimen	References
<i>Clostridioides difficile</i>	Gastrointestinal	2-furancarboxaldehyde; 5-methyl-2-furancarboxaldehyde	Feces	Probert et al., 2004
		propan-1-ol; 3-methylbutanal; ethyl propionate; hexanoic acid; <i>p</i> -cresol; dodecane; indole		Patel et al., 2019
<i>Vibrio cholerae</i>		dimethyl disulfide; <i>p</i> -menth-1-en-8-ol		Garner et al., 2009
<i>Campylobacter jejuni</i>		1-octen-3-ol		Garner et al., 2007
<i>Helicobacter pylori</i>		hydrogen nitrate; hydrogen cyanide	Breath	Lechner et al., 2005
<i>Staphylococcus aureus</i>	Respiratory	undecane; 1,4-pentadiene; acetone		Neerincx et al., 2016
<i>Pseudomonas aeruginosa</i>		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

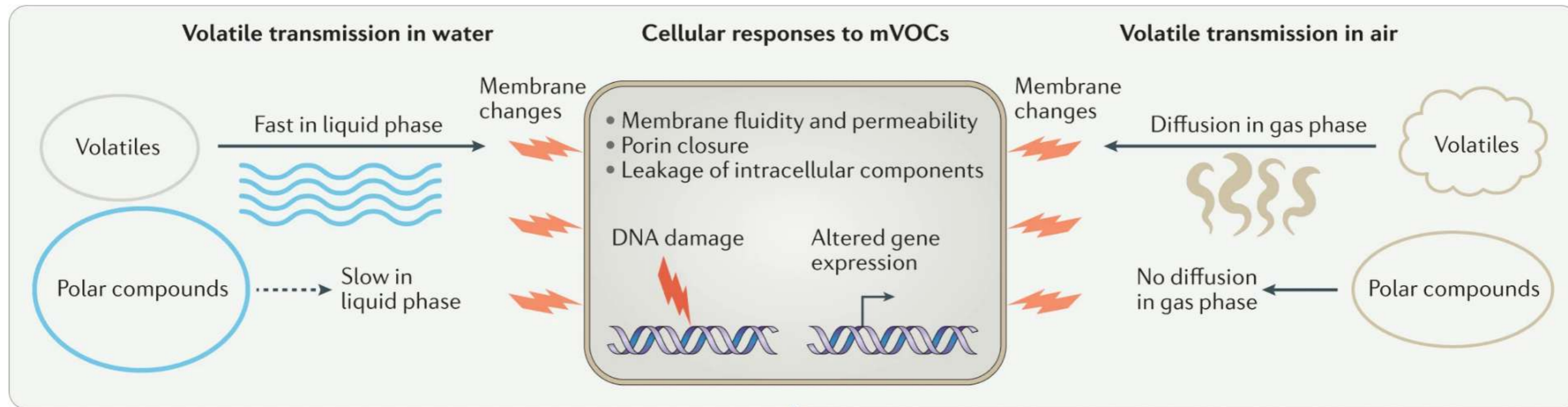
<i>Pseudomonas aeruginosa</i>		2-nonanone		Savelev et al., 2011
		2-butanone; 3-methyl-2-butanone	Bronchoalveolar lavage	Nasir et al., 2018
<i>Acinetobacter baumannii</i>		1-undecene; nonanal; decanal; 2,6,10-trimethyl-dodecane; 5-methyl-5-propyl-nonane; longifolene; tetradecane; 2-butyl-1-octanol	Breath	Gao et al., 2016
<i>Mycobacterium tuberculosis</i>		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
<i>Escherichia coli</i>	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
<i>Pseudomonas aeruginosa</i>		acetic acid; acetone		Allardyce et al., 2006
		1-vinyl aziridine; trimethylamine		Chingin et al., 2015
<i>Staphylococcus</i>		butyric acid; isovaleric acid		Chingin et al., 2015

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

Major biosynthetic pathways of microbial volatile organic compounds

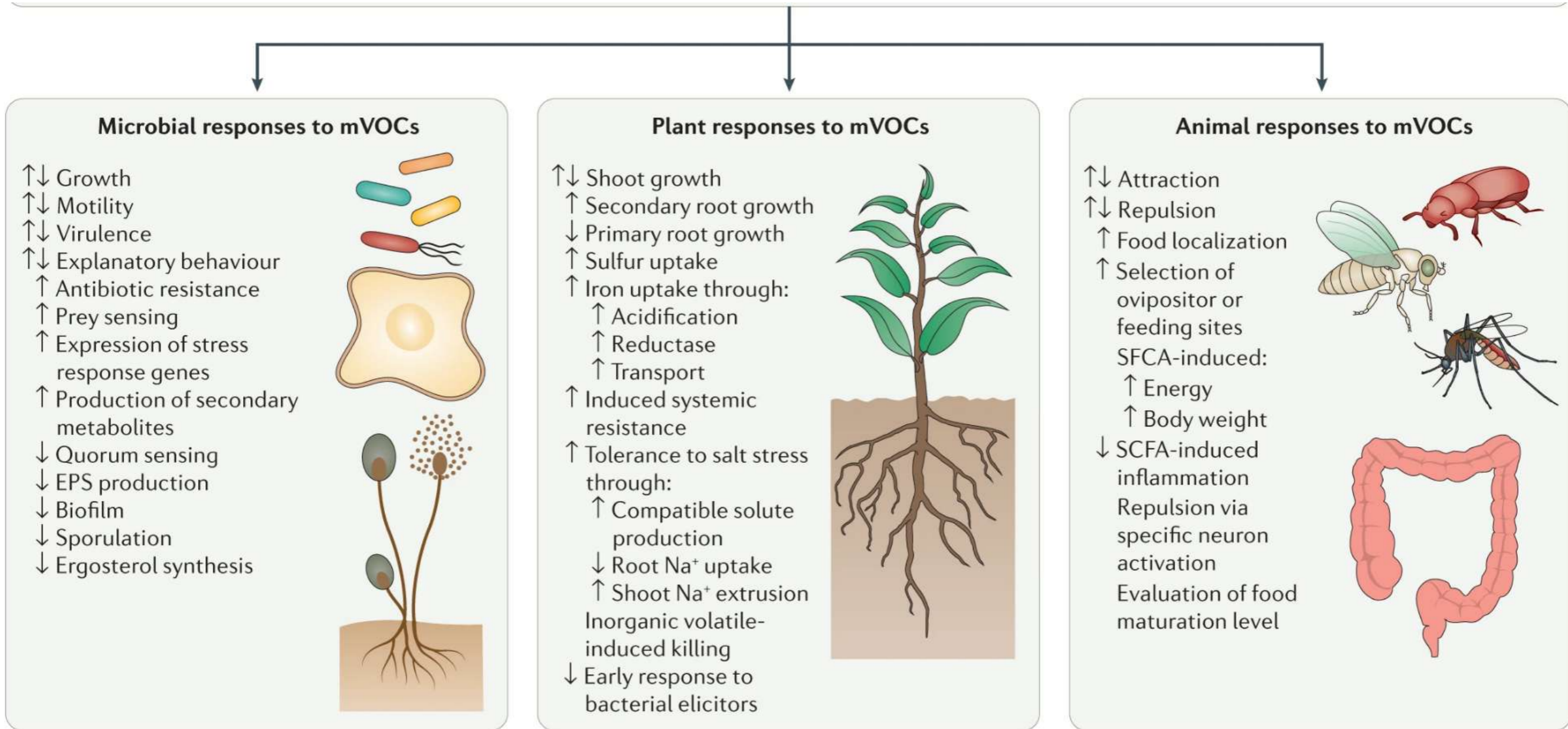
	Primary metabolism	Fatty acid pathway	Aromatic	Sulfur	Pyrazines	Terpenoid
Common	 <p>3-Methylbutanol 3-Methyl-4-butanolide Acetoin</p>  <p>Butane-2,3-diol 3-Methylbutanoic acid Ethyl acetate</p>  <p>Acetic acid Butyl 2-methylbutanoate NH₃ (ammonia) HCN (hydrogen cyanide)</p>	 <p>Nonan-2-one</p>  <p>Nonanal</p>  <p>10-Methylundecan-2-one</p>  <p>Nonanoic acid</p>	 <p>2-Phenylethanol</p>  <p>Indol</p>  <p>Methyl benzoate</p>	 <p>Dimethyl sulfide</p> <p>CH₃SH</p>  <p>Dimethyl disulfide</p>  <p>Dimethyl trisulfide</p>	 <p>Methylpyrazine</p>  <p>2,5-Dimethylpyrazine</p>  <p>Trimethylpyrazine</p>	
Group	 <p>Schleiferone A</p>  <p>Schleiferone B</p>	 <p>1-Undecene</p>  <p>(S)-9-Methyldecan-3-ol</p>  <p>Conophthorin</p>	 <p>2-Aminoacetophenone</p>  <p>Tropone</p>	 <p>2-Methyl-dihydrothiophen-3(2H)-one</p>  <p>S-Methyl butanthioate</p>  <p>4-(Methylthio)butan-2-one</p>	 <p>2,5-Diisopropylpyrazine</p>  <p>2-Isopropyl-3-methoxy-pyrazine</p>	 <p>10-Epi-cubebol</p>  <p>Geosmin</p>  <p>2-Methylisoborneol</p>
Specific		 <p>Streptopyridine</p>  <p>Salinilactone B</p>	 <p>Methyl (E)-2-(cyclohex-2-en-1-ylidene)acetate</p>	 <p>3,3,6,6-Tetramethyl-1,2,5-trithiepane</p>	 <p>1-(3-Methoxypyrazin-2-yl)-2-methylpropan-1-ol</p>	 <p>Albaflavenone</p>  <p>Sodorifen</p>

Modes of diffusion of microbial volatiles

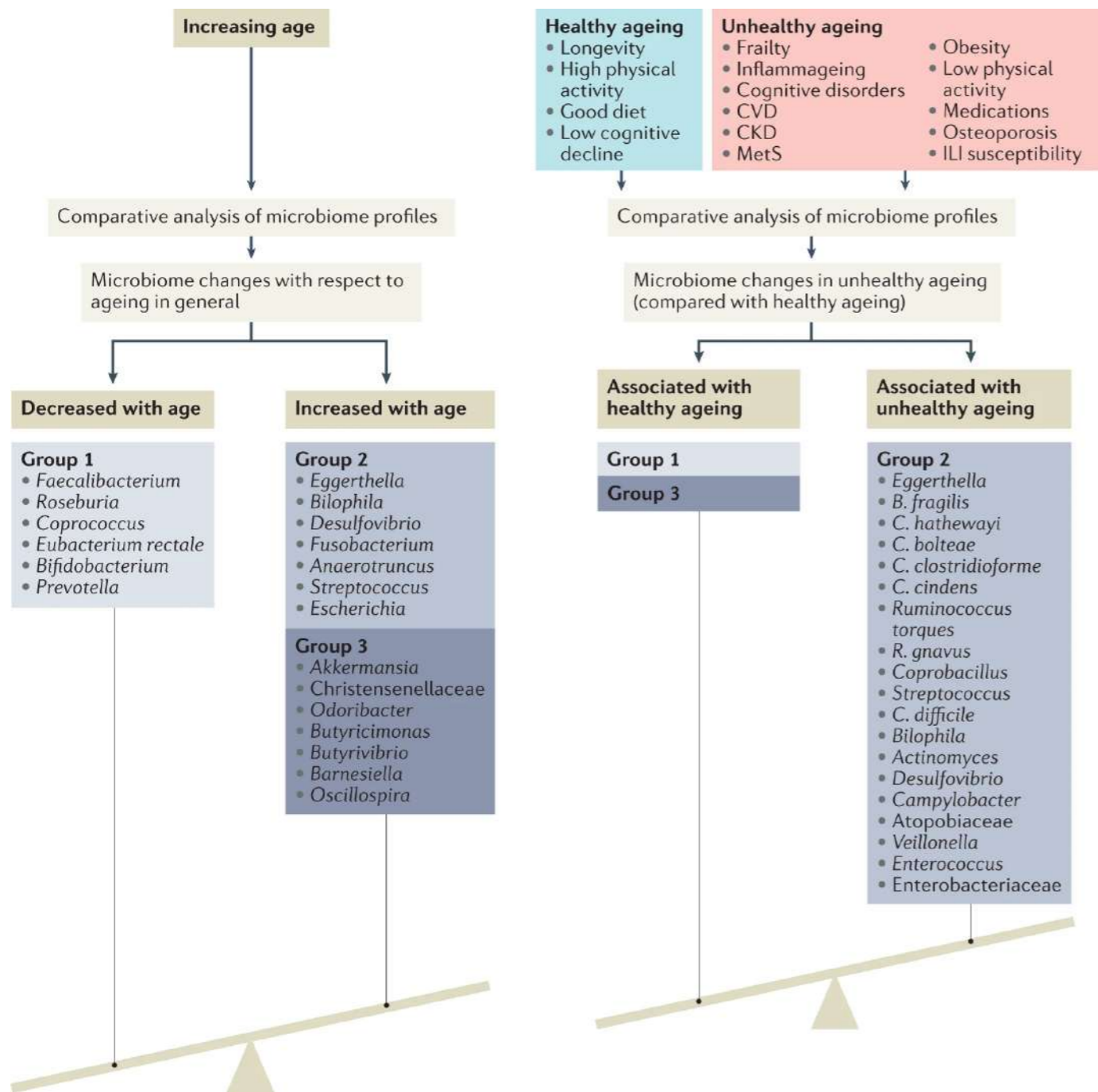


In bacteria, mVOCs have also been shown to modulate **antibiotic resistance** (for example, 1-methylthio-3-pentanone, 2-aminoacetophenone and trimethylamine), **quorum sensing** (for example, dimethyl disulfide and dimethyl trisulfide) and **biofilm formation** (for example, indole and 1-butanol)

Responses in microorganisms, plants and animals to mVOCs



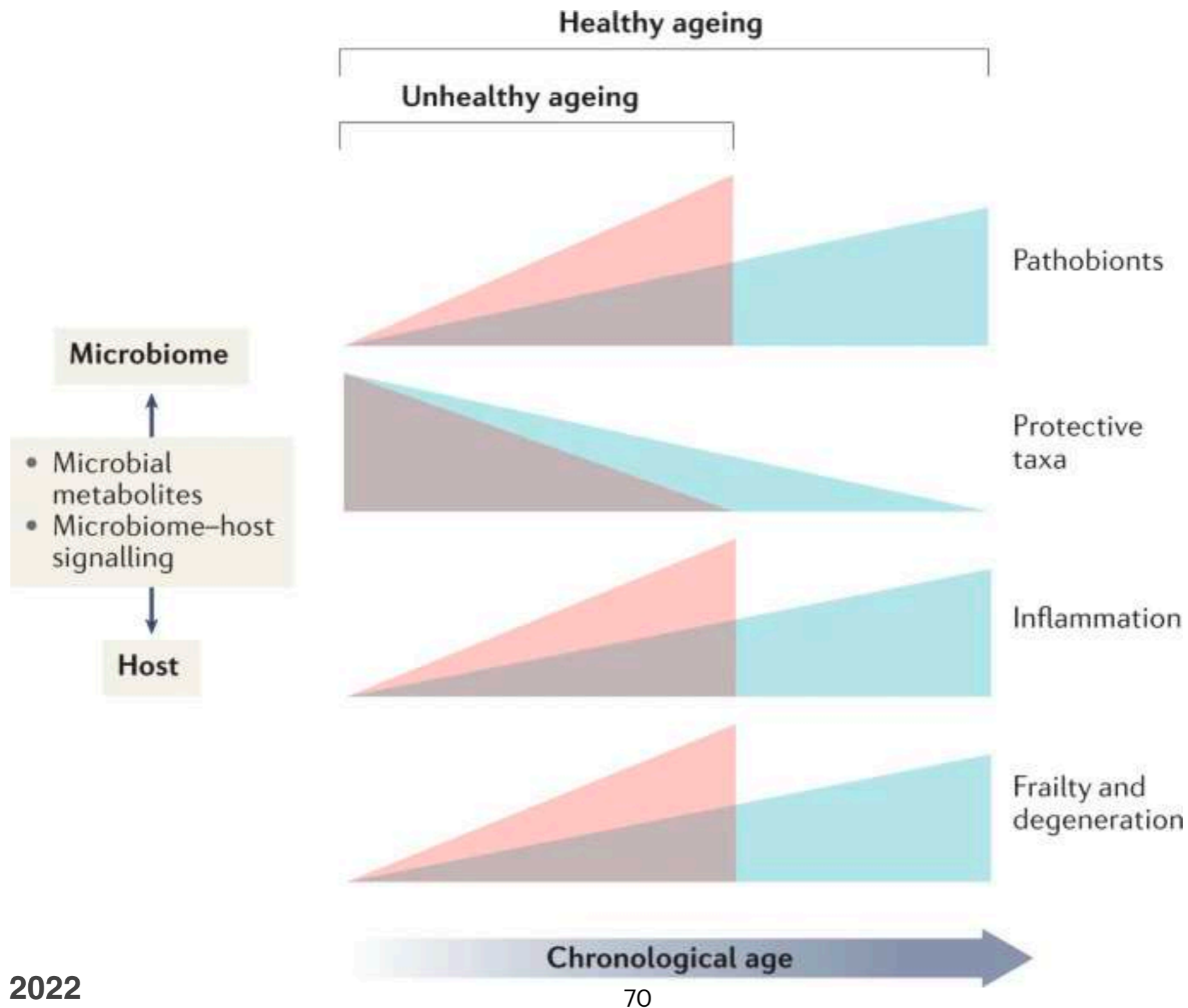
The gut microbiome as a modulator of healthy aging



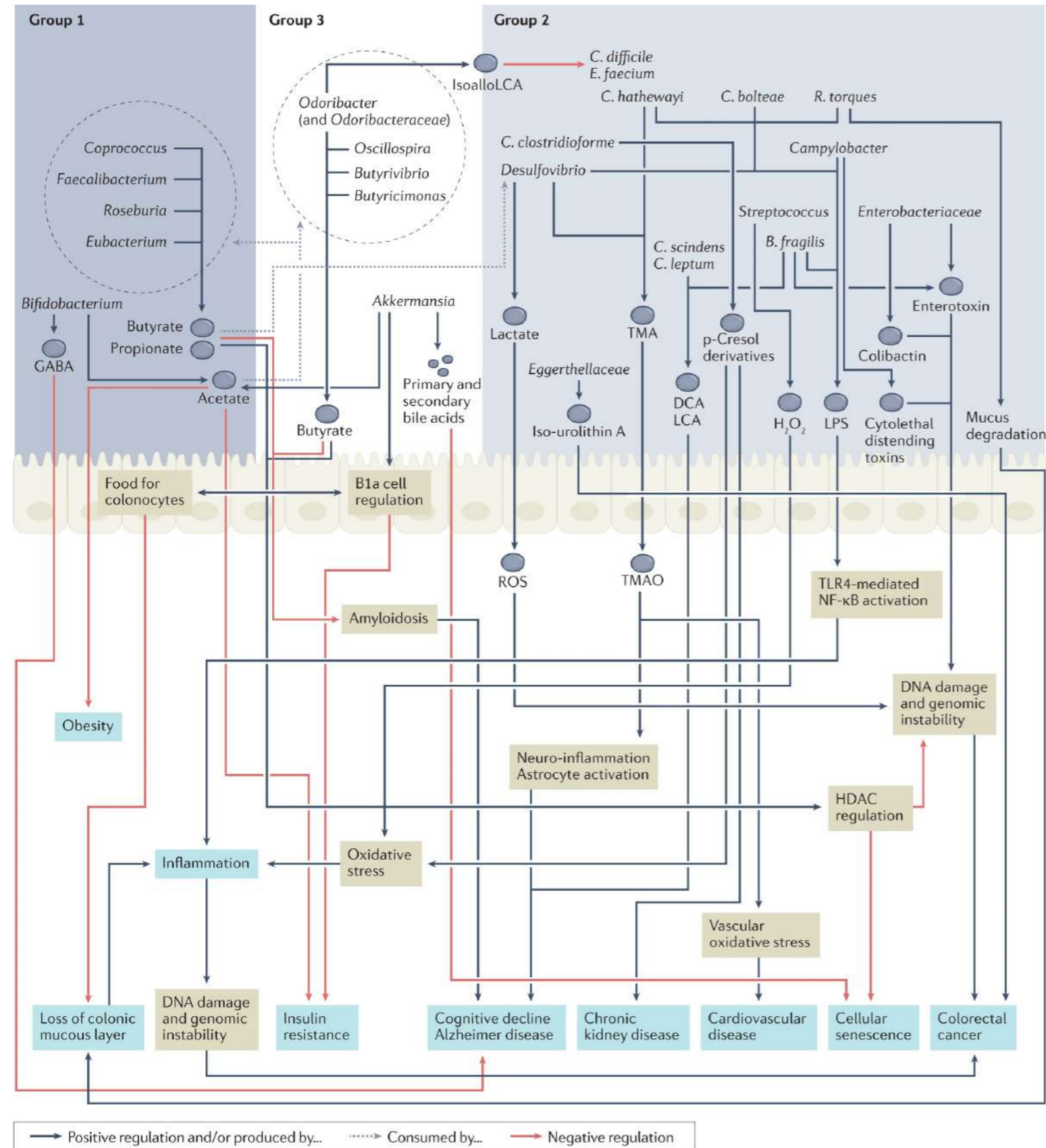
- Group 1 taxa decreased with age and were associated with healthy aging
- Group 2 consisted of the pathobionts that increased with age and were associated with unhealthy aging
- Group 3 increased with age but were observed to be depleted in unhealthy aging

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



Functional implications of microbiome alterations on host physiology in aging

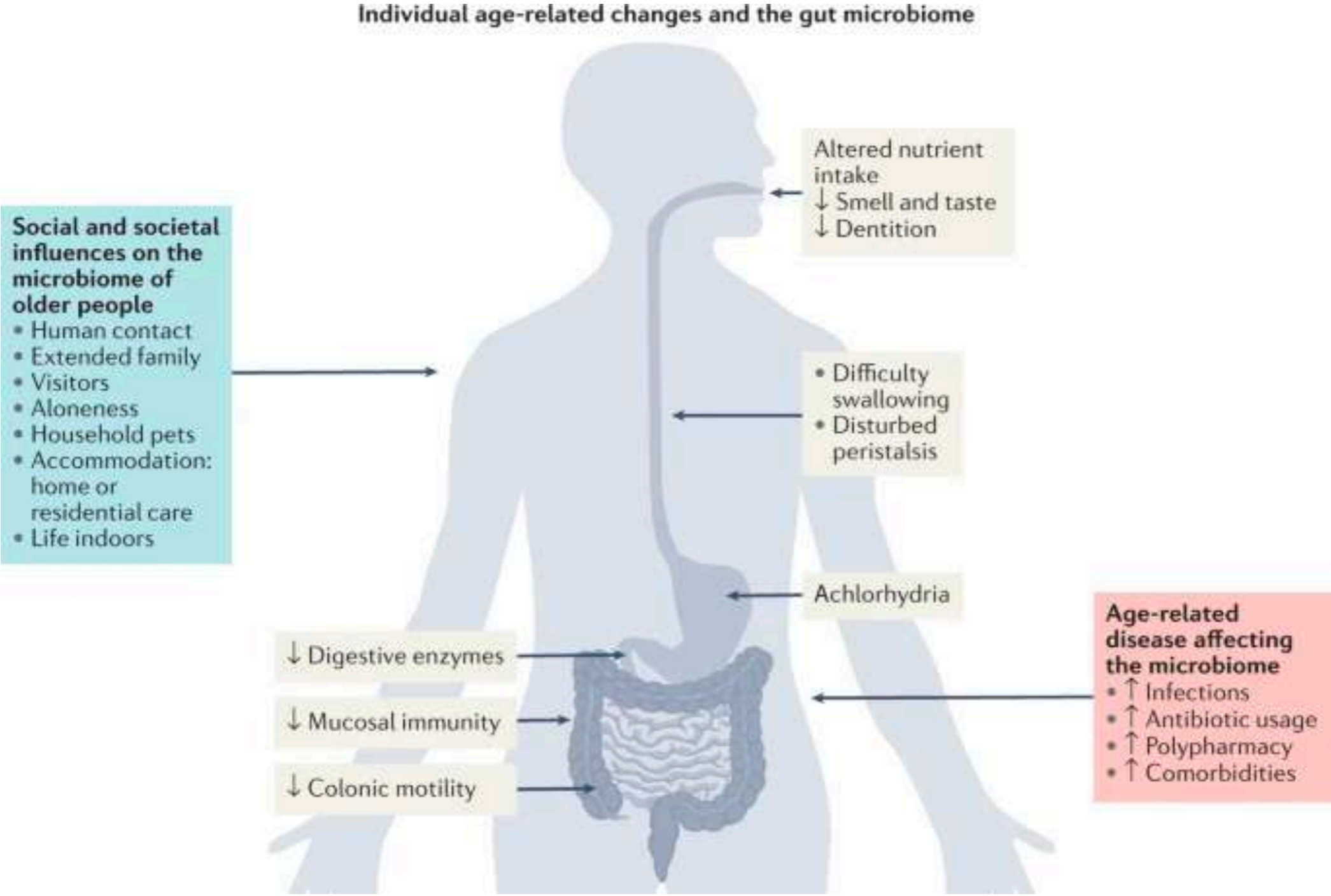


Metabolic capabilities of the three taxa groups are linked to unhealthy aging-linked decline in host physiology

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, trimethylamine-N-oxide

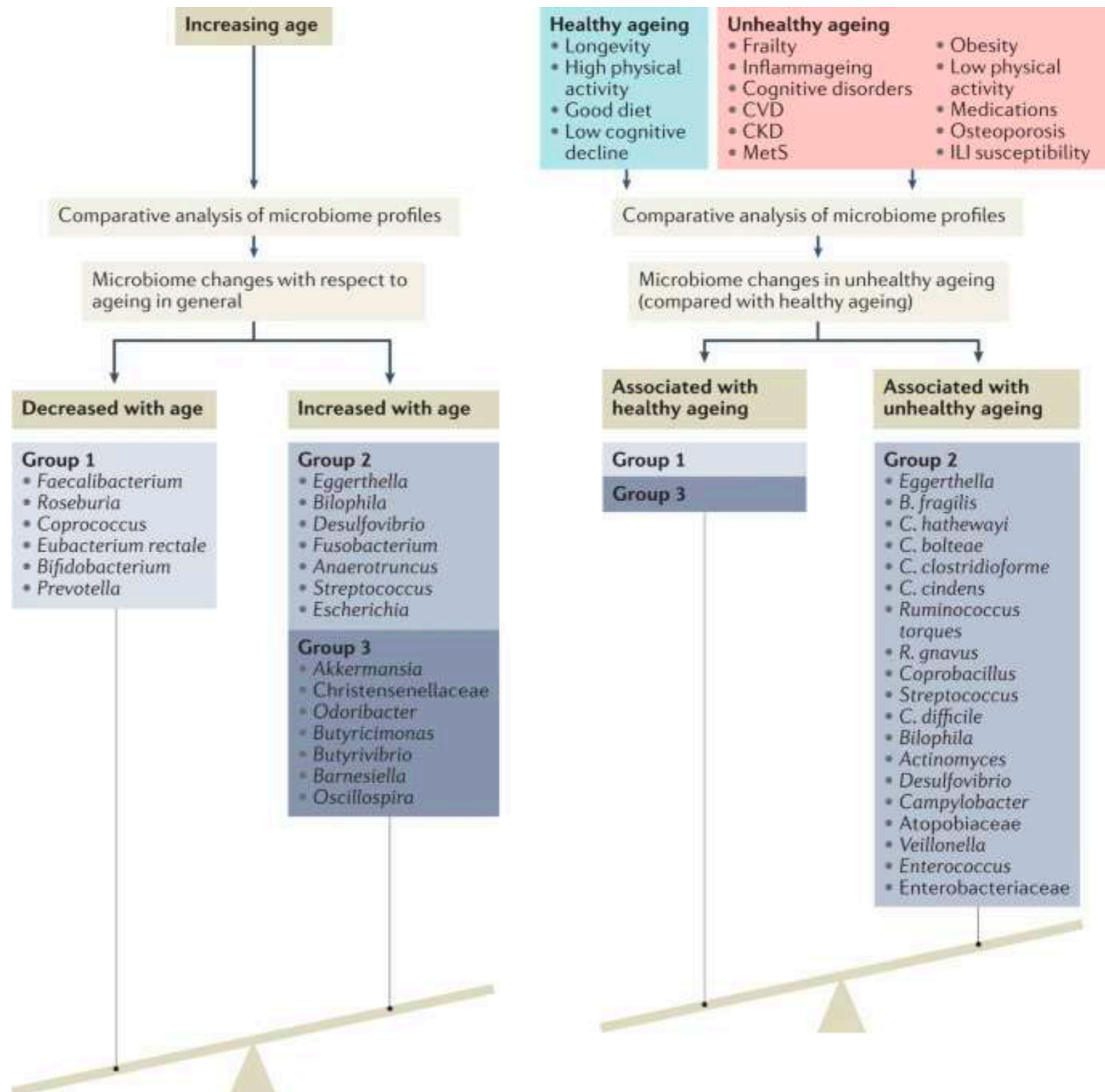
Physiological, social and disease-related influences on the microbiome of older people



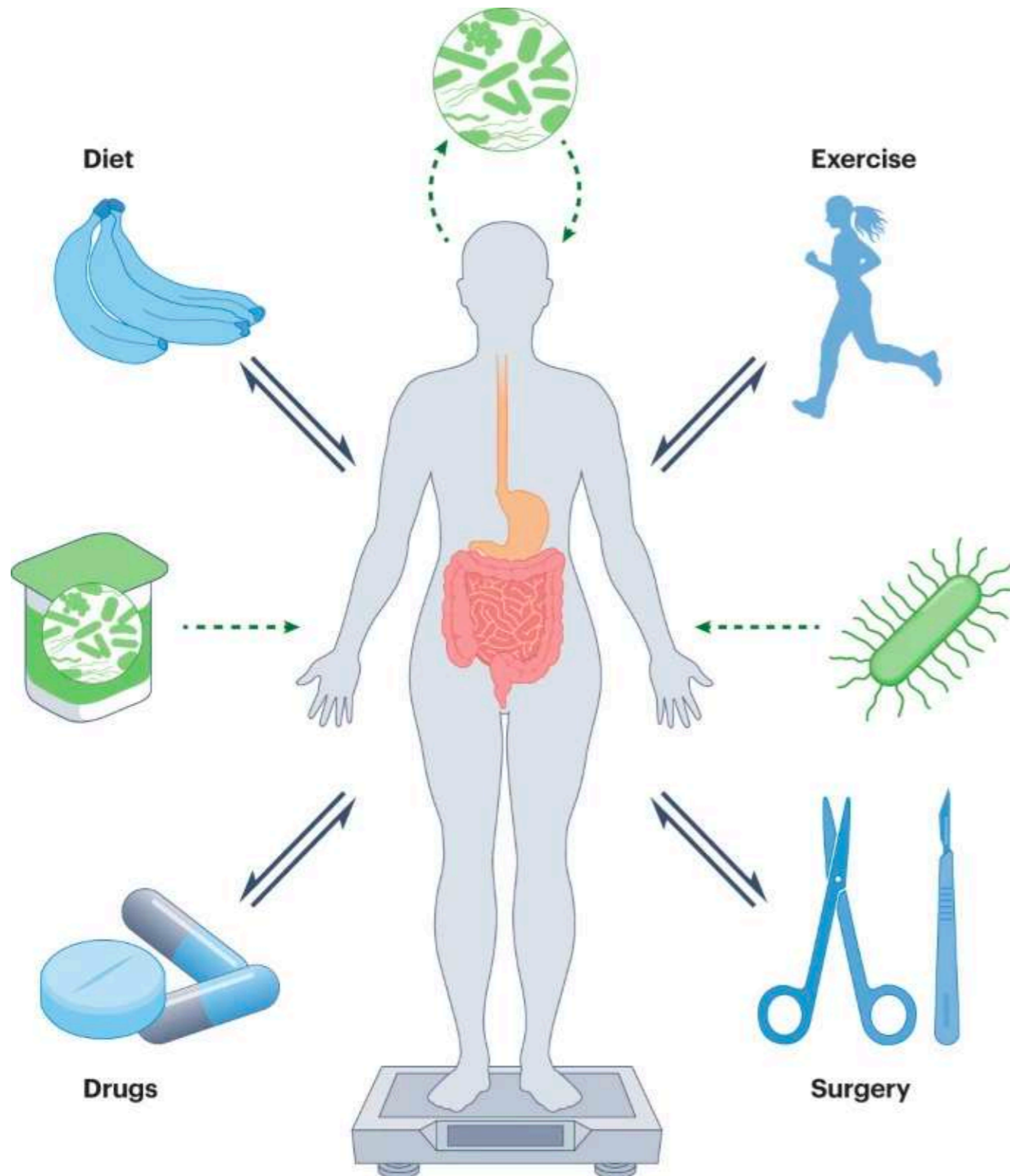
Microbiome alterations in ageing (and unhealthy ageing)

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.



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

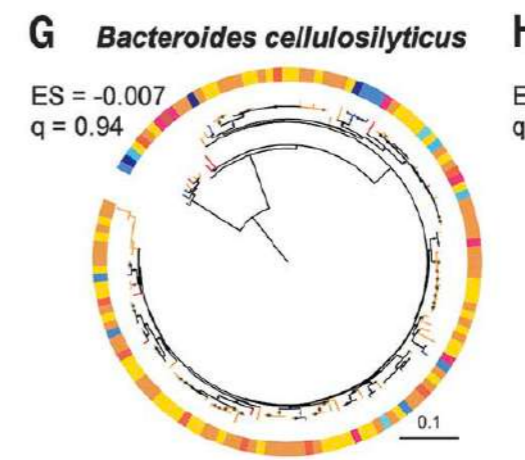
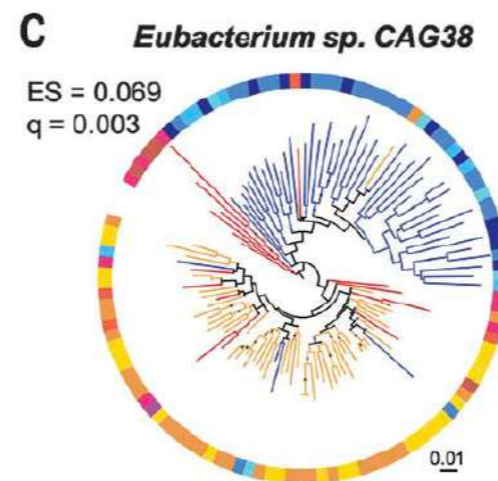
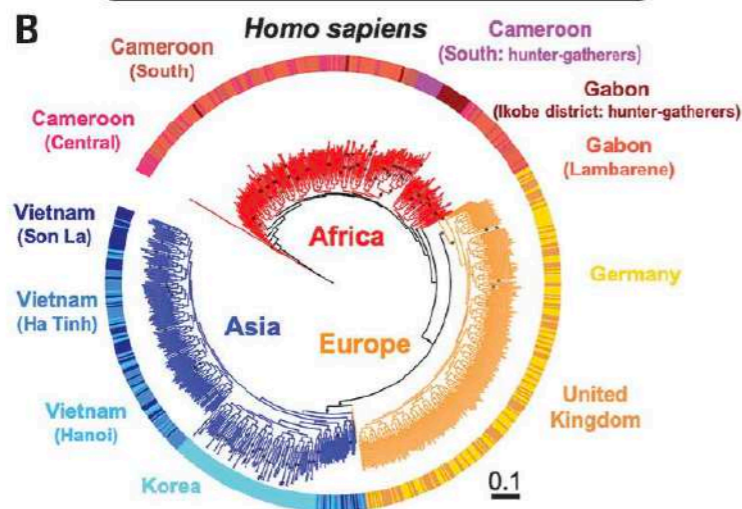
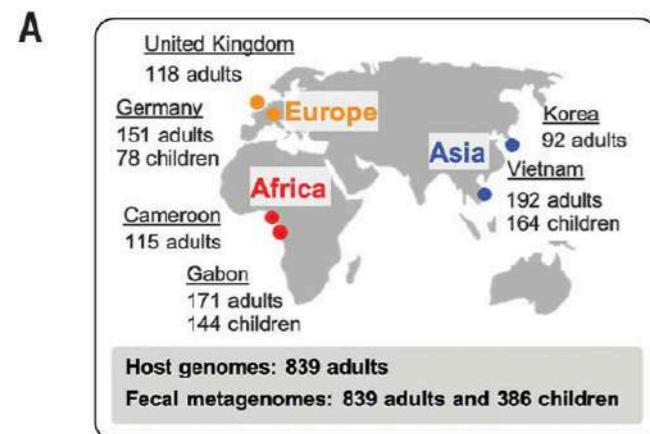
Where do human gut microbiota come from?

Vertical and horizontal transmission

Transmission modes differ by microbial taxa —>

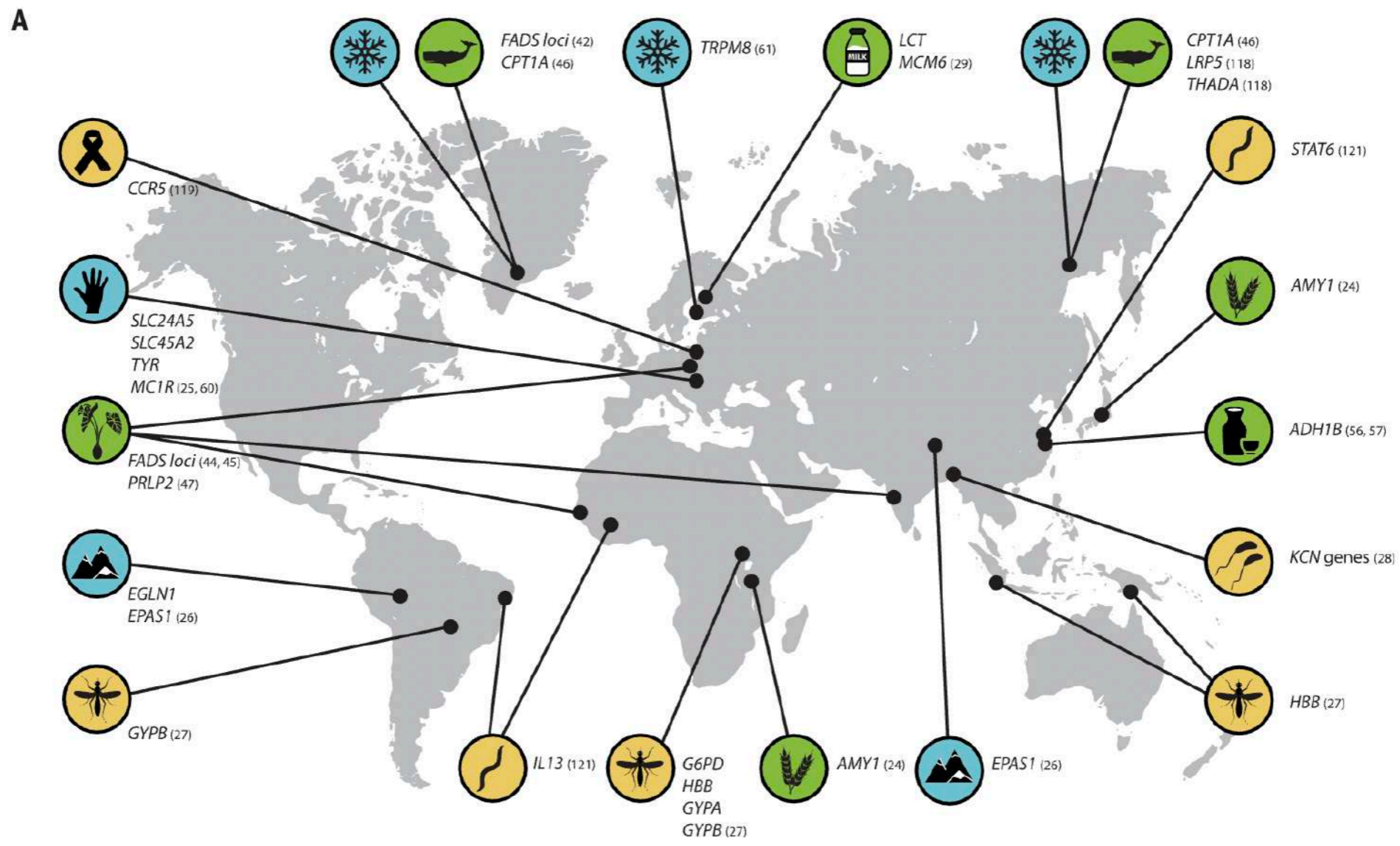
the degree of horizontal transmission predicted bacterial genera with pathogenic representatives responsible for human infections and hospitalizations

Vertical transmission for thousand of generations following human dispersal



Firmicutes coevolved/cophylogeny with Humans
Smaller the genome/larger the cophylogeny —> intimate symbiosis
Vertical transmission in populations

Local adaptations in humans where the involvement of microbiota has also been suggested, I



Local adaptations in humans where the involvement of microbiota has also been suggested, II

B

Selective agents and/or traits that are associated with the microbiome

High-milk intake



↑ **Bifidobacterium* (33, 67)

High-starch diet



↑ **Ruminococcus* (37)

High-plant diet



PUFA-metabolizing bacteria
(e.g., *Lactobacillus plantarum*) (48-51)
↑ *Treponema* (52-54)
↑ *Prevotella* (52-54)

High-fat diet



PUFA-metabolizing bacteria
(e.g., *Lactobacillus plantarum*) (48-51)
↑ *Bacteroides* (55)
↑ Clostridiales (55)

High-alcohol intake



↑ Proteobacteria
↓ Bacteroidetes
↑ *Streptococcus* (58, 59)

Cold stress



↓ Verrucomicrobia (63, 64)
↑ Deferribacteraceae (63-65)
↑ Lachnospiraceae (63-66)
↑ Parabacteroides (65)

Energy harvest



↓ Christensenellaceae and consortium (67)
↓ **Akkermansia* (73)
↑ ratio of Firmicutes/Bacteroidetes (62)

Skin pigmentation



Induction of pigmentation in melanocytes by bacteria and yeast (77)

High-altitude



↑ *Prevotella*
↑ SCFA-producing bacteria
↑ ACE-producing bacteria (83)

Malaria resistance



↑ *Lactobacillus*
↑ *Bifidobacterium* (87)

Cholera resistance



↑ *Blautia obeum* (90, 91)
↑ *Lactococcus lactis* (92)
↑ *Prevotella* spp. (91)
↓ *Paracoccus aminovorans* (91)

Helminth infection resistance



↑ *Bifidobacterium*
↑ *Lactobacillus* (11)

HIV-related disease resistance



↓ *Prevotella* in genitals reduce risk of transmission
↑ *Bifidobacterium*
↑ *Lactobacillus* (120)