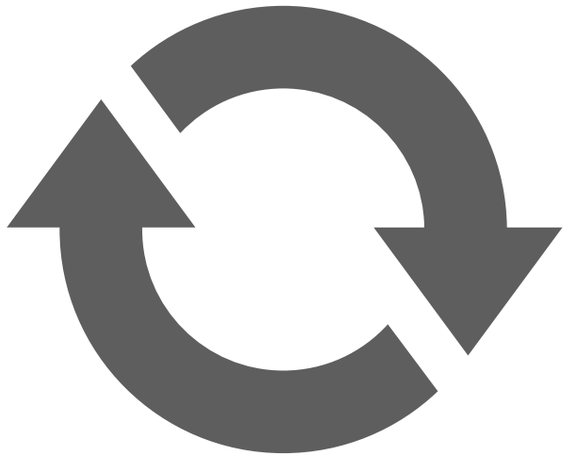
L08c

Symbiosis

- **Mutualism**
- **Parasitism**
- **Commensalism**

Dysbiosis



Holobiont

Dysbiosis

- ***Dysbiosis:*** *A status in which the relationship or interactions are heavily altered, possibly related to a major stress or infection event, are reversible (unhealthy state of the organisms), antonym is* ***Eubiosis***

- ***Dysbiosis*** *can cause/worsen a* ***disease***

HUMANS

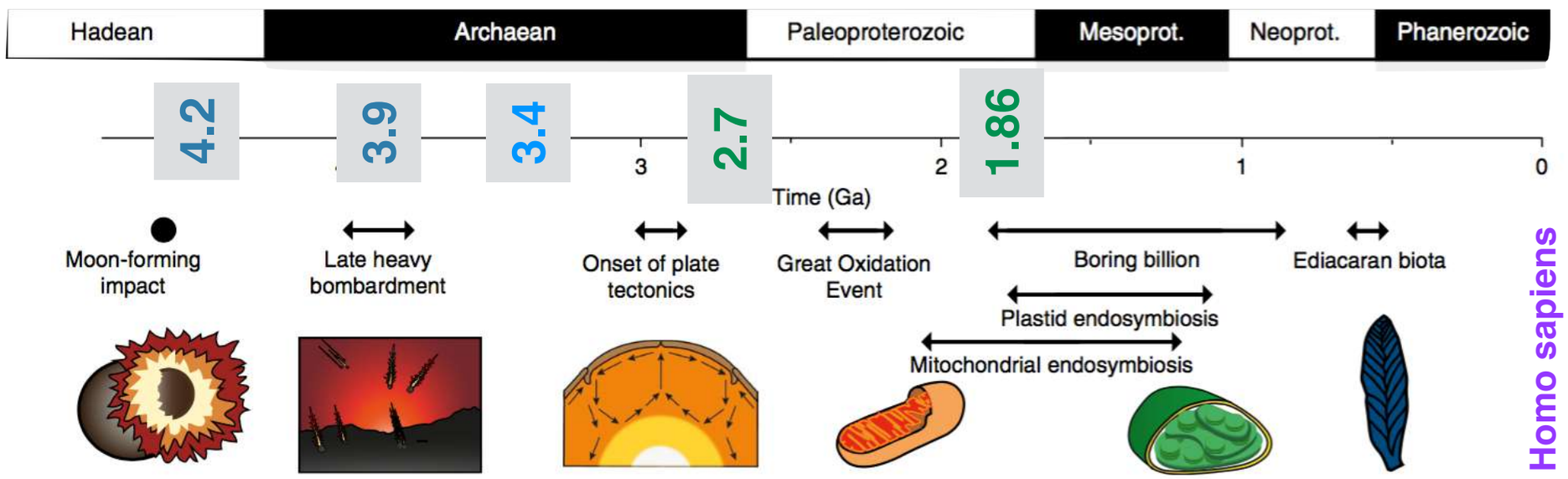
Microbial life on Earth

Strelley Pool Formation, stromatolites, Australia

Ocean formation

Modelling

Sterilization



Betts et al., 2018
Moody et al., 2024

LUCA

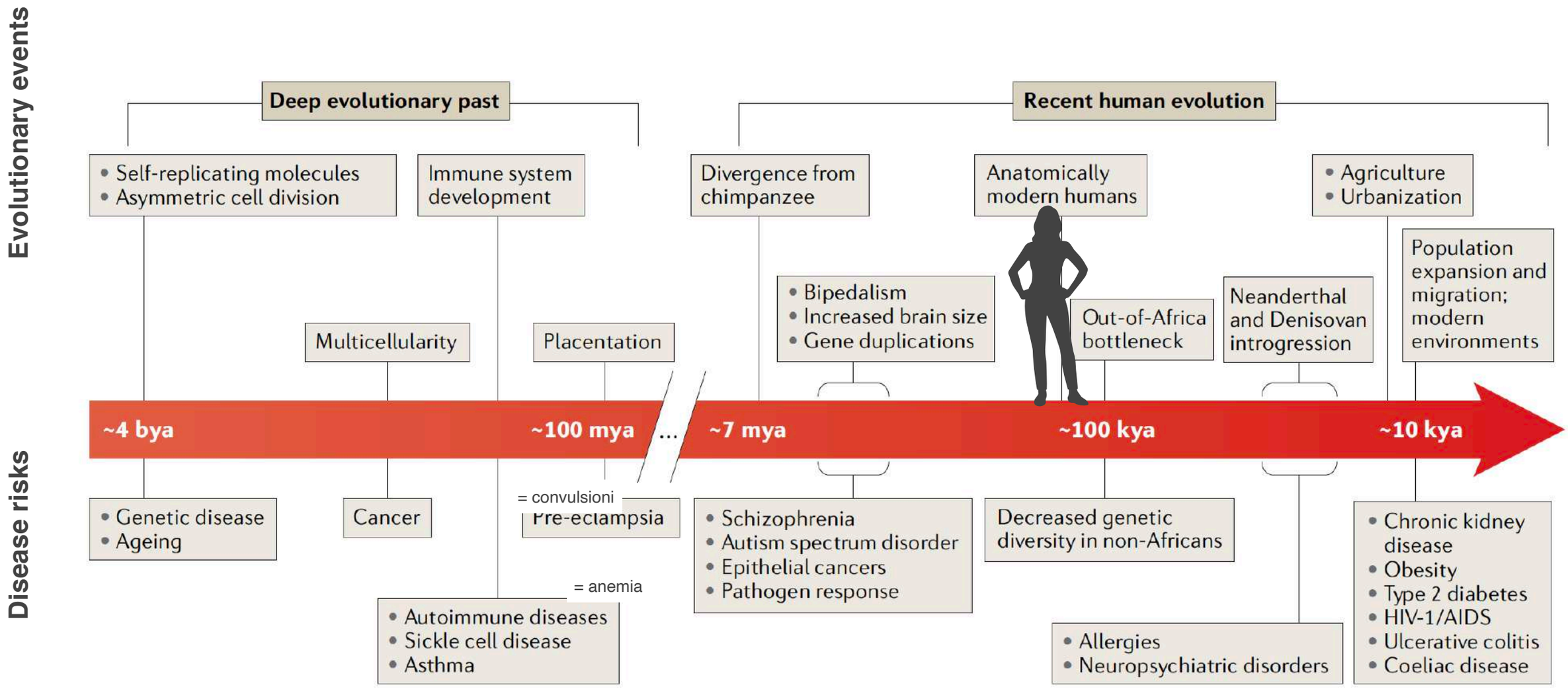
Bac & Arc

Euk

…a path for microbial symbiosis

LUCA: Last Universal Common Ancestor

VERY OLD and yet not so old SYMBIOSIS



A timeline of evolutionary events in the deep evolutionary past and on the human lineage and associated microbes

Benton et al., 2021

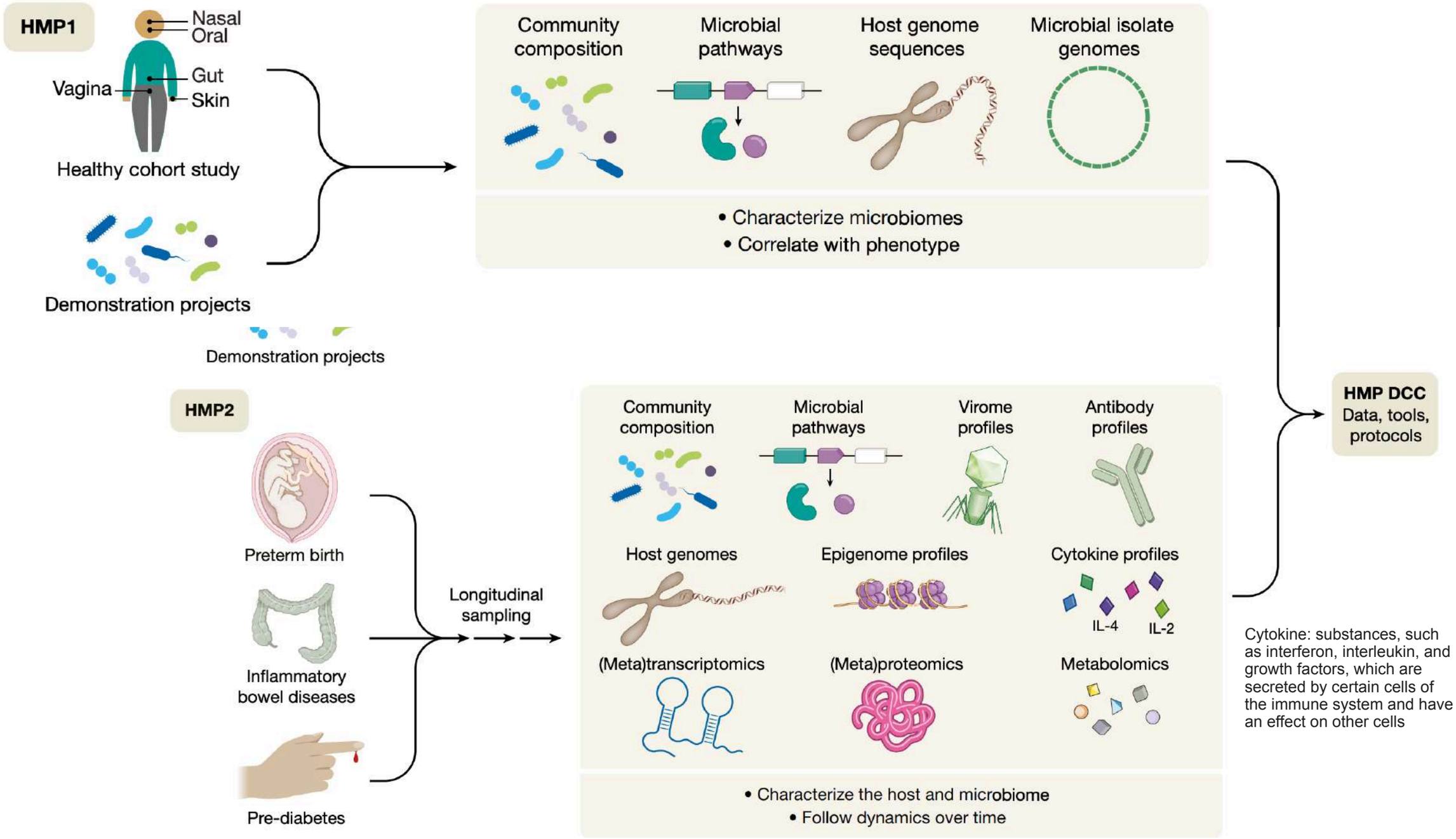
Ab initio

Prior 1983:

- **Knowledge based on culturable gut bacteria only**
- **Gut was considered as pretty axenic place**
- **Humans are humans**

Paradigm shift

HMP 1 & HMP 2

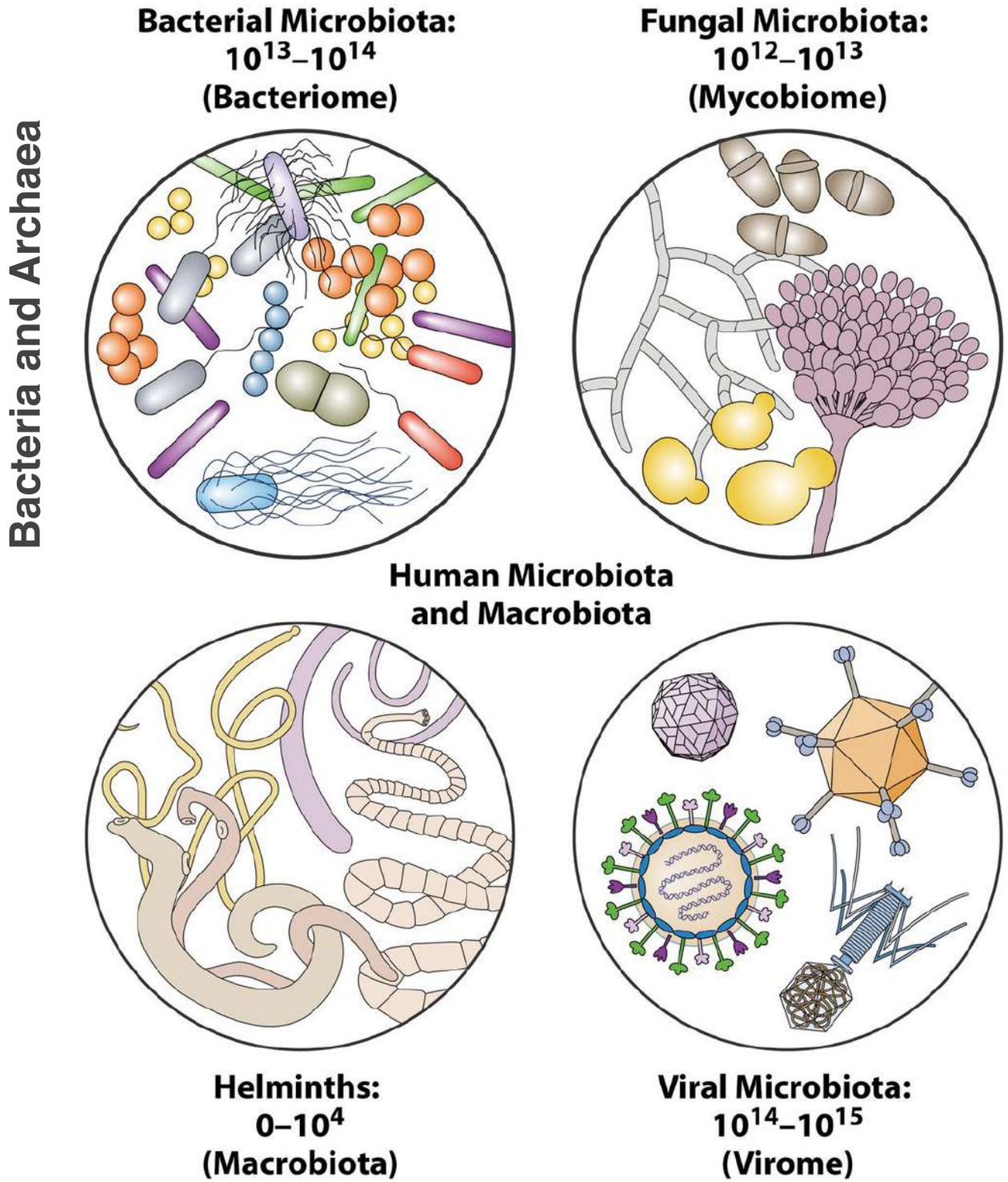


Cytokine: substances, such as interferon, interleukin, and growth factors, which are secreted by certain cells of the immune system and have an effect on other cells

iHMP, 2019

What is a human being?

- Complex microbial ecosystem
- Cross-Domain and Viral Interactions
- Multitude of microrganisms
- Humans are microbial zoos
- Humans and microbes are interconnected for life



Rowan-Nash et al., 2019

Microbes on/in Humans

Major questions:

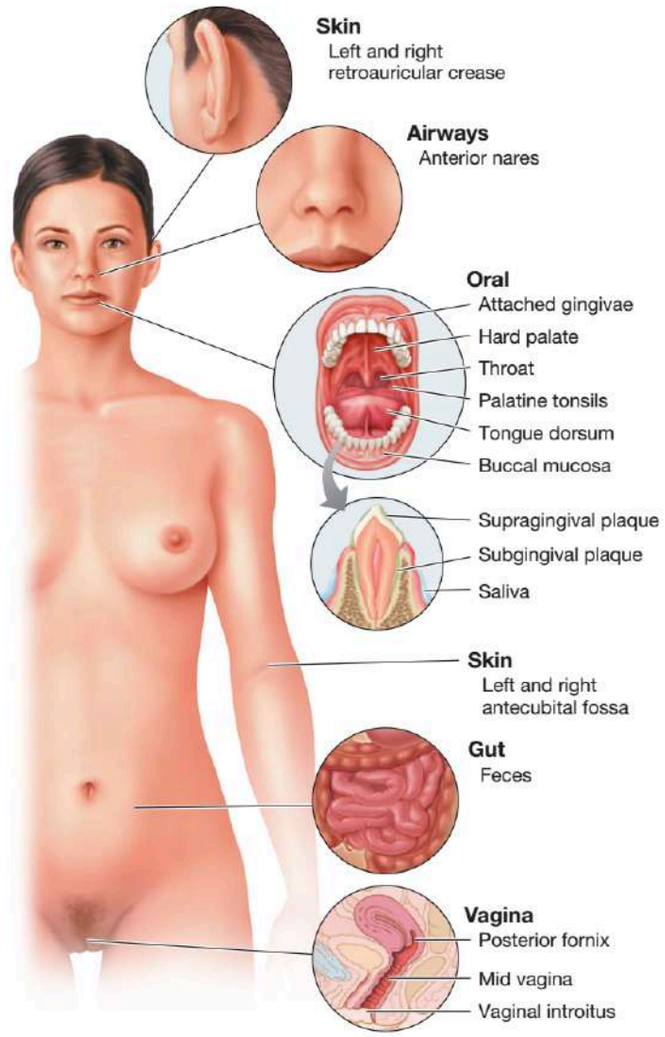
- Do individuals share a core human microbiome?
- Is there a correlation between the composition of microbiota colonizing a body site and host genotype?
- Do differences in human microbiome correlate with human health?
- Are differences in the relative abundance of specific bacterial populations important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

Now we now:

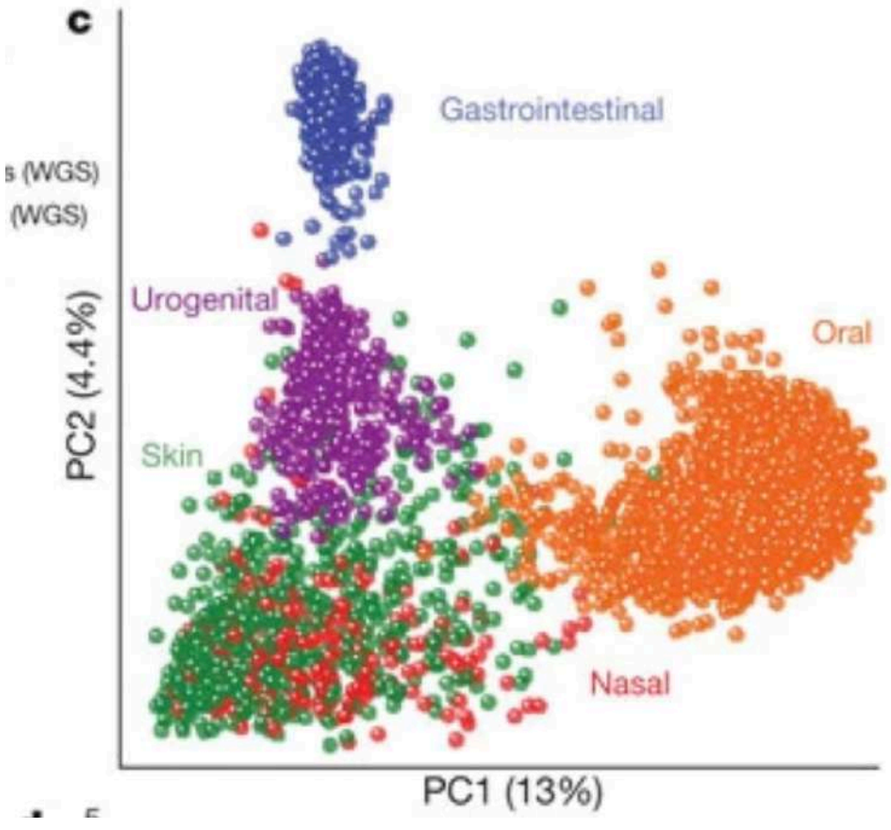
Microbial community (1) competes for and generates nutrients, (2) influences and is shaped by the host innate and adaptive systems, and (3) protects against pathogens and also triggers acute and chronic disease

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

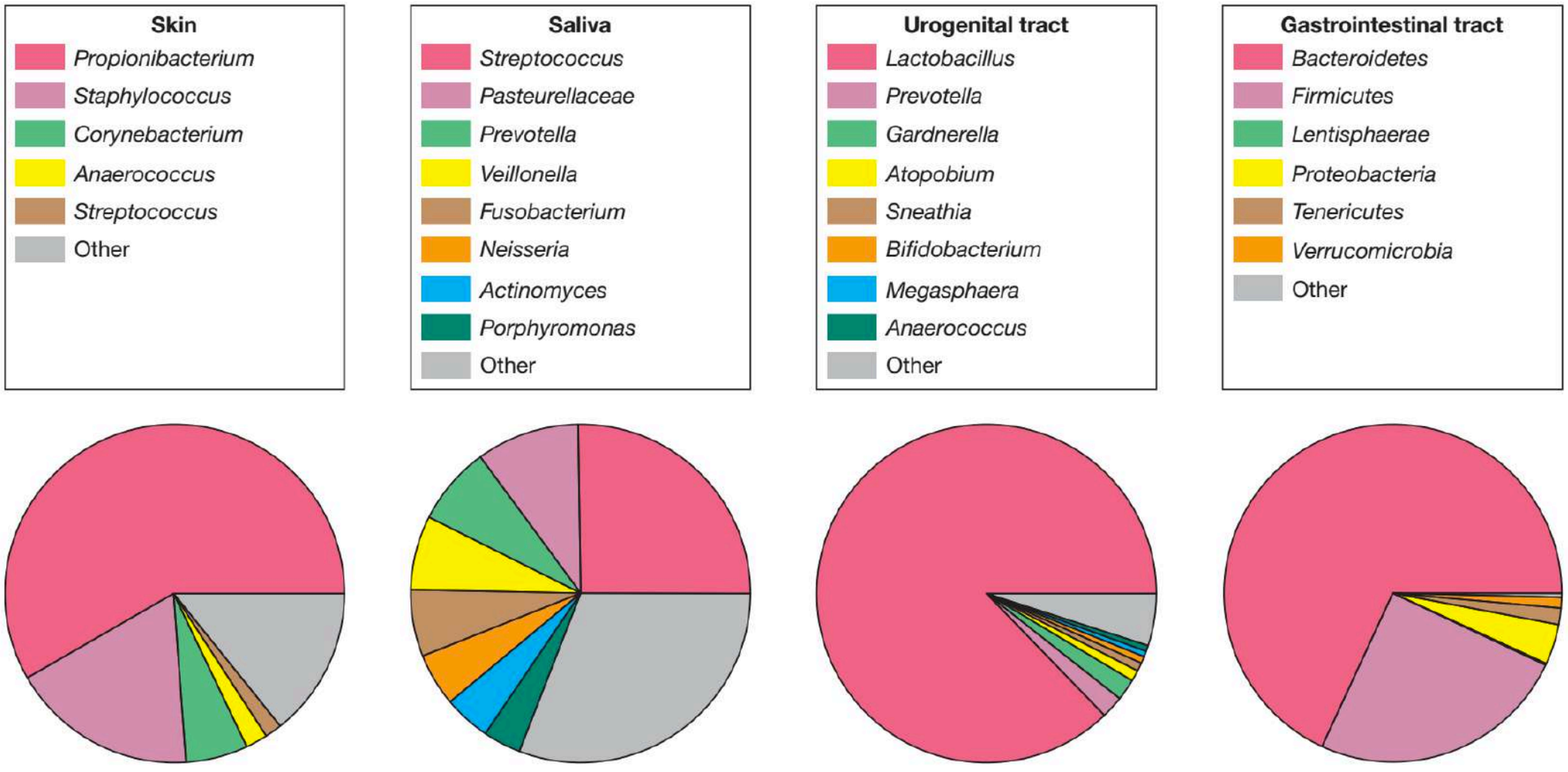


The Human Microbiome Project Consortium, 2012

What about viruses?

Human-microbes an ecosystem within ecosystems

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

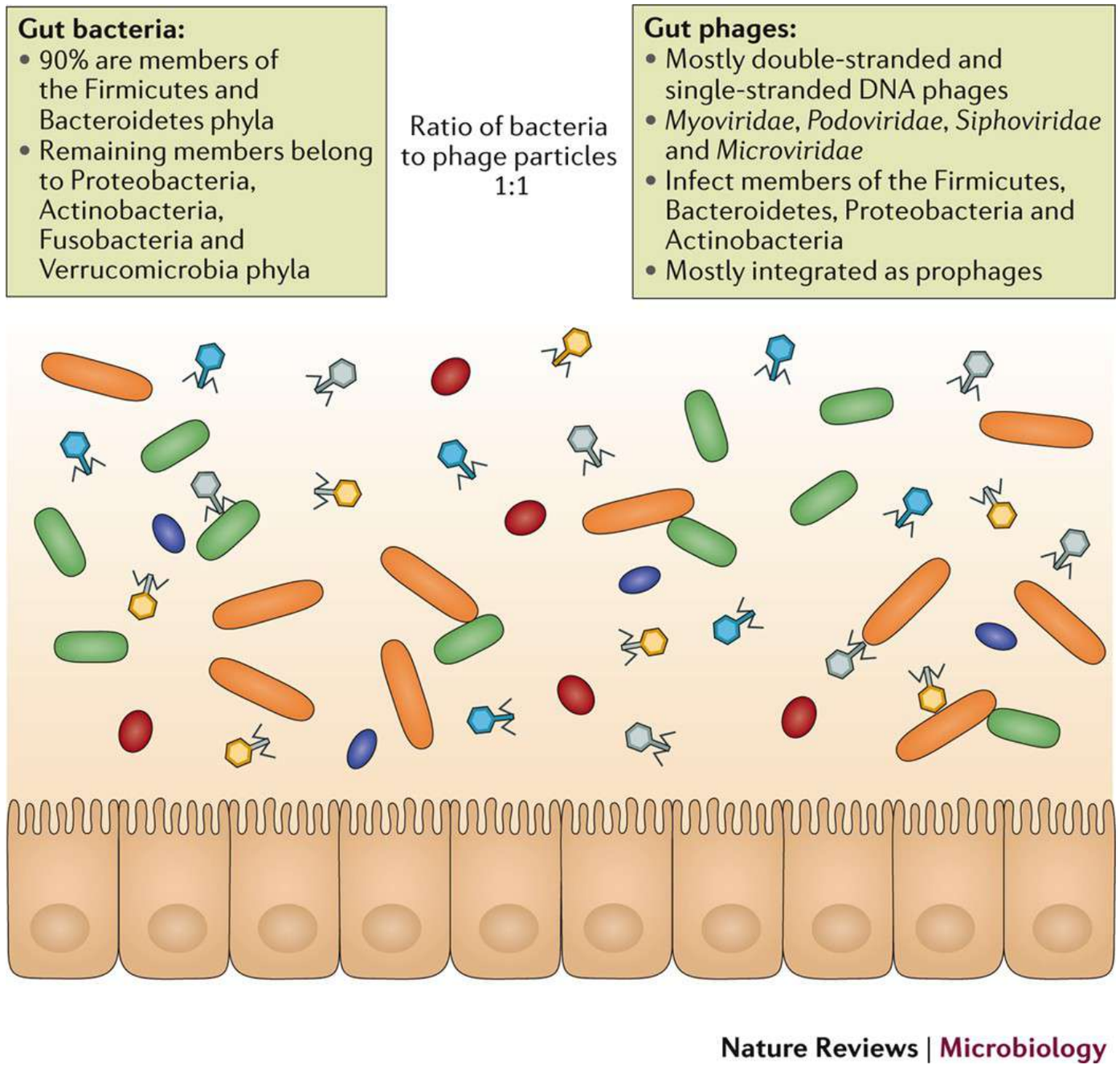


- 16S rRNA gene: species cluster with > 97% sequence similarity, culture-independent method

Madigan et al. 2018

Human Virome

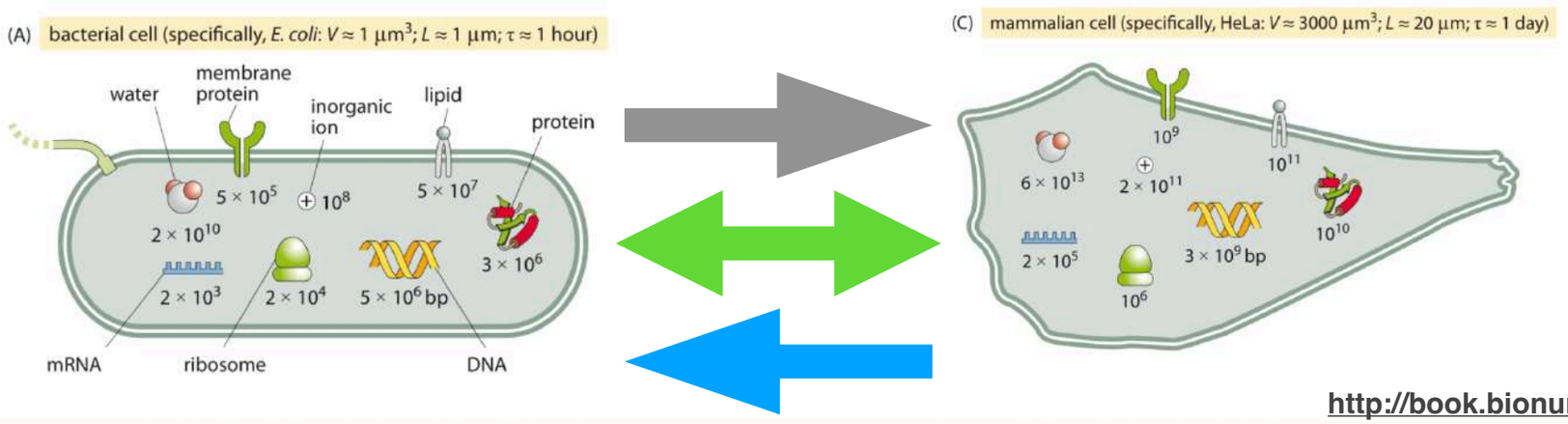
- The human gut is home to dense bacterial and **phage populations**
- —> regulating human health
- Phages regulate bacterial abundance, diversity and metabolism
- Phage effects in human gut remain largely unexplored
- Despite high bacterial abundance and metabolism
- Majority of described phages in the gut are integrated within their bacterial hosts (—> specific dynamic interactions)



Khan Mirzaei & Maurice, 2017

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

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

How do microbes interact with and within human as a whole unit?

What do microbes do for us?

How do microbe affect our functioning and our health?

Microbial factories for human health, I

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).

Madigan et al. 2018

Microbial factories for human health, II

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.

Madigan et al. 2018

Microbial factories for human health, III

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

Window of opportunity for interactions in order to train the immune system

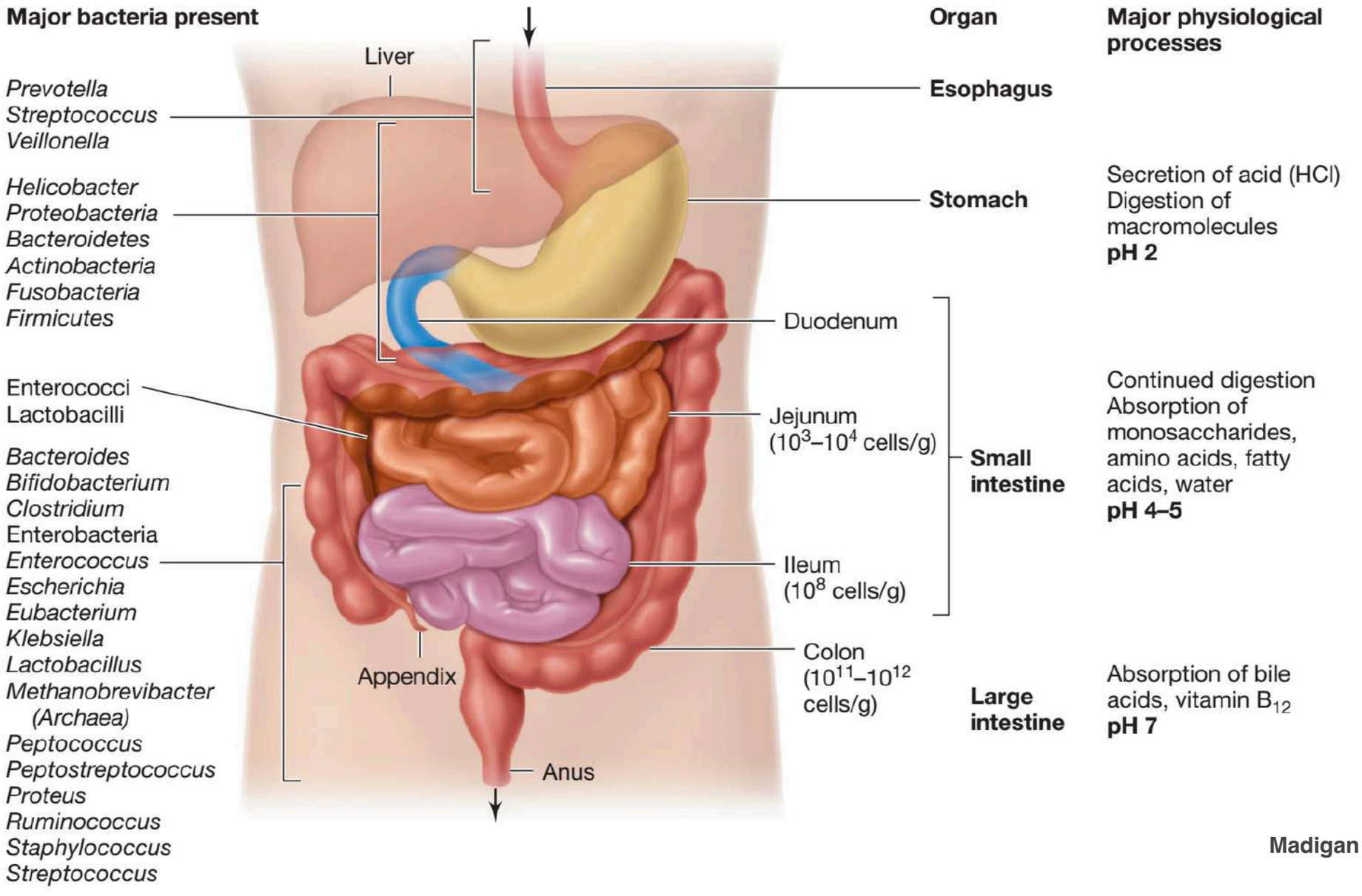
Madigan et al. 2018

The center stage: THE GUT

Gut-microbes association

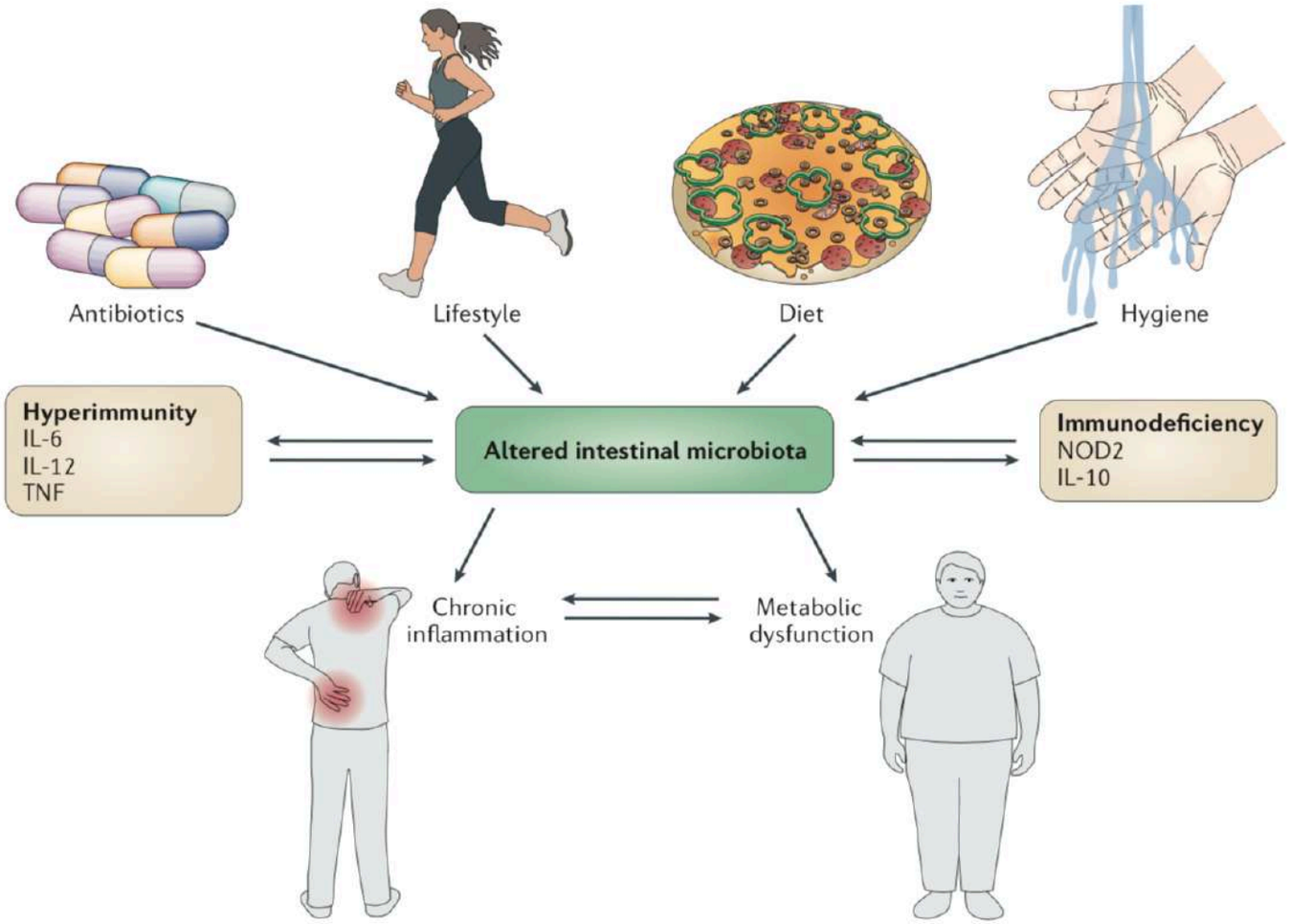
- Changing in space and time
- Changing with age host and health status
- Changing with food ingested and drugs

Ever-changing microbial communities and abundance



Madigan et al. 2018

Factor shaping microbial gut community

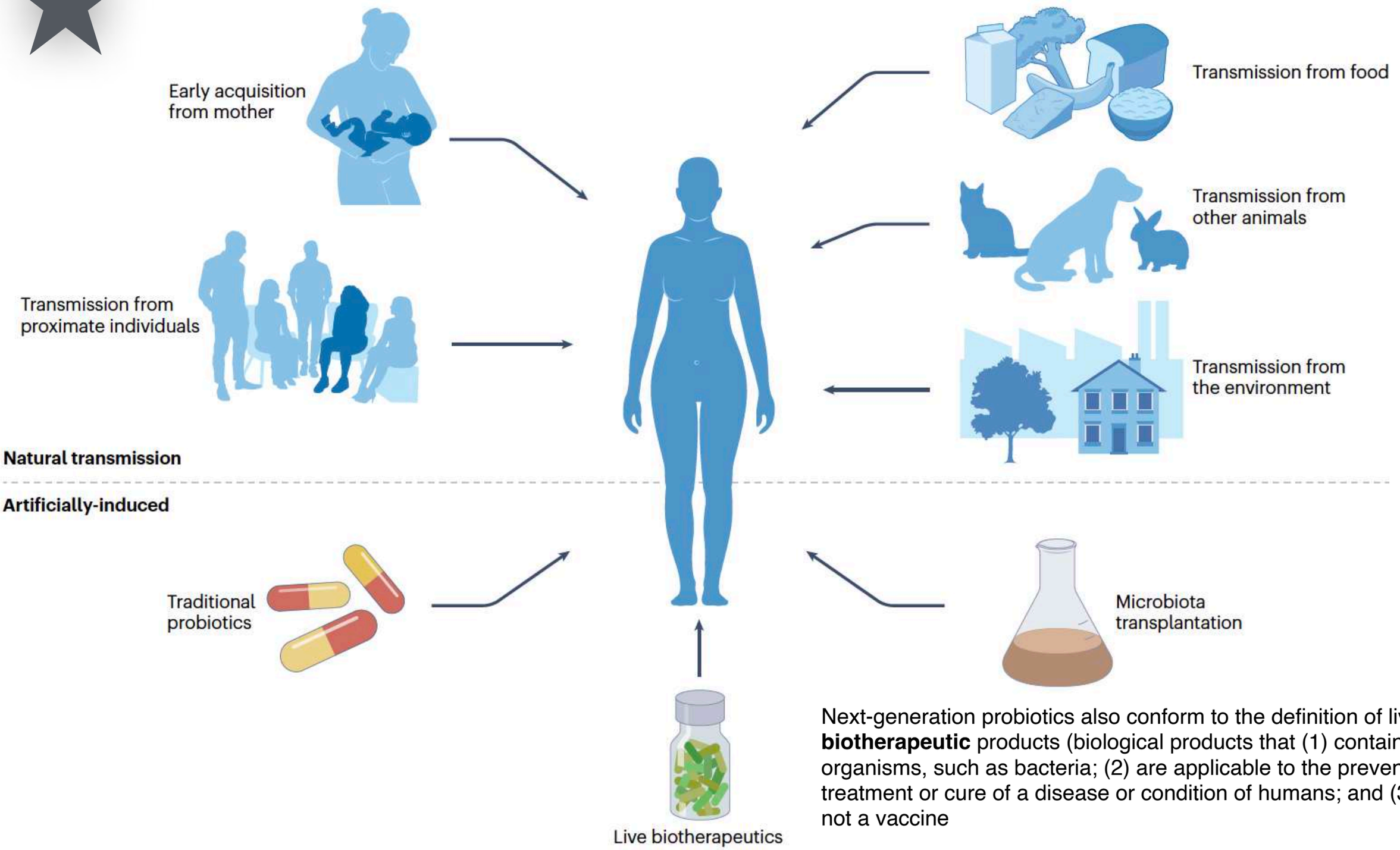


- Environmental factors: **antibiotics, lifestyle, diet and hygiene preferences**
- Host's **genetic** disposition has a role in influencing gut microbiota composition
- **Hyperimmunity** (owing to **over-representation of pro-inflammatory** mediators such as interleukin-6 (IL-6), IL-12 or tumour necrosis 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 c**hronic inflammation and metabolic dysfunction**

Sommer & Bäckhed, 2013

Which are the sources of microbes for us?

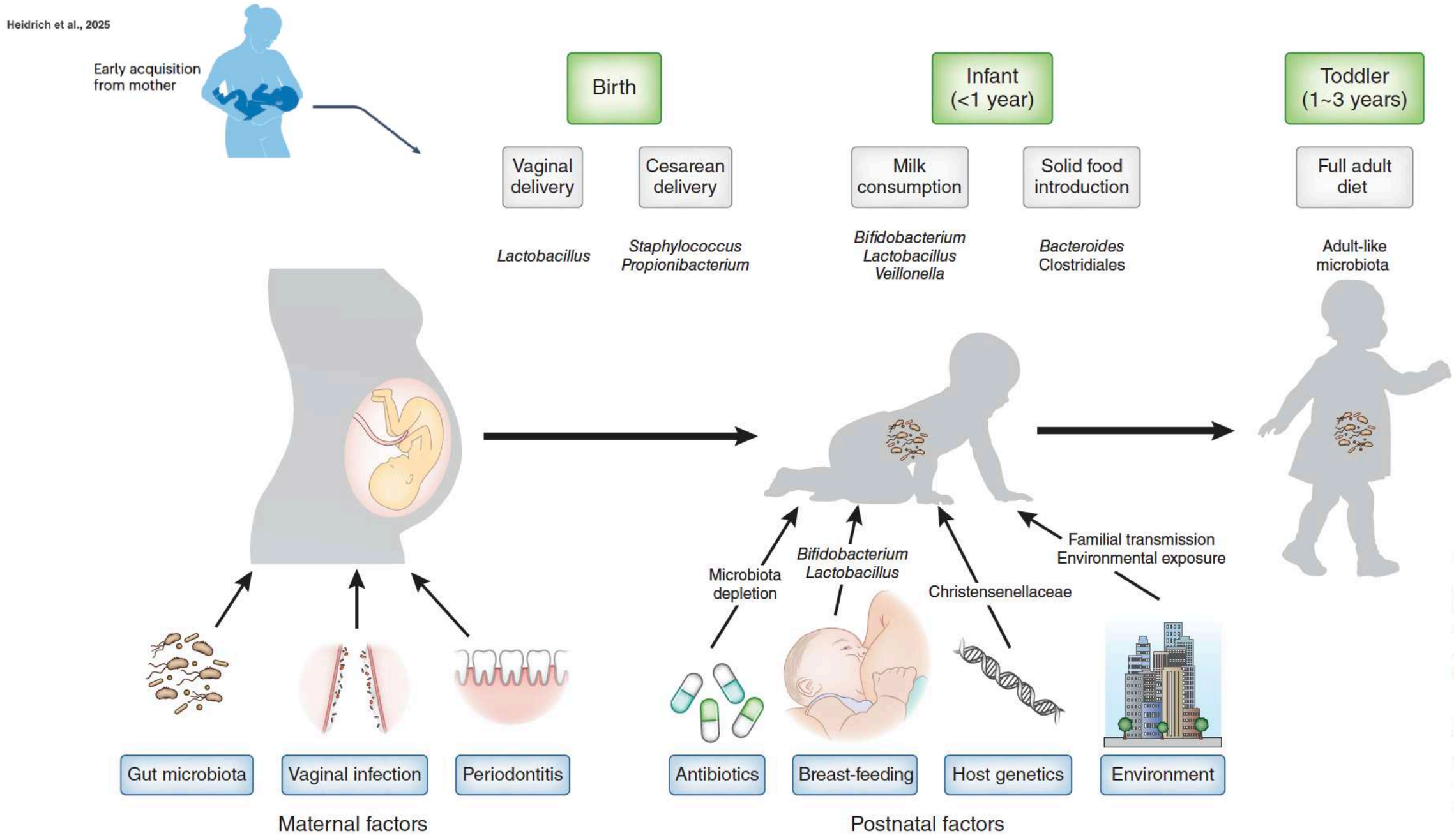
Diverse natural sources of human microbiome strains



Next-generation probiotics also conform to the definition of live **biotherapeutic** products (biological products that (1) contain live organisms, such as bacteria; (2) are applicable to the prevention, treatment or cure of a disease or condition of humans; and (3) are not a vaccine

Heidrich et al., 2025

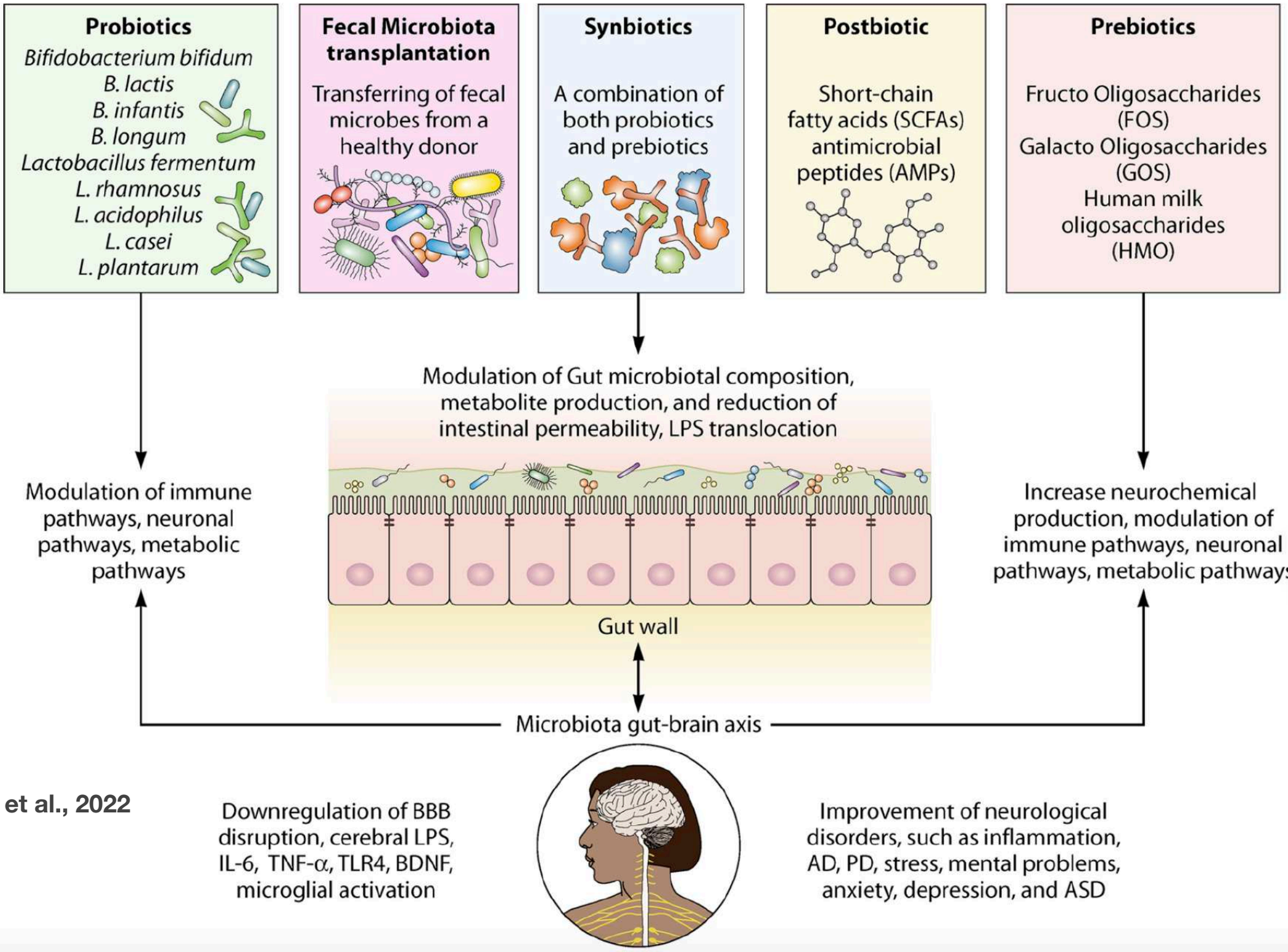
Focus on neonatal microbiome



Marina Corral Spence/Nature Publishing Group

How do we modulate the microbial community in our body?

Modulation of gut microbiota by therapeutic microbial interventions



Sorboni et al., 2022

Dysbiosis, I

- **Dysbiosis** is defined as a **disruption or imbalance** in the normal symbiotic microbial communities of the human body, which can contribute to disease
- C**hanges in microbial functional composition and metabolic activities, or changes in microbial local distribution**

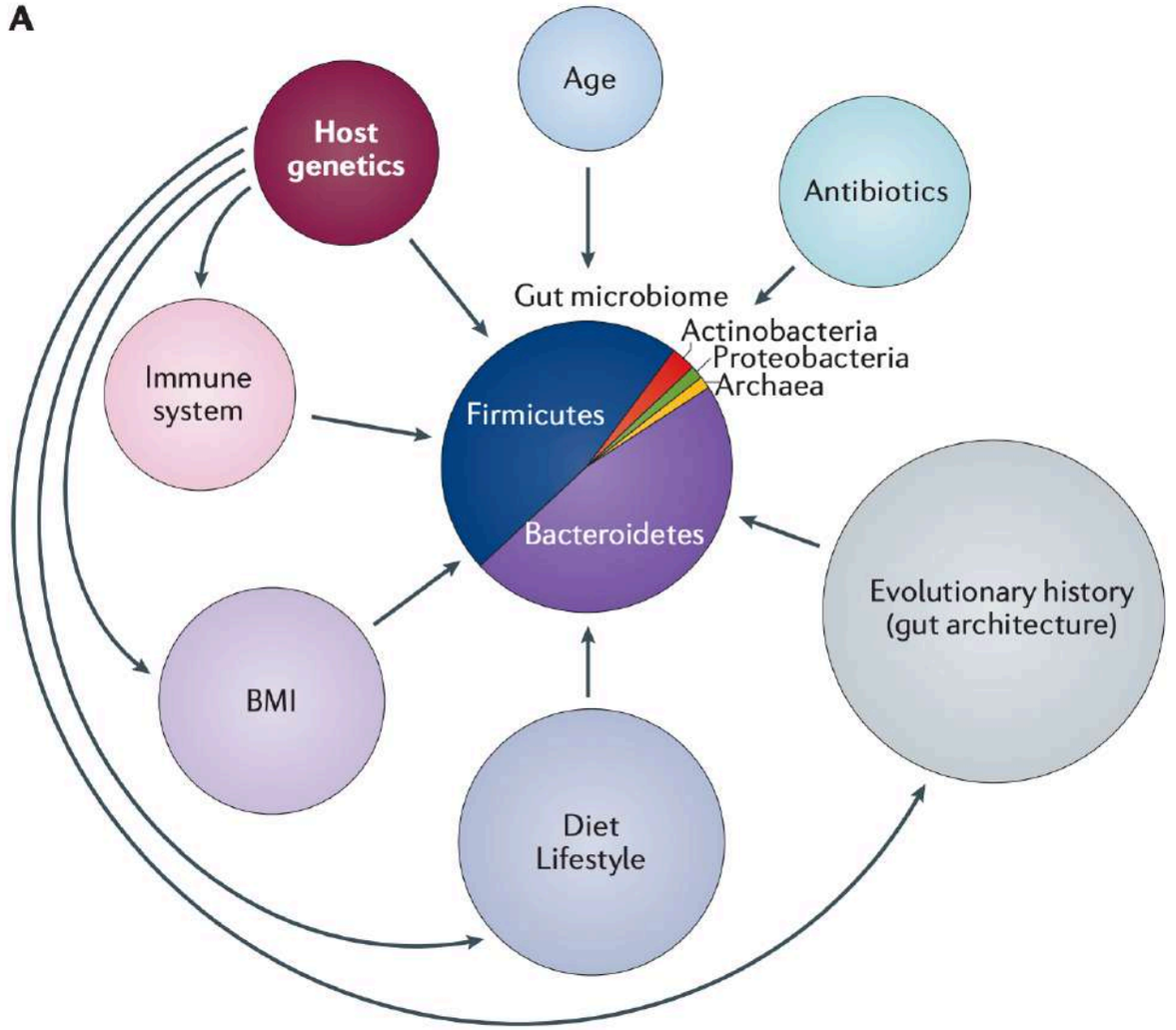
In general, dysbiosis can be categorized into three different types:

1) Loss of beneficial organisms

2) Excessive growth of potentially harmful organisms

3) Loss of overall microbial diversity

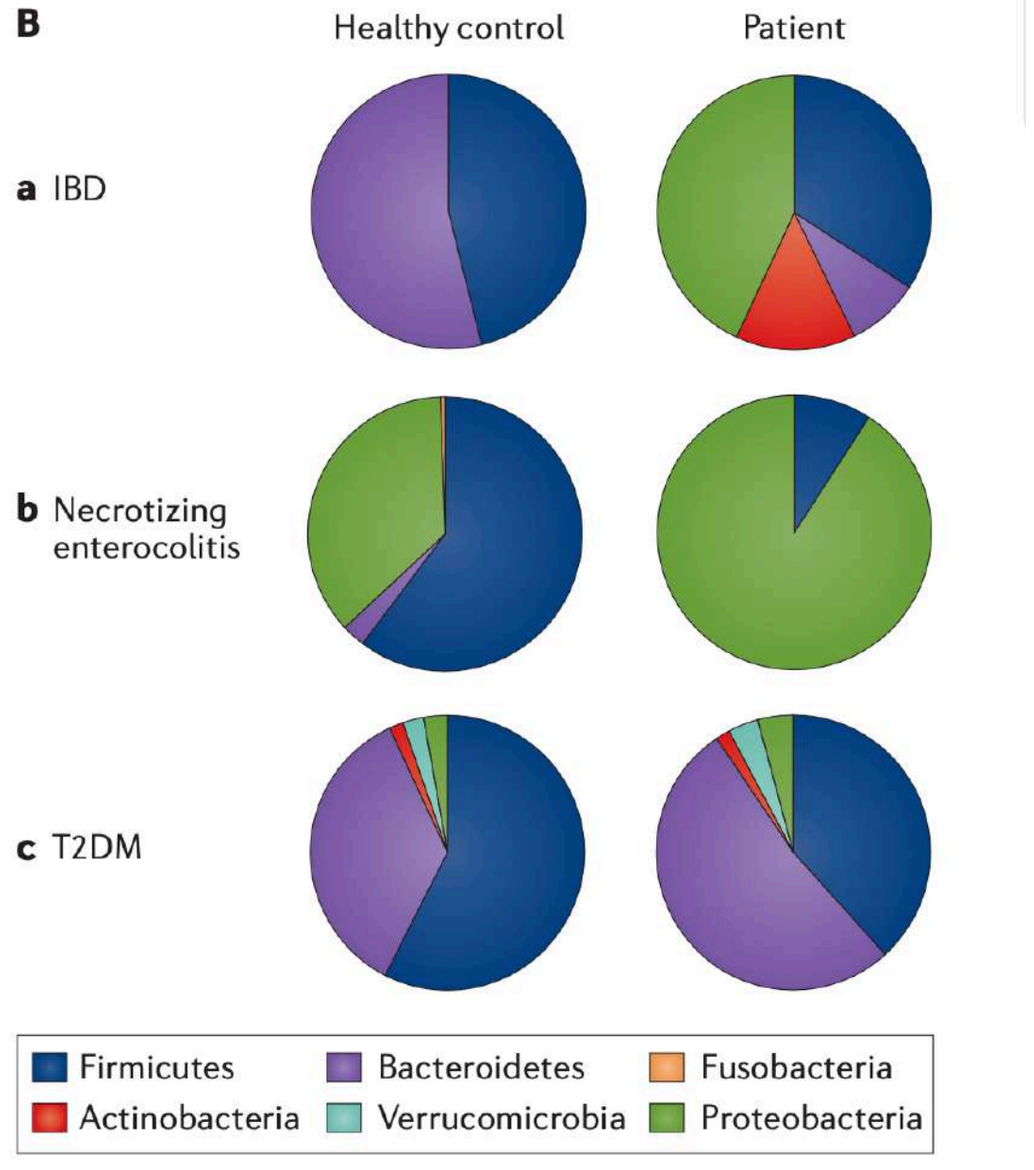
Changes of interactions among microbes due to changes in communities



Hall et al. 2017

Dysbiosis, II

- **Dysbiosis (altered microbial community)** of the gut microbiome has been implicated in multiple diseases:
  - Inflammatory bowel disease (IBD)
  - Necrotizing enterocolitis (in premature infants)
  - Type 2 diabetes mellitus (T2DM)
  - Colorectal cancer

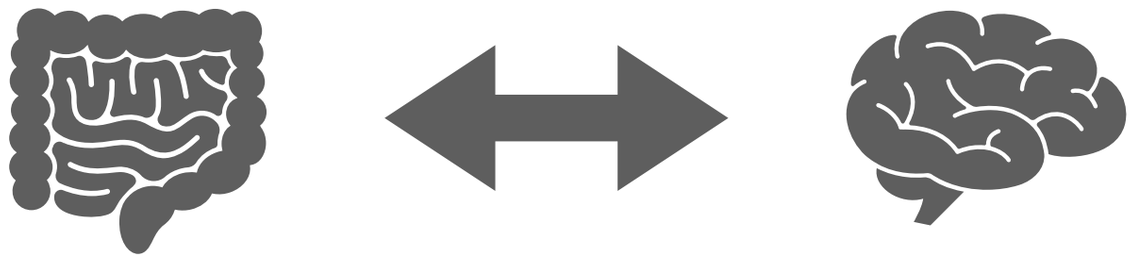


Hall et al. 2017

Gut-Brain axis

Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

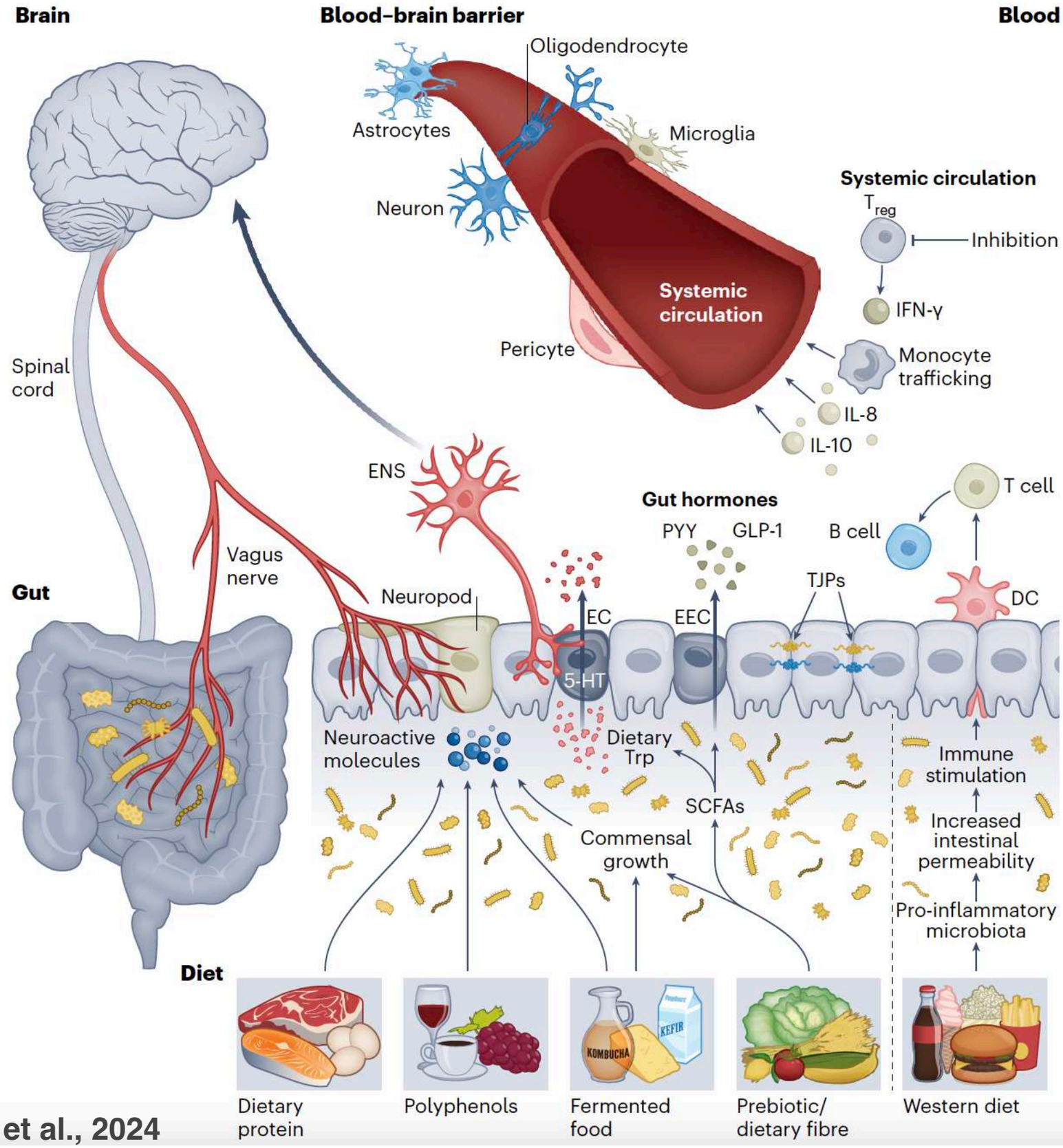
Discovery: microbes play important roles in keeping us healthy and happy



Gut as a second brain

https://www.who.int/about/accountability/governance/constitution#:~:text=Health%20is%20a%20state%20of,absence%20of%20disease%20or%20infirmity.

Mechanisms of action



DC, dendritic cell;
EC, enterochromaffin;
EEC, enteroendocrine cell;
ENS, enteric nervous system;
IFN-γ, interferon gamma;
Treg regulatory T cell;
TJPs, tight junction proteins;
Trp, trypotophan

Schneider et al., 2024

- Mechanisms of action: schematic overview of the several pathways of bidirectional communication through which the diet–microbiota–gut–brain axis impacts on cognition and emotion.

- Healthy dietary patterns, rich in fibre, fruits and vegetables, promote microbial diversity in the gut and the production of beneficial metabolites such as SCFAs.

- These metabolites can travel to the brain directly through the bloodstream, enhancing cognitive and emotional processing.

- Additionally, a healthy diet supports gut barrier integrity, preventing harmful substances from entering the bloodstream, and modulates the immune system to promote anti-inflammatory responses that benefit brain function.

- Neural pathways, such as signalling via the vagus nerve, also play a crucial role in transmitting signals from the gut microbiota to the brain.

- Conversely, the consumption of high-fat and high-sugar foods typical of the Western diet leads to a reduction in beneficial gut bacteria and increases the production of pro-inflammatory metabolites.

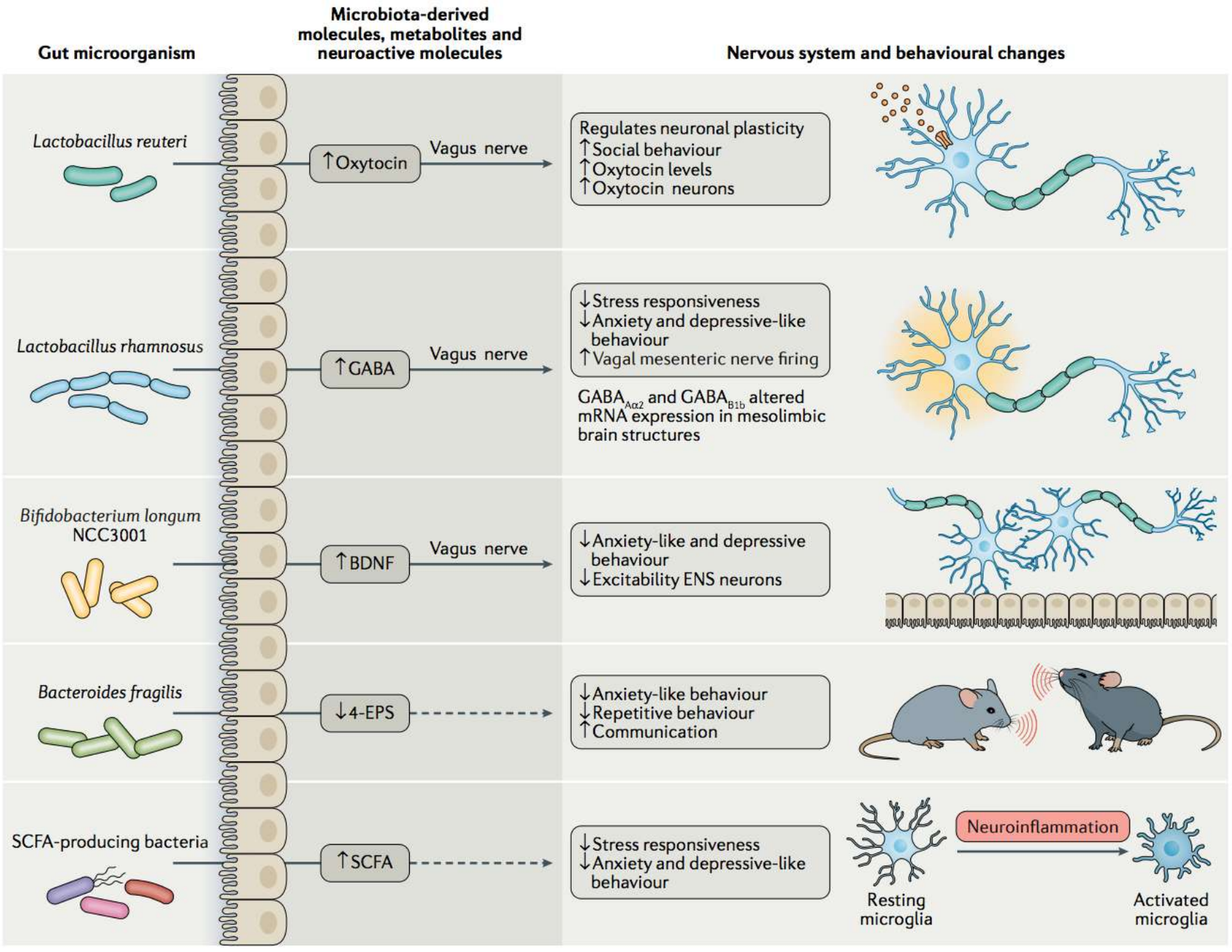
- This weakened gut barrier allows harmful substances to leak into the bloodstream, resulting in systemic inflammation that can negatively impact the brain.

- Inflammatory responses travel through the bloodstream and reach the brain, potentially affecting behaviour, cognition and emotional states.

- The schematic underscores the critical role of dietary choices in influencing mental health and cognitive function through these interconnected pathways involving gut microbiota and associated metabolic and inflammatory processes.

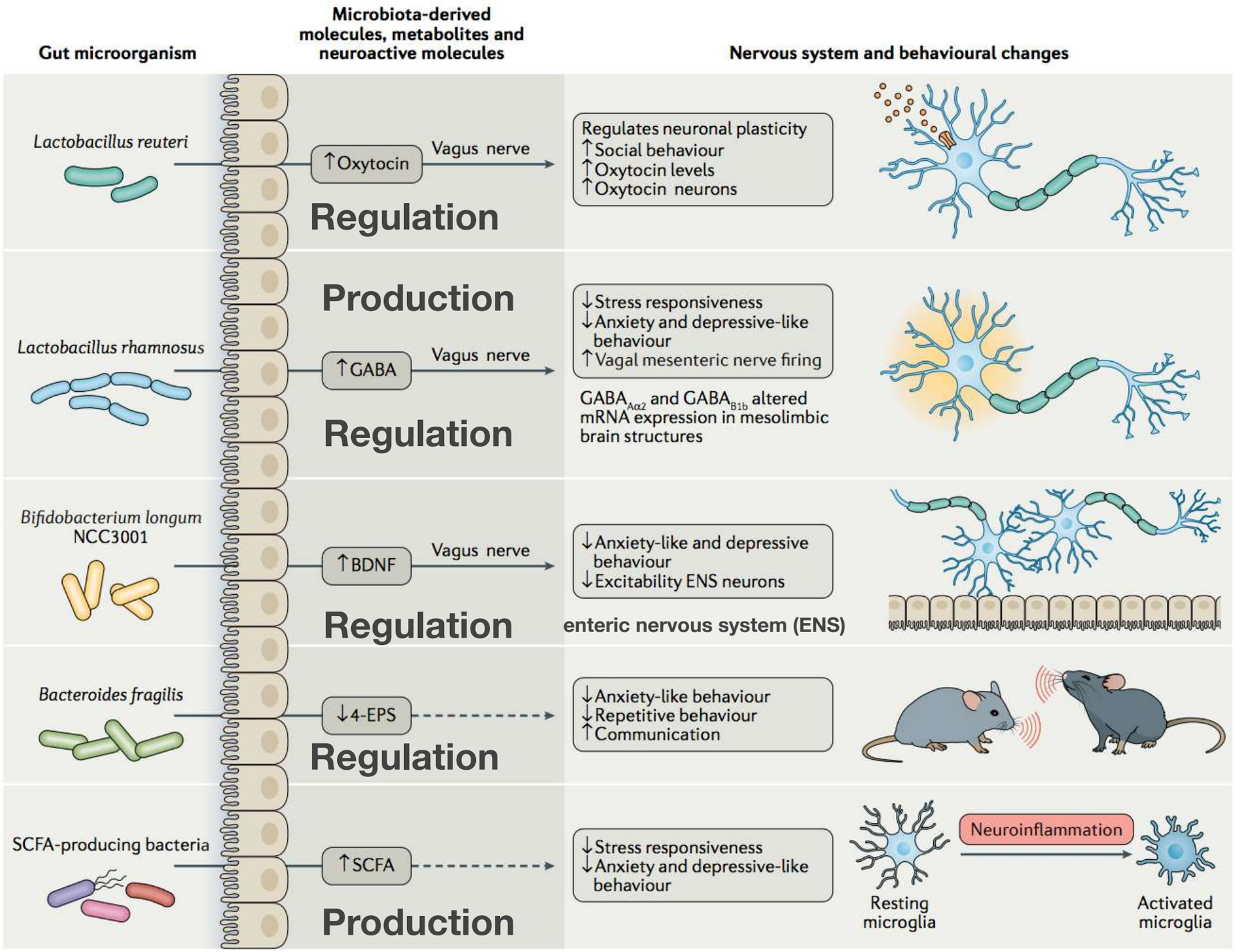
Microbiota and microbial-derived molecules modulate host behaviour and nervous system function

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)

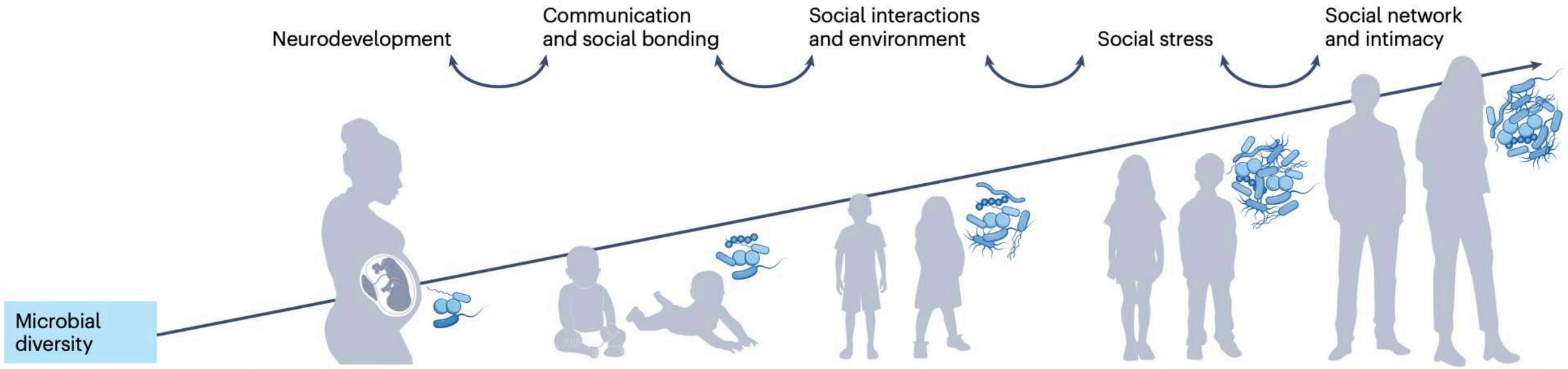
Brain-derived neurotrophic factor (BDNF)

4-ethylphenylsulfate (4-EPS)

Short-chain fatty acids (SCFAs)

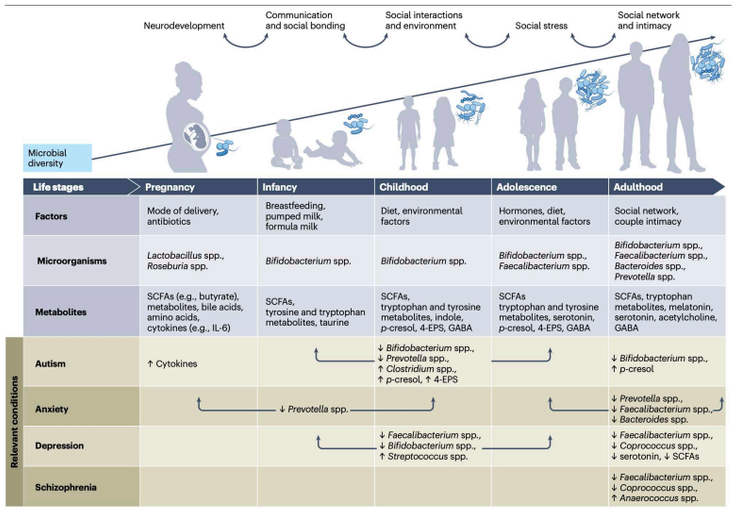
Morais et al., 2020

Influence of microbiota and metabolites on social behaviours across life stages



Life stages	Pregnancy	Infancy	Childhood	Adolescence	Adulthood
Factors	Mode of delivery, antibiotics	Breastfeeding, pumped milk, formula milk	Diet, environmental factors	Hormones, diet, environmental factors	Social network, couple intimacy
Microorganisms	*Lactobacillus* spp., *Roseburia* spp.	*Bifidobacterium* spp.	*Bifidobacterium* spp.	*Bifidobacterium* spp., *Faecalibacterium* spp.	*Bifidobacterium* spp., *Faecalibacterium* spp., *Bacteroides* spp., *Prevotella* spp.
Metabolites	SCFAs (e.g., butyrate), metabolites, bile acids, amino acids, cytokines (e.g., IL-6)	SCFAs, tyrosine and tryptophan metabolites, taurine	SCFAs, tryptophan and tyrosine metabolites, indole, *p*-cresol, 4-EPS, GABA	SCFAs tryptophan and tyrosine metabolites, serotonin, *p*-cresol, 4-EPS, GABA	SCFAs, tryptophan metabolites, melatonin, serotonin, acetylcholine, GABA
Relevant conditions					
Autism	↑ Cytokines		↓ *Bifidobacterium* spp., ↓ *Prevotella* spp., ↑ *Clostridium* spp., ↑ *p*-cresol, ↑ 4-EPS		↓ *Bifidobacterium* spp., ↑ *p*-cresol
Anxiety		↓ *Prevotella* spp.			↓ *Prevotella* spp., ↓ *Faecalibacterium* spp., ↓ *Bacteroides* spp.
Depression			↓ *Faecalibacterium* spp., ↓ *Bifidobacterium* spp., ↑ *Streptococcus* spp.		↓ *Faecalibacterium* spp., ↓ *Coprococcus* spp., ↓ serotonin, ↓ SCFAs
Schizophrenia					↓ *Faecalibacterium* spp., ↓ *Coprococcus* spp., ↑ *Anaerococcus* spp.

Griffiths et al., 2026



Influence of microbiota and metabolites on social behaviours across life stages. Changes in gut microbial diversity, microbial composition and metabolite production occurring across different life stages influence critical aspects of social behaviours, including social immunity, communication, social bonding, social interactions and stress responses. Pregnancy: mode of delivery (vaginal versus caesarean) and antibiotic exposure notably affect maternal and fetal microbial diversity. Microorganisms such as Lactobacillus and Roseburia dominate and produce metabolites such as short-chain fatty acids (SCFAs; for example, butyrate), bile acids, amino acids and cytokines (for example, IL-6), which modulate social immunity and neurodevelopment. Infancy and childhood: breastfeeding promotes the colonization of beneficial microorganisms such as Bifidobacterium, which produce metabolites such as

SCFAs, tryptophan derivatives, gamma amino butyric acid (GABA) and phenolic compounds (p-cresol), contributing to early communication and social bonding, and influencing social interactions. Adolescence: hormonal and dietary changes regulate the microbiota composition, dominated mostly by Bifidobacterium and Faecalibacterium, and microbially derived SCFAs, serotonin and GABA support stress resilience and social cognition. Adulthood: social networks, couple intimacy, lifestyle and cohabitation (including shared diet) stabilize the diversity and maturity of the microbiome. Dominant microorganisms such as Bacteroides and Prevotella produce metabolites such as melatonin, serotonin, acetylcholine and GABA, regulating emotional wellbeing and intimate relationships. Microbial influences on relevant neurological disorders with social behavioural impairments are also highlighted (relevant conditions). 4-EPS, 4-ethylphenyl sulfate.

The gut microbiome shapes social behaviour across animal species

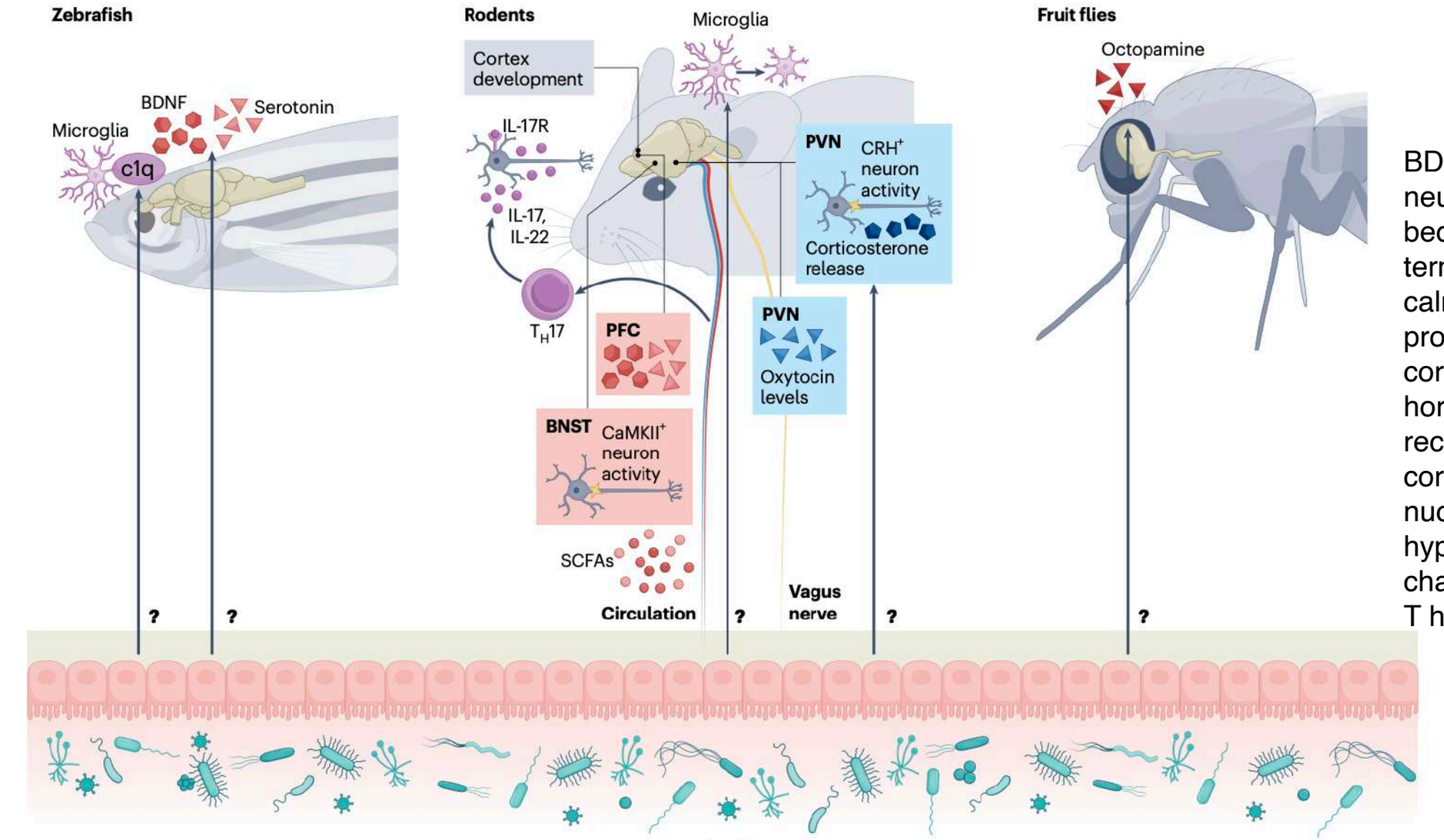
Table 1 | Known routes of gut–brain axis influence on social behaviour in laboratory animals

Type of model	Microbial alteration	Physiological effects	Behaviour
Rodent models	Germ free	–	↓ Social interaction
	Penicillin treated (early life)	↓ Hippocampal *Bdnf*	↓ Social recognition
	Antibiotic treated (early life)	↓ Oxytocin receptor, ↓ myelin genes in the PFC	↓ Social interaction
	Antibiotic treated (ongoing)	↑ HPA axis activation	↓ Social interaction
	SCFAs	↑ Activation of $CaMKII^{+}$ neurons in the BNST	↓ Social novelty, ↑ social interaction in mouse models
	Lactobacillus rhamnosus[a]	–	↑ Sociability
	Enterococcus faecalis[b]	↓ Corticosterone	↑ Social interaction
	Bacteroides fragilis[b]	(In MIA model): ↑ gut barrier integrity, ↓ MIA metabolites (such as 4-EPS)	↑ Social communication
	Lactobacillus reuteri[a]	↑ Oxytocin, ↑ tetrahydrobiopterin (BH4) synthesis	↑ Social interaction
	Bifidobacterium[b]	–	↑ Resilience, ↑ sociability
	Mucosa-associated fungi[a]	↑ IL-17R-dependent signalling in neurons	↑ Social interaction
	Commensal gut virome[c]	↓ Corticosterone	↑ Resilience, ↑ sociability
Fruitfly model	Germ free	↓ Octopamine	↓ Aggression, ↓ male mate competition
	Antibiotic treated	↓ Cuticular hydrocarbons	↓ Matings with untreated flies
	Wolbachia[d,e,f]	↓ Octopamine	↑ Male mating rates, ↓ aggression
	Lactobacillus plantarum[g]	–	↑ Sociability in genetic *kdm5* knockout
	Pseudomonas aeruginosa[h]	–	↓ Attractiveness to potential mates
Zebrafish model	Germ free	↓ Microglia	↓ Social interaction
	Lactobacillus rhamnosus[i]	↑ Serotonergic signalling, ↑ *bdnf*	Modifies shoaling

[a]Cultured bacteria added to drinking water. [b]Oral gavage of cultured microorganism. [c]Oral gavage of purified extract from faecal material. [d]Separated from controls through screening of carriers. [e]Generated control lines by treatment with antibiotics, then microbiota homogenization. [f]Transferred bacteria by carrier line. [g]Cultured bacteria added to *Drosophila* media. [h]Cultured bacteria applied through abdominal prick. [i]Cultured bacteria added to flask water. Bdnf, brain-derived neurotrophic factor; BNST, bed nucleus of the stria terminalis; CaMKII, calcium–calmodulin-dependent protein kinase II; HPA, hypothalamic–pituitary–adrenal; IL-17R, IL-17 receptor; kdm5, lysine demethylase 5; MIA, maternal immune activation; PFC, prefrontal cortex; SCFA, short-chain fatty acid; 4-EPS, 4-ethylphenyl sulfate.

Griffiths et al., 2026

Mechanisms for gut–brain interactions with consequences on social behaviour



Griffiths et al., 2026

BDNF, brain-derived neurotrophic factor; BNST, bed nucleus of the stria terminalis; CaMKII, calcium–calmodulin-dependent protein kinase II; CRH, corticotropin- releasing hormone; IL-17R, IL-17 receptor; PFC, prefrontal cortex; PVN, paraventricular nucleus of the hypothalamus; SCFA, short-chain fatty acid; TH17, CD4+ T helper 17 cell

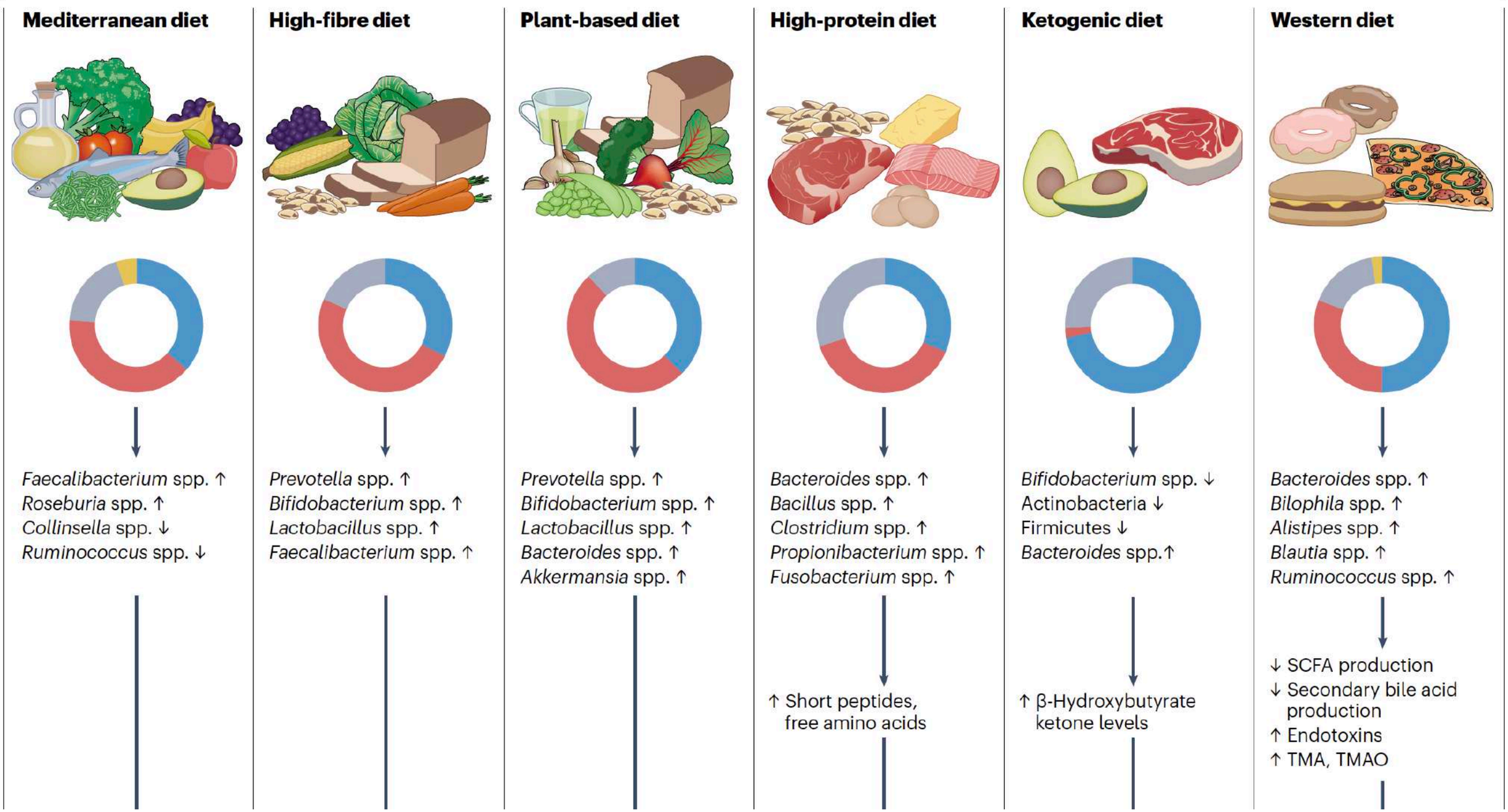
- The gut microbiome (bottom) has known functional effects on brain function (top) that shape social behaviour in laboratory animals (zebrafish, rodents and fruitflies)
- Common mechanisms include signalling via **small molecules**, the **stress response and/or hormones** and **immune mediators**
- These pathways might **work independently or in concert**, and can **vary** by context in the same organism or over time
- Known mechanisms cell transport via the circulatory system or vagus nerve propagation

	More social relationships result in greater microbiome diversity	Social interactions drive microbiome similarity within social group	Microbes contribute to olfactory cues of social group	Other microbiome and social behaviour associations
Honeybee 			✓	Microbiome depletion leads to reduction in social behaviour
Bumblebee 				Social spread of Gammaproteobacteria protects against parasite infection
Leafcutter ant 			✓	
Termite 			✓	
Vole 				Social stress from overcrowding causes microbiome shifts related to stress and ageing
Wild wood mouse 	✓	✓		
Welsh mountain pony 	✓			
Spotted hyena 	✓ Theorized		✓	
Chimpanzee 	✓	✓		Yearly fluctuations in sociability correlate with fluctuations in microbiome similarity
Baboon 		✓		The bacteria that have the strongest links to social behaviour are anaerobic and non-spore forming
Howler monkey 		✓		
Red-bellied lemur and red-fronted lemur 		✓		
Black-and-white colobus monkey 		✓		

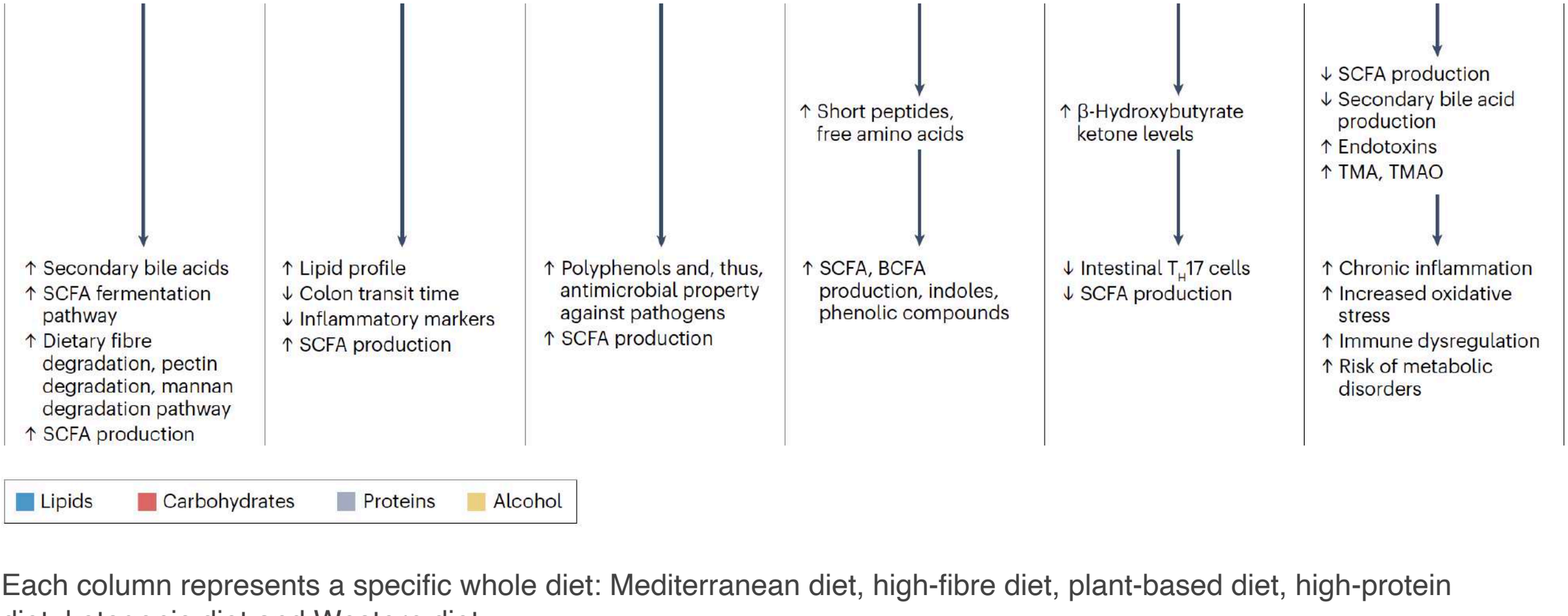
Griffiths et al., 2026

Diet is generally recognized as a key determinant of gut microbiome variations

Interplay between diet and the gut microbiome



Ross et al., 2024



Each column represents a specific whole diet: Mediterranean diet, high-fibre diet, plant-based diet, high-protein diet, ketogenic diet and Western diet.

Pie charts detail the distribution of macronutrients (lipids, carbohydrates and proteins) and alcohol content for each diet.

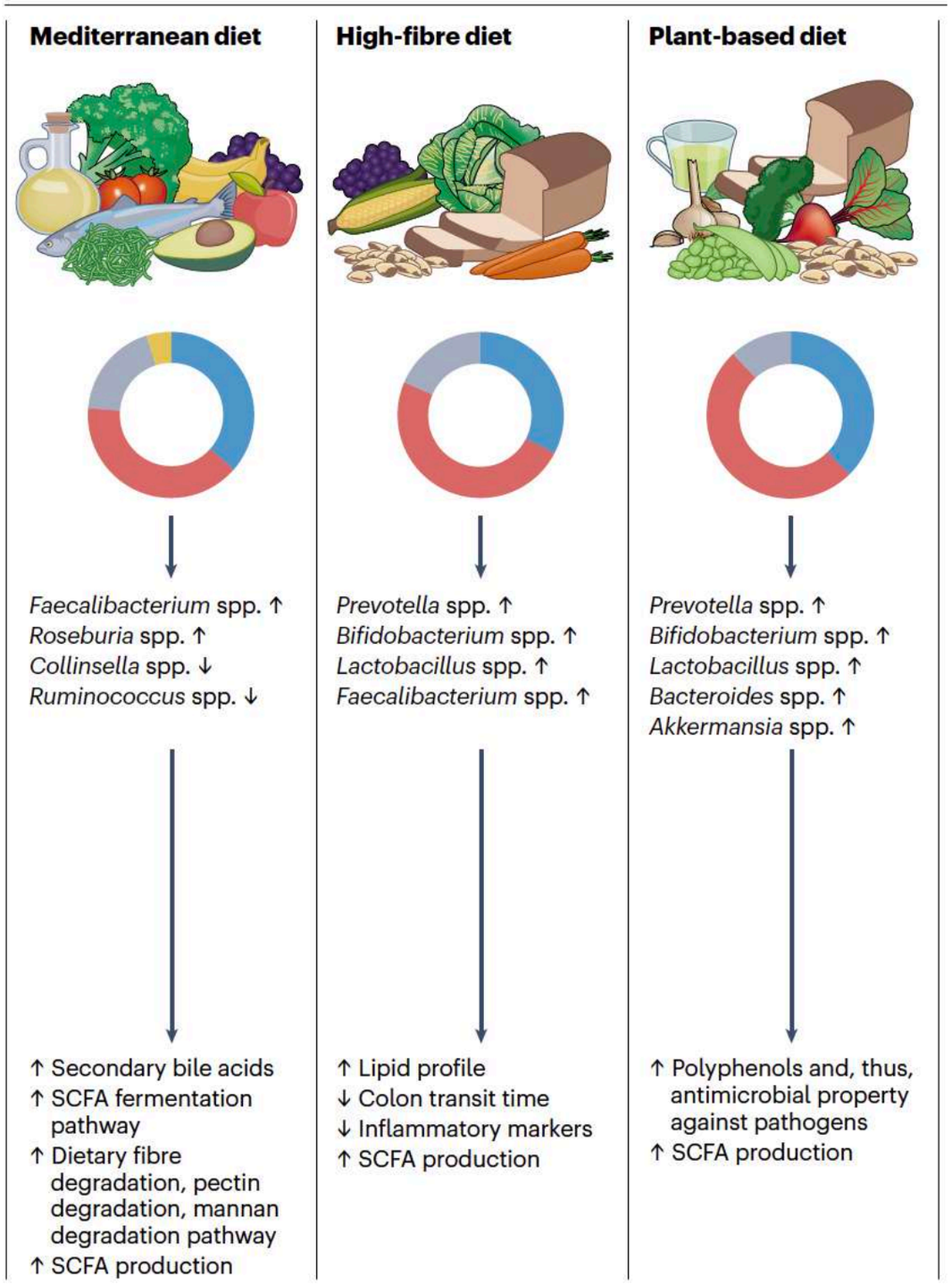
The figure illustrates the alterations of bacterial taxa associated with each diet and the consequent effects on metabolite production.

Upward arrows refer to an increase in bacterial taxa or metabolites, whereas downward arrows denote a reduction in bacterial taxa or metabolites.

This comprehensive depiction elucidates how different dietary compositions can modulate the gut microbiota, providing insights into their potential implications for overall health and well-being. TH17, T helper 17 cells; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

Ross et al., 2024

We are what we eat, I



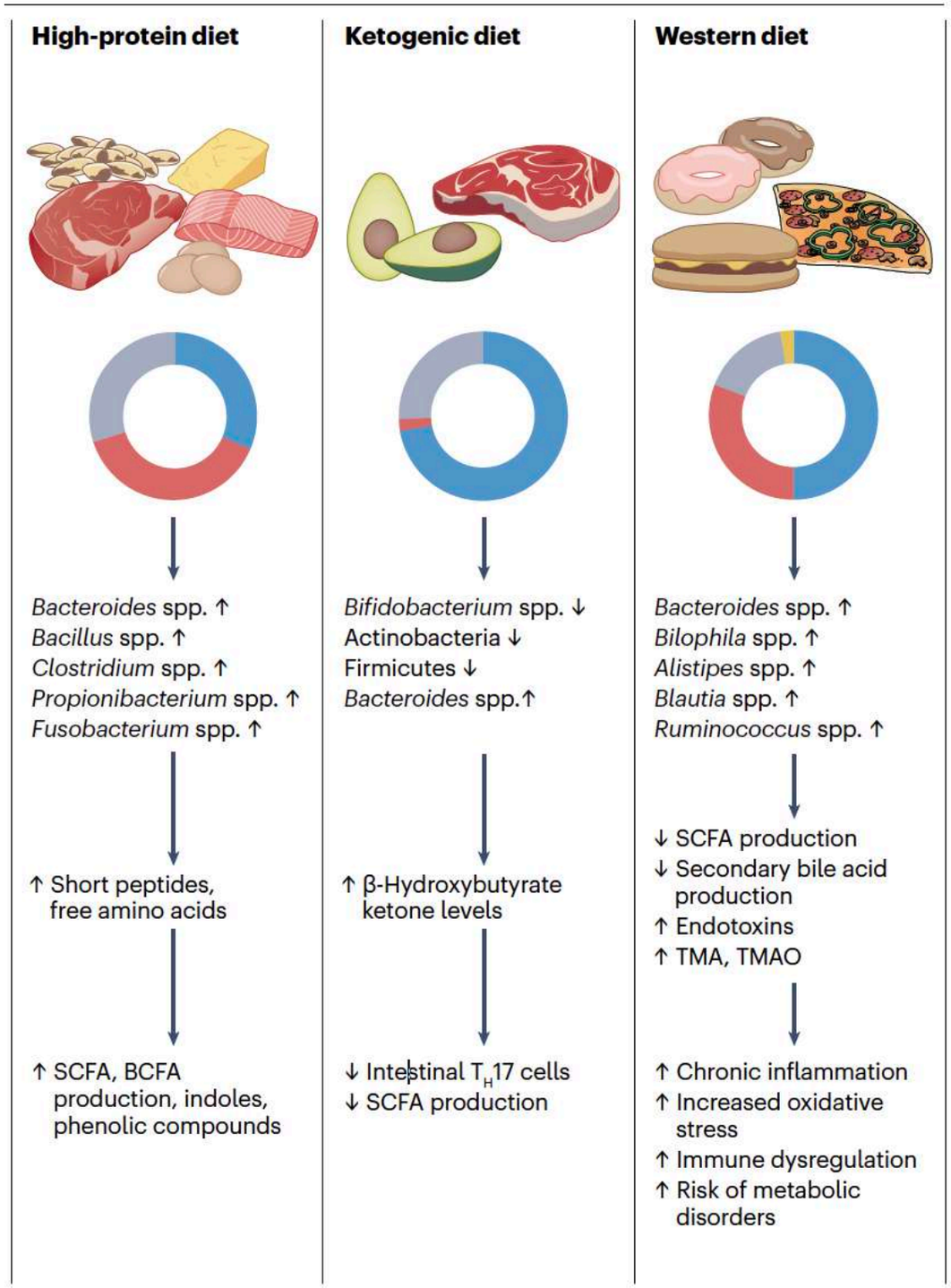
Ross et al., 2024

The Mediterranean diet is associated with increased *Faecalibacterium* spp. and is associated with **short-chain fatty acids (SCFAs)** and production of **anti-inflammatory molecules**

The high-fibre diet is associated with enriched *Prevotella* and *Faecalibacterium* species, which are associated with **enriched SCFA production** and also a **decrease in colon transit time**

A plant-based diet is associated with increased abundance of *Prevotella* and *Akkermansia* species, together with an **enrichment in polyphenols and SCFA production**

We are what we eat, II



Ross et al., 2024

A high-protein diet is associated with enriched *Bacteroidetes* and *Fusobacterium* species, with **higher production of branched-chain fatty acids (BCFAs), indoles and short peptides**

The ketogenic diet is linked to decreased *Firmicutes* and *Actinobacteria* species and shows **high ketone levels**

A Western diet is associated with increased abundance of *Blautia* spp., *Bacteroides* spp. and *Ruminococcus* spp., which is in turn linked to **increased risk of metabolic disorders and chronic inflammation**

Short-Chain Fatty Acids

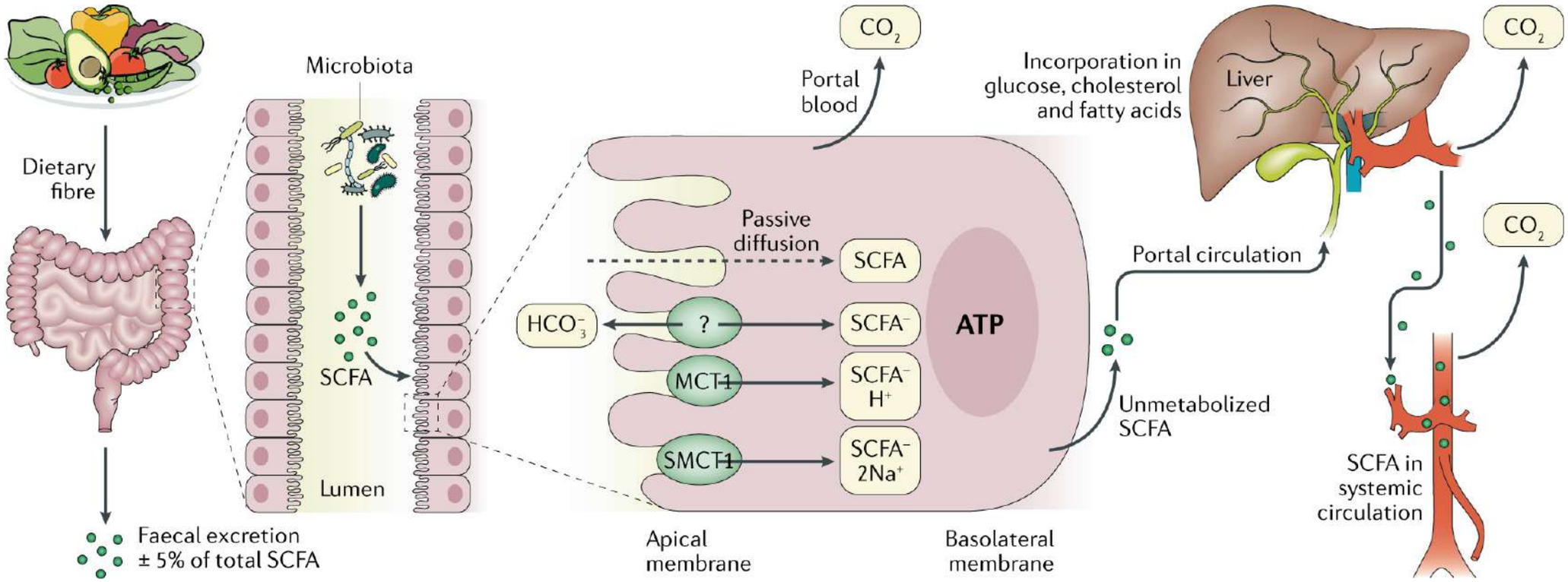
Short-chain fatty acids are volatile fatty acids produced mainly by microbial fermentation

Human physiology: SCFAs are produced in the **proximal colon by microbial fermentation** of oligo- and polysaccharides that have escaped digestion by mammalian enzymes further up the gastrointestinal tract

The major short-chain fatty acids are **acetic, propionic, and butyric**

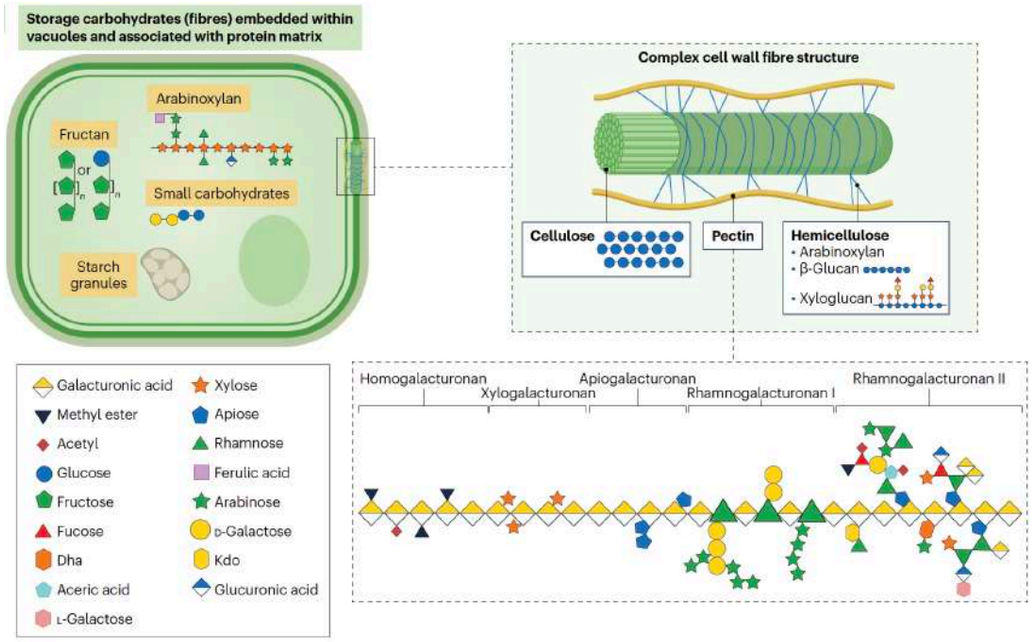
They are very soluble and are absorbed easily from the gut lumen into the bloodstream

In humans, acetate is usually the major short-chain fatty acid present in the circulation



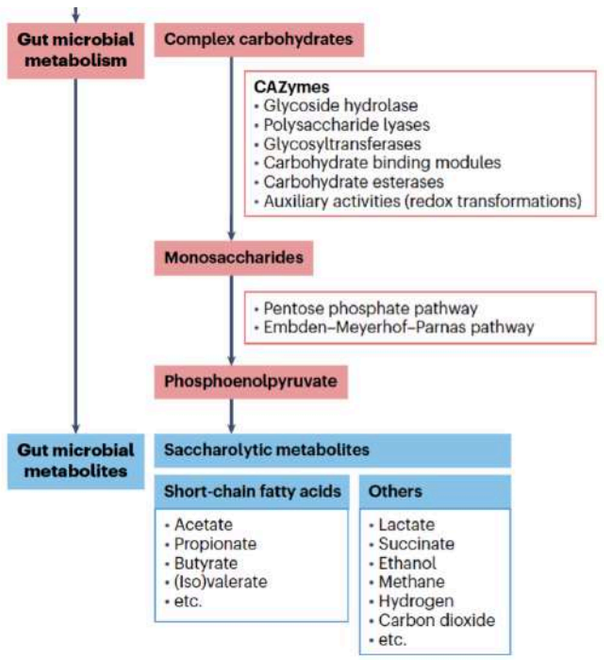
Dalile et al., 2019

Fibres



Delzenne et al., 2024

Dietary fibres either form a complex 3D structure that constitutes the backbone of plant cells, or are encapsulated as storage carbohydrates with various other nutrients such as lipids, proteins and polyphenols in the plant vacuole



Substrates	Dietary source	Fermenting genera
Resistant starch	Cashew, green banana, white beans, oat and potato	• *Ruminococcus* • *Bacteroides*
Cellulose	Seaweed and cereal bran	• *Bacteroides* • *Ruminococcus*
Hemi-celluloses (xylan and arabinoxylan)	Cereal bran	• *Bacteroides* • *Roseburia* • *Prevotella*
Pectin	Apples, apricots, cherries, oranges and carrots	• *Eubacterium* • *Bacteroides* • *Faecalibacterium*
Fructans (inulin and fructooligosaccharides)	Asparagus, leek, onions, banana, wheat, garlic, chicory and artichoke	• *Bacteroides* • *Faecalibacterium*
Milk oligosaccharides	Breast milk	*Bifidobacterium*
Lactose (only in lactose-intolerant people)	Milk, yogurt, buttermilk and cheese	*Bifidobacterium*
β-Glucan	Oat, barley, wheat, rye, mushrooms and seaweed	• *Eubacterium* • *Atopobium* • *Enterococcus* • *Lactobacillus* • *Prevotella* • *Clostridium* cluster XIVa
Gum arabic	Acacia tree and prepared food additive	• *Bifidobacterium* • *Lactobacillus* • *Ruminococcus*
Guar gum	Guar bean and prepared food additive	• *Bifidobacterium* • *Ruminococcus*
Laminarin	Seaweed	*Prevotella*
Galacto-oligosaccharides	Artichoke, beans, beetroot, broccoli, chickpeas, fennel, lentils, lettuce, radicchio and onion	*Bifidobacterium*
Raffinose and stachyose	Cottonseed flour, soy flour, onions, chickpeas, beans, peas and lentils	• *Bifidobacterium* • *Lactobacillus*

Dalile et al., 2019

Dysbiosis case studies:

Obesity

Metabolic and intestinal disorders

Type 2-Diabetes

Colon rectal cancer

Pre-term birth

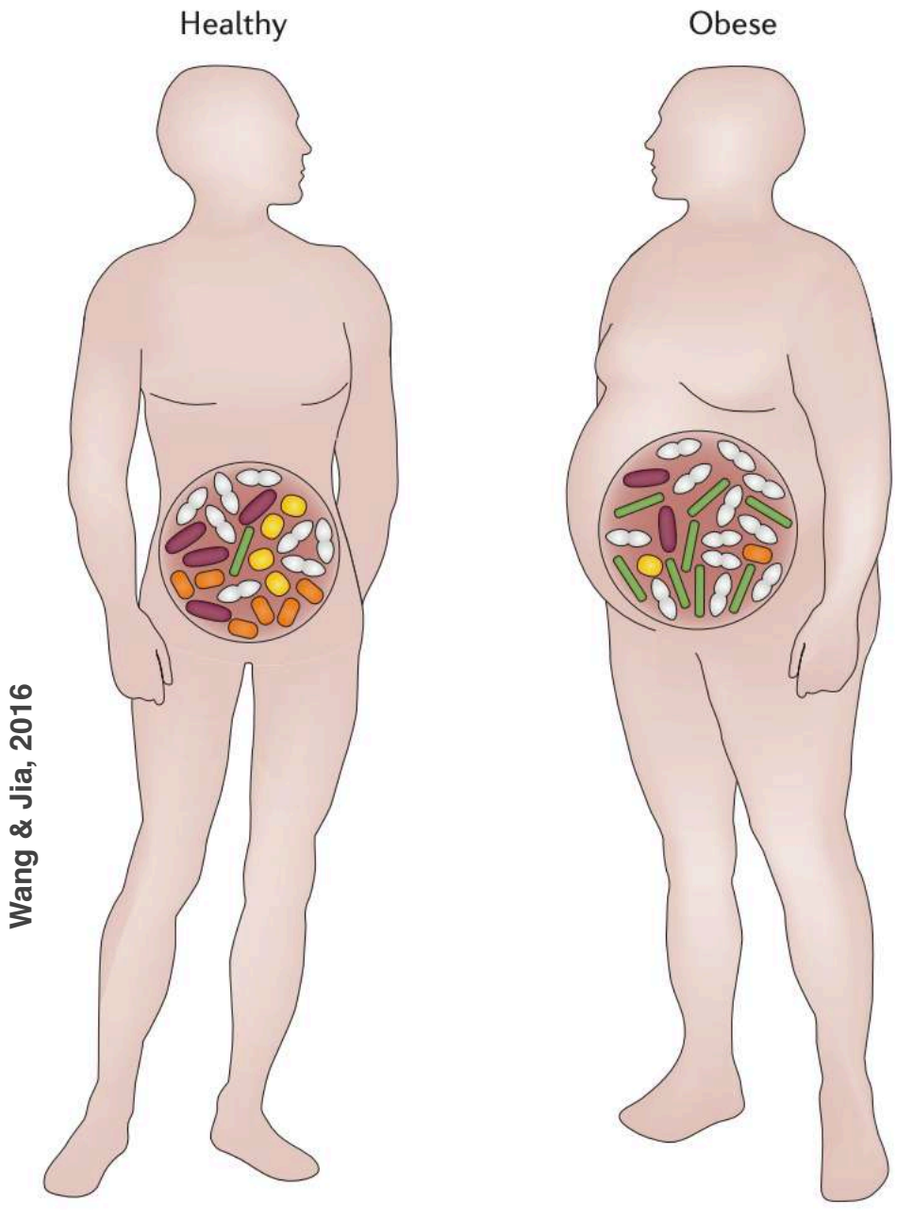
Athlete motivation

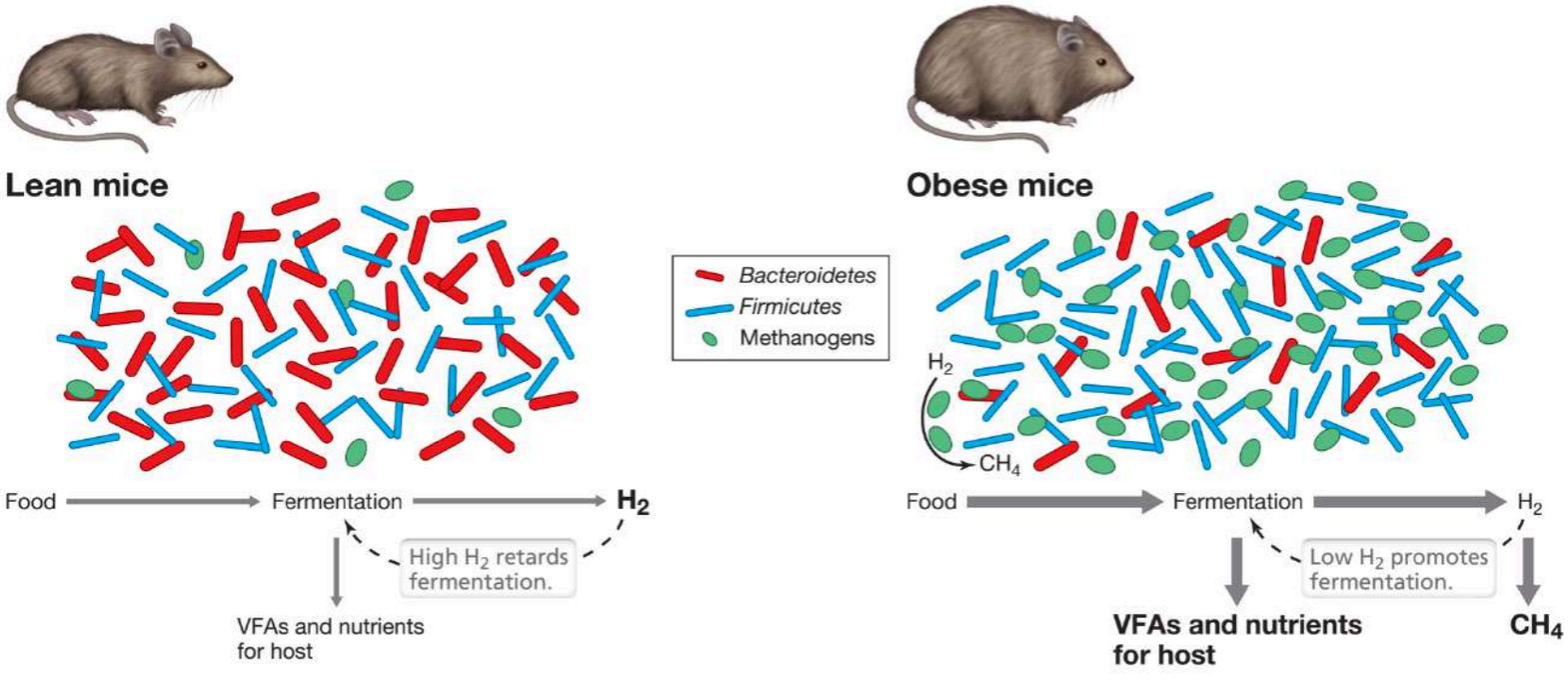
Neurodegenerative disease

Aging

Obesity (energy shift)

- 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





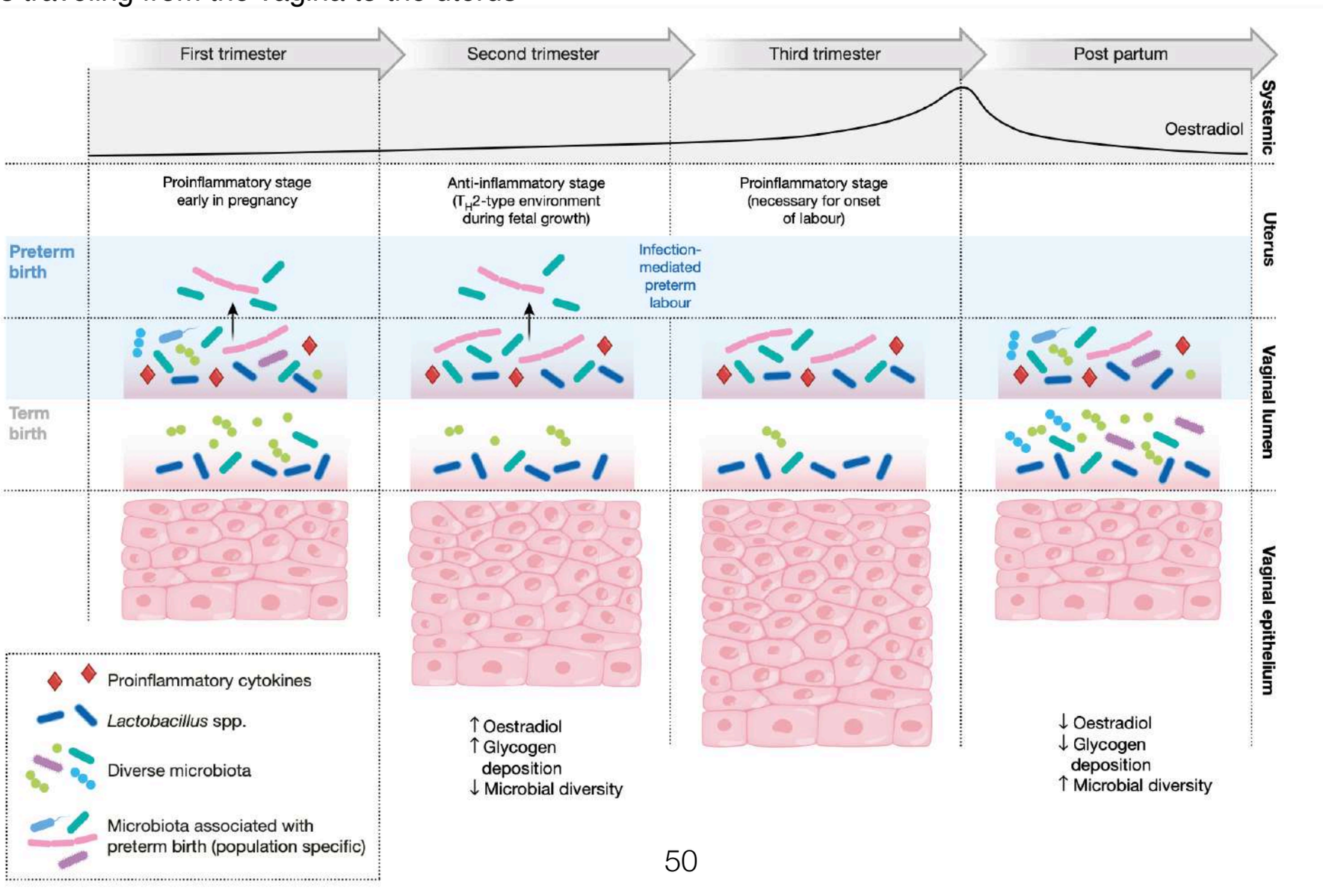
Madigan et al. 2018

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

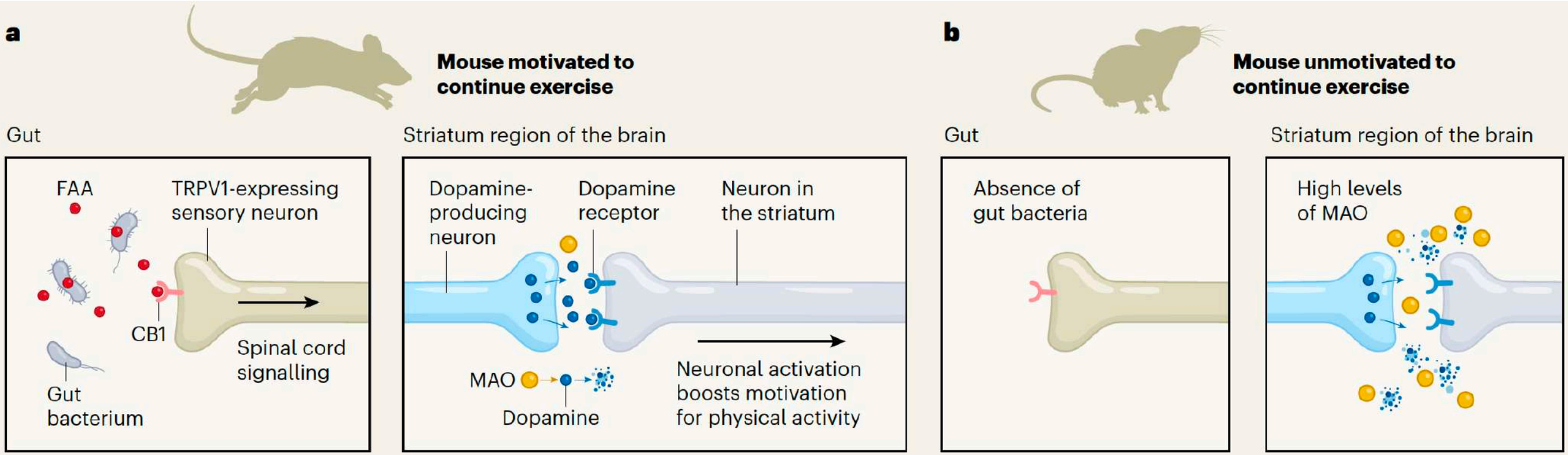
The uterus switches from an early pro-inflammatory condition to an anti- inflammatory condition in the second trimester, and then back to a pro- inflammatory condition before the onset of labour

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

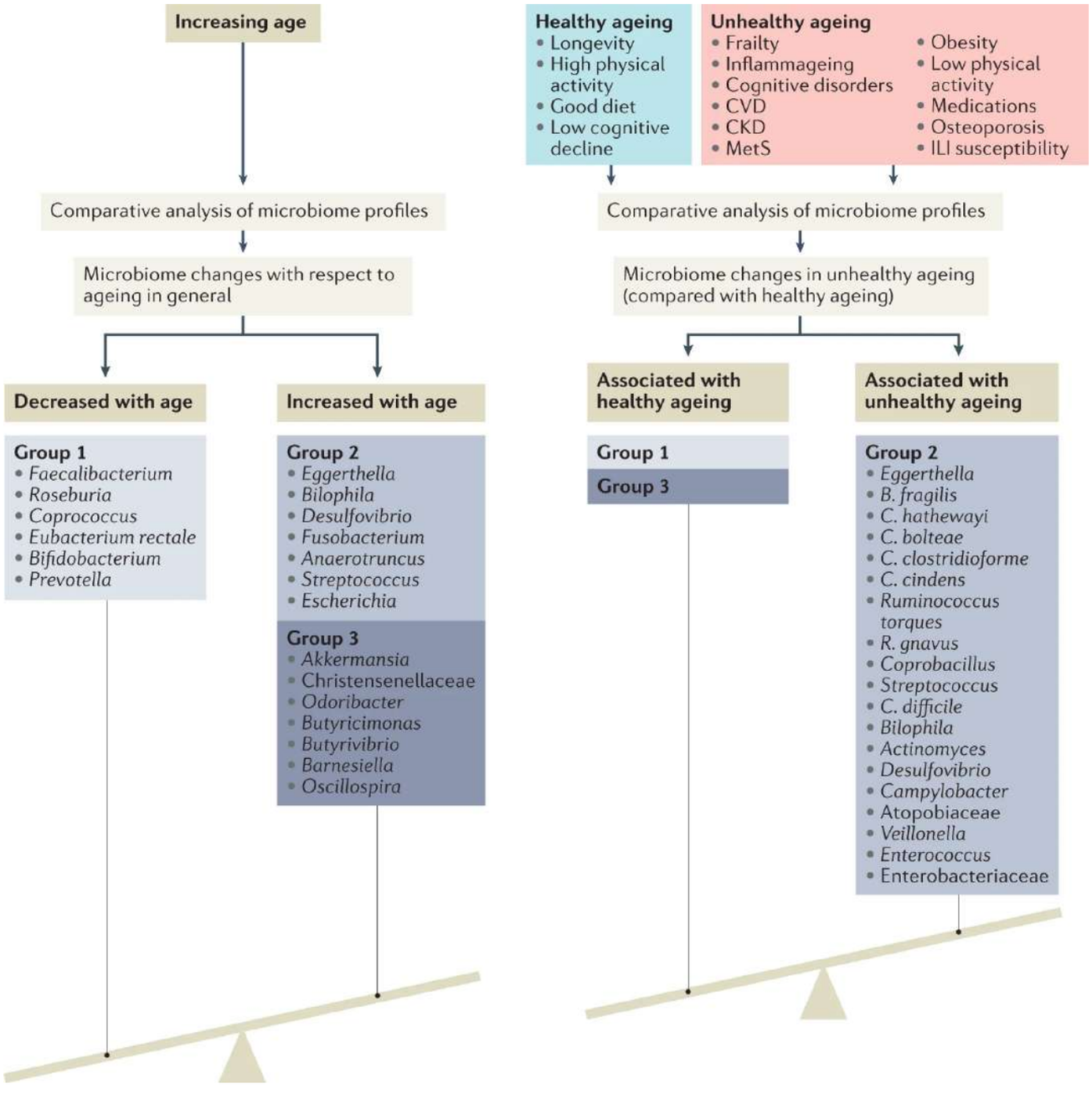
Gut microbes shape athletic motivation



Dohnalova' et al. 2023

- 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**

The gut microbiome as a modulator of healthy aging

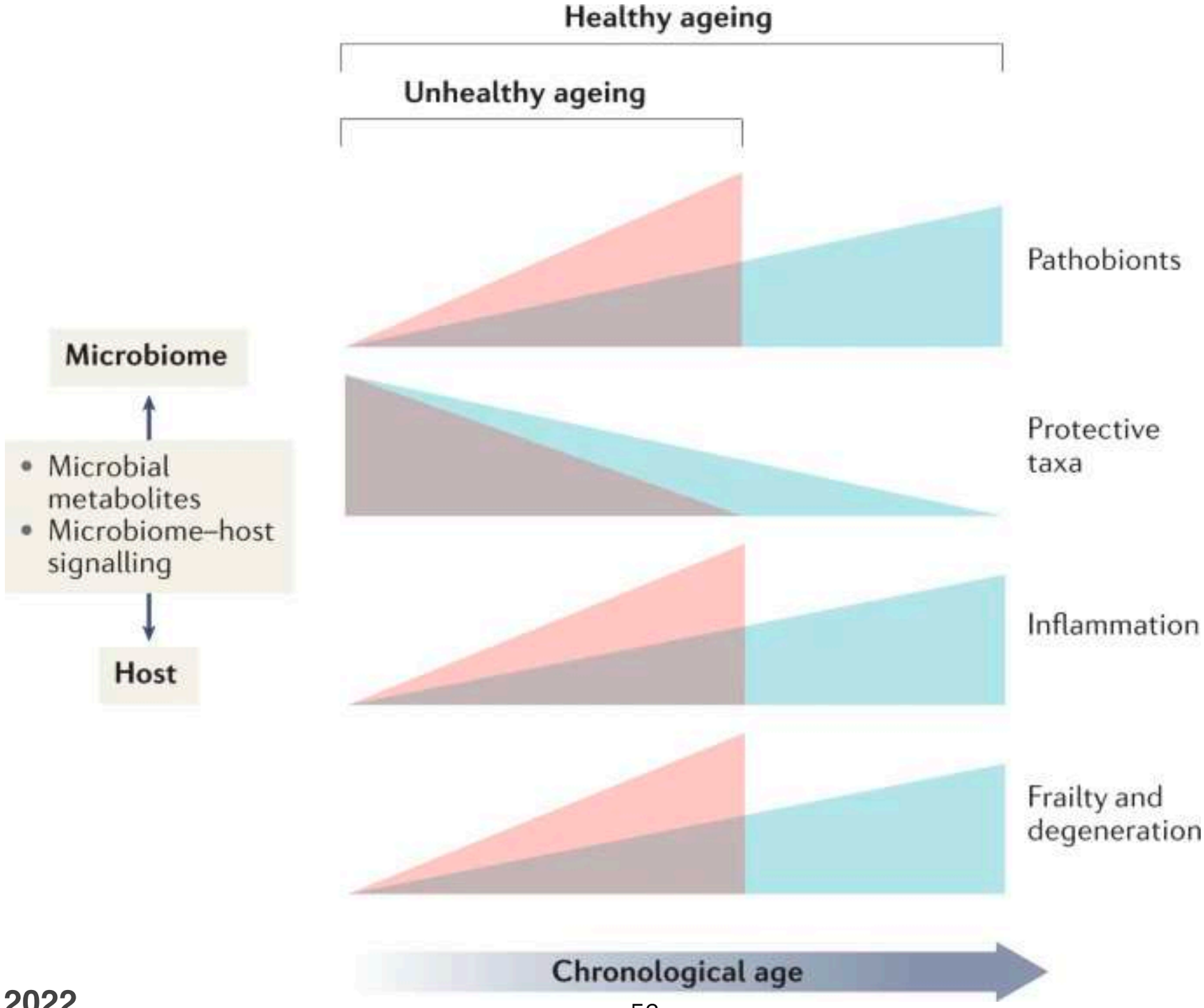


Gosh et al., 2022

- 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

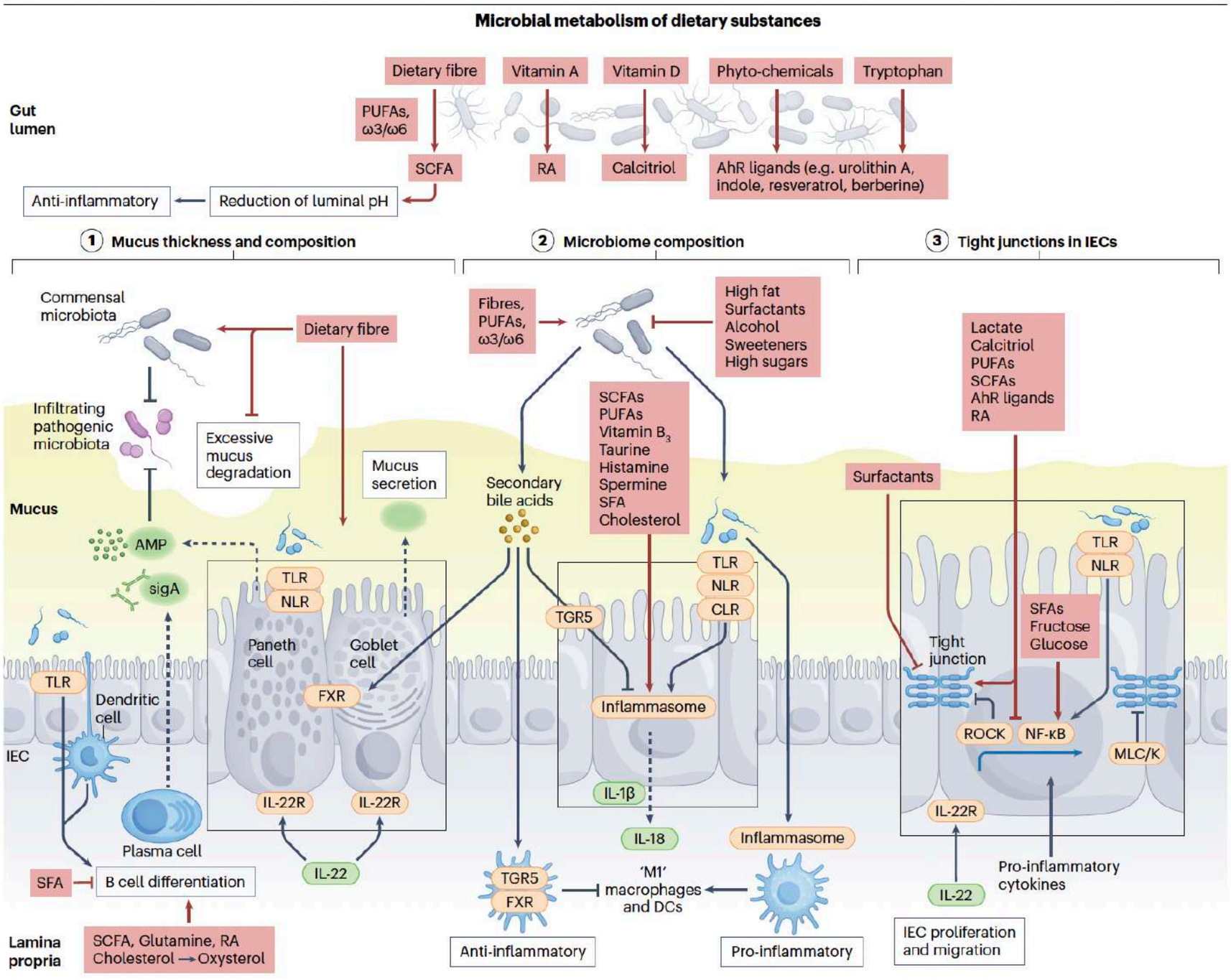
Microorganism–host signalling as a contributor to healthy or unhealthy aging



Gosh et al., 2022

Comunications between microbes-human being

Dietary orchestration of gut barrier and immunity is linked to the microbiome



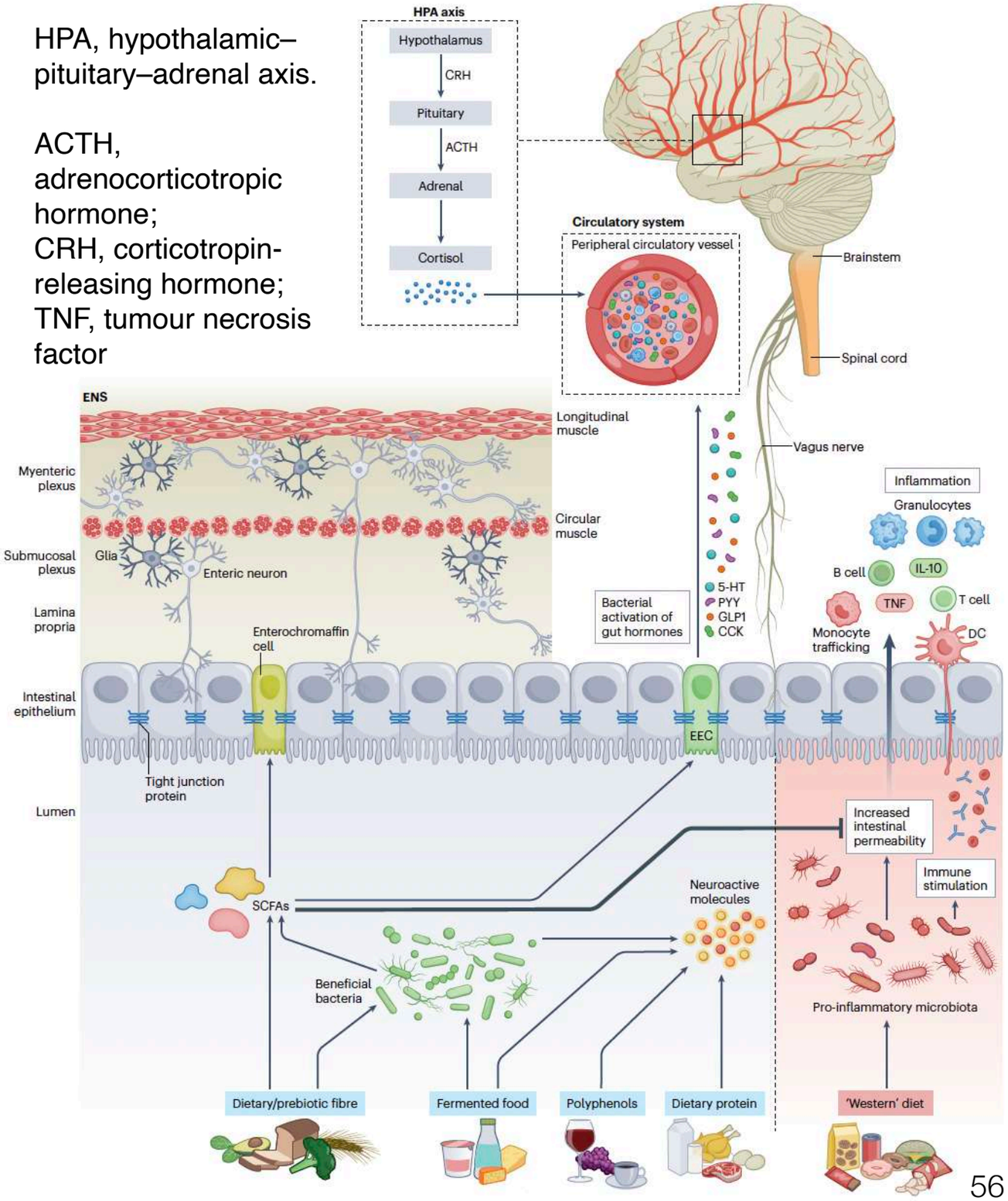
Dietary substances and their microbially produced metabolites (in red) modulate intestinal barrier integrity and immunity through various mechanisms involving the resident microbiome.

Sanz et al., 2025

Diet and gut microbiome interactions orchestrate nervous system function

HPA, hypothalamic–pituitary–adrenal axis.

ACTH, adrenocorticotropic hormone;
CRH, corticotropin-releasing hormone;
TNF, tumour necrosis factor



Diets rich in fibre, fermented foods, and polyphenols, and with moderate levels of proteins sustain the growth of mutualistic microorganisms (beneficial bacteria) and contribute to the generation of **metabolites that favourably regulate nervous system function**.

Short-chain fatty acids (**SCFA**) **induce the secretion of the anorexigenic peptides glucagon-like peptide 1 (GLP1), peptide tyrosine-tyrosine (PYY) and cholecystokinin (CKK) by enteroendocrine cells (EEC),** which **act on** the **hypothalamus centres of food intake control.**
SCFAs strengthen the gut barrier integrity and induce protective immune responses, preventing chronic inflammation.

Gut bacteria participate in the provision and metabolism of amino acids that are **precursors of neurotransmitters such as tryptophan, which can be transformed to 5-hydroxytryptamine (5-HT) in enterochromaffin cells, or tyrosine which can be converted to catecholamines** (for example, noradrenaline and dopamine) **which can interact with the enteric nervous system (ENS) or stimulate vagal sensory neurons in the gut, leading to activation in the brain structures, controlling mood, behaviour and mental health**

DC, dendritic cell

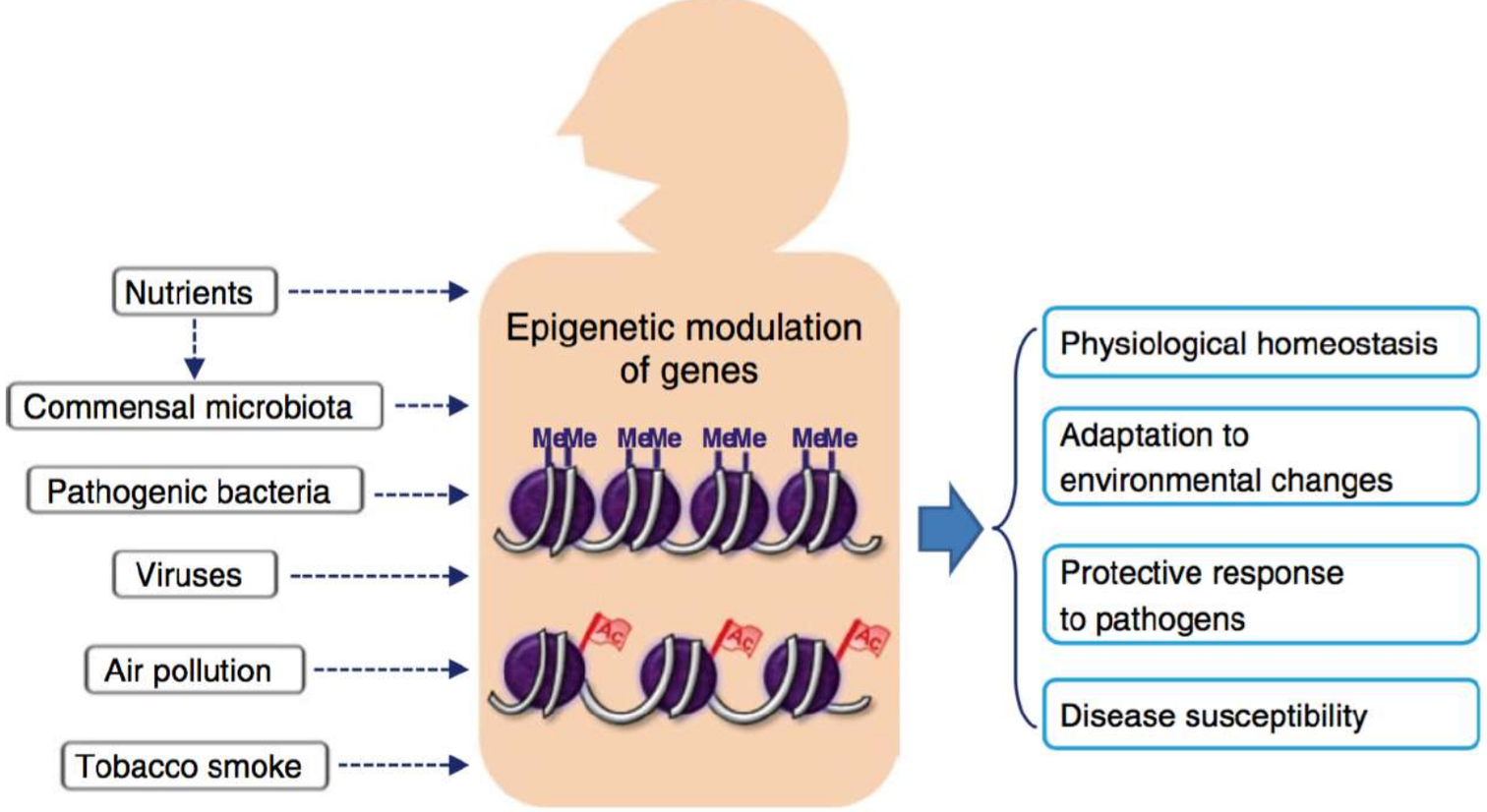
Sanz et al., 2025

Parental diet and offspring health: a role for the gut microbiome via epigenetics

Yang et al., 2025

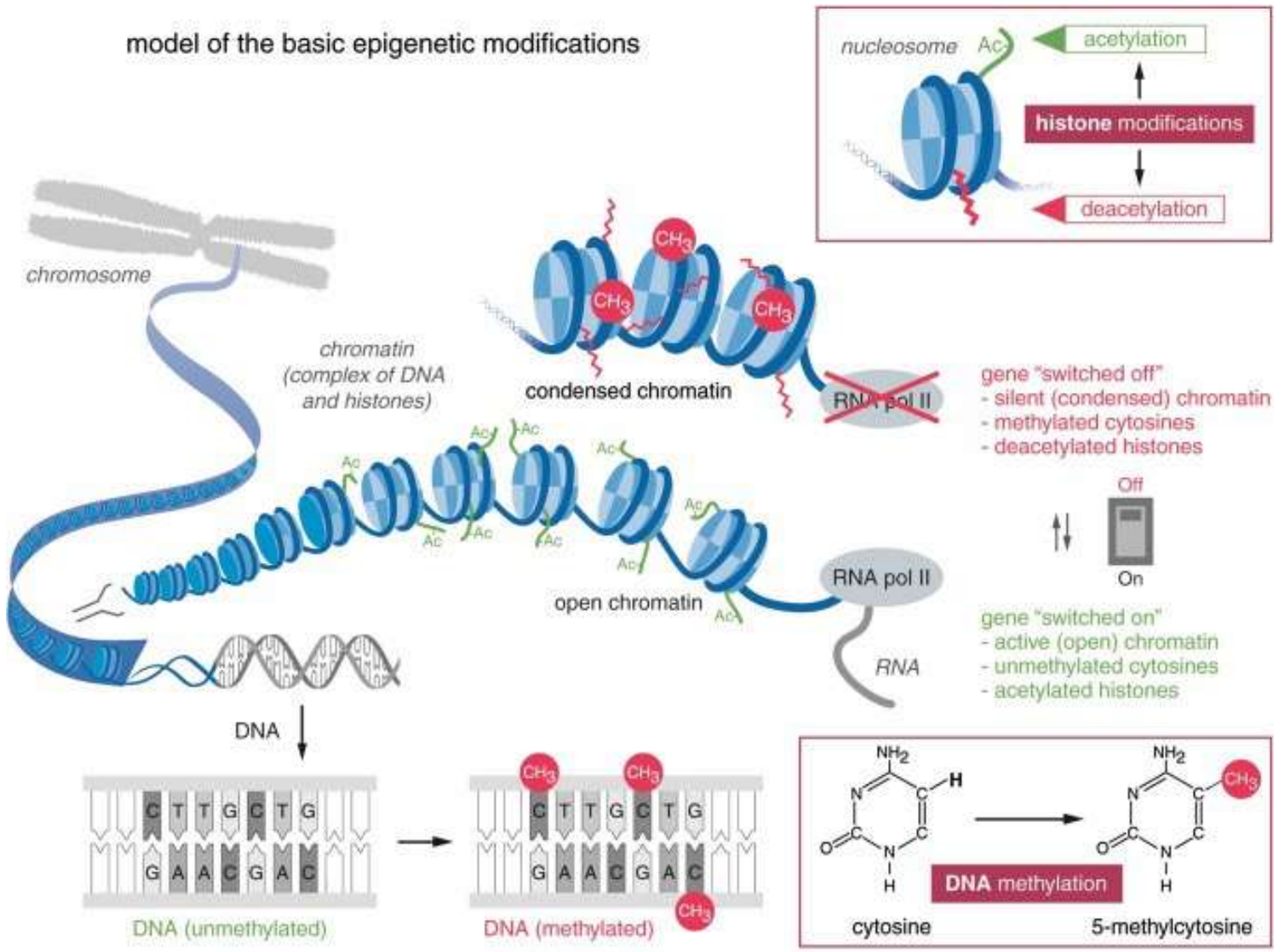
Epigenetics 101

- The word “epigenetics” was originally coined by Conrad Waddington in 1942, referring to how genotypes give rise to phenotypes during development
- Now we refer as the study of **phenomena and mechanisms that cause chromosome-bound, heritable changes to gene expression** that are **not dependent on changes to DNA sequence** (Deans and Maggert 2015)
- In Humans, gene expression is regulated prior to transcriptional initiation by the **chemical modification of DNA or the histone proteins** that together form chromatin



Takahashi, 2014

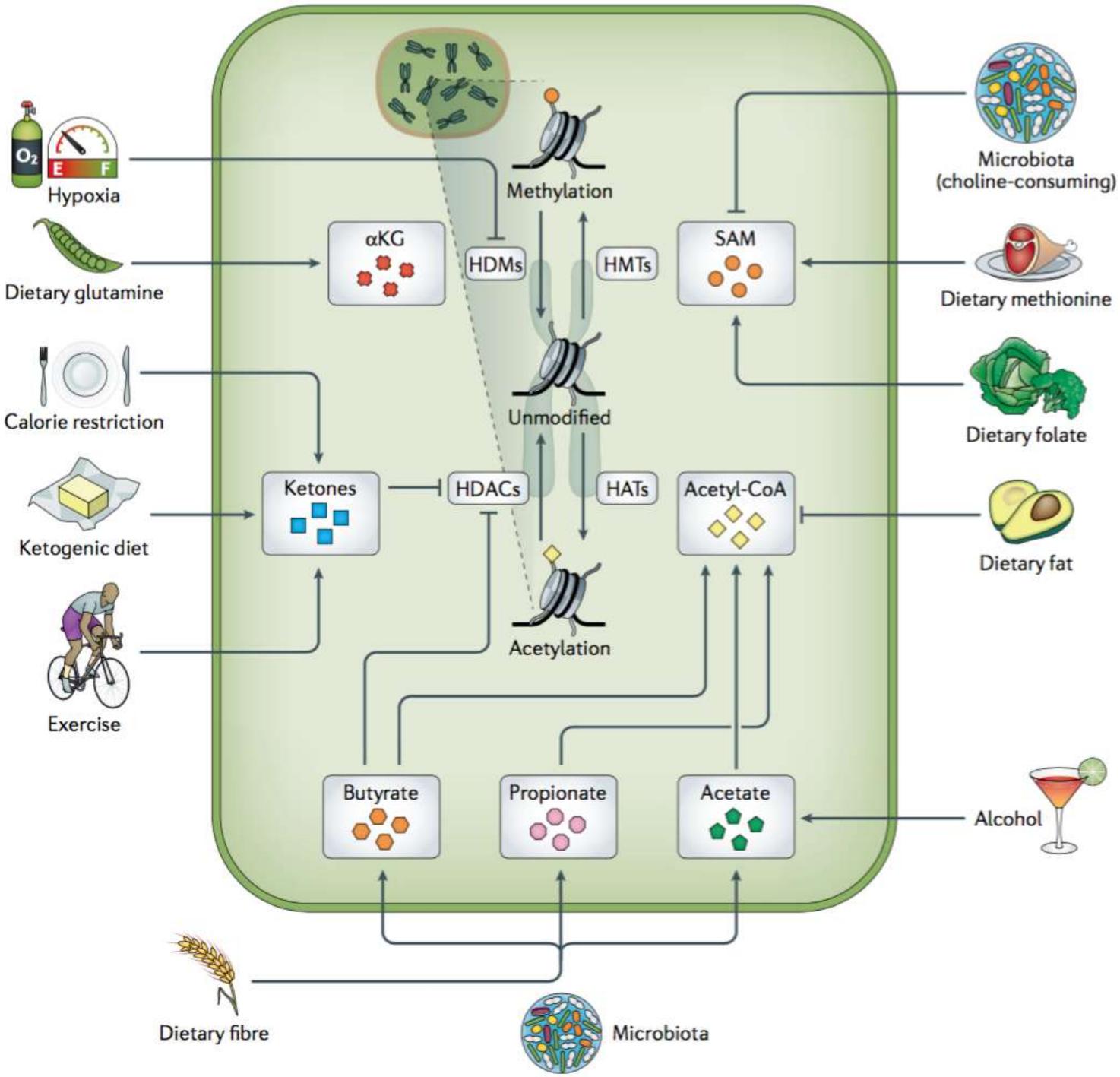
Epigenetic modifications of chromatin by DNA methylation and histone acetylation



Vilcinskas, 2015

- Methyl group transfer to cytosine —> 5-methylcytosine (m5C) pairs with guanosine
- m5C has different interactions with regulatory proteins
- **Chromatin structure** depends on net **charge** of core **histones**
- **Acetyl groups** promoting formation of *open* and **accessible** euchromatin vs **deacetylation** promoting the formation of *compact* and **inaccessible** heterochromatin

Influences of environmental factors on histone acetylation and methylation via microbiome



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

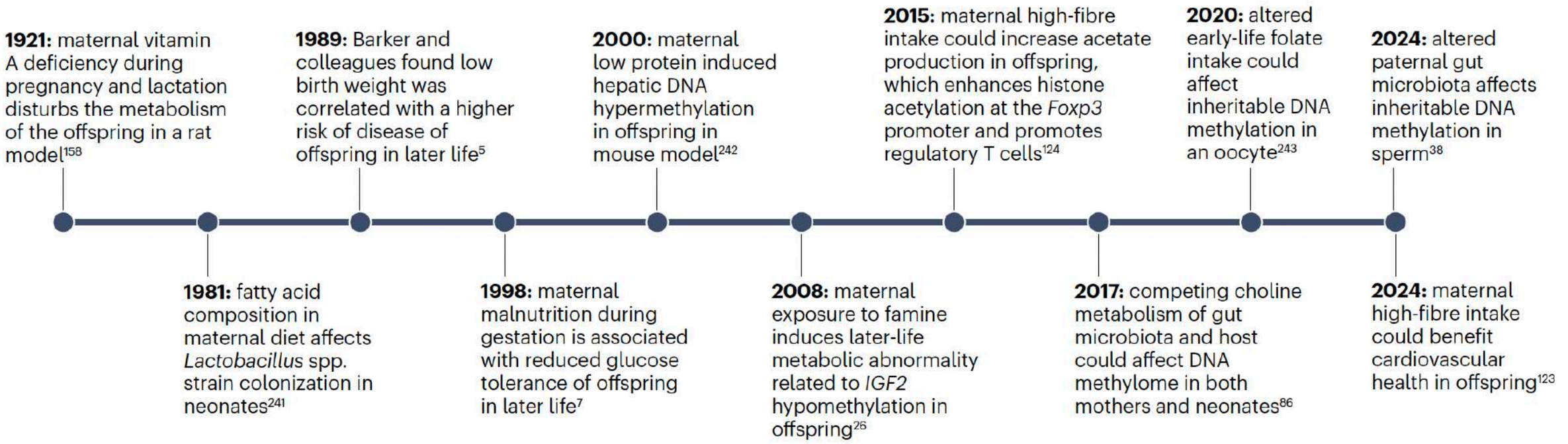


Fig. 1 | Key historical findings on the effect of maternal diet on the offspring. Key findings[5,7,26,38,86,123,124,158,241–243] include: 1921: discovery that maternal vitamin A deficiency disrupts offspring metabolism in rats, the earliest evidence that maternal diet affects offspring health; 1981–2000: gut microbiota and the epigenome identified as key mediators of the effects of maternal diet on offspring health; 2015–2024: recent findings show the roles of crosstalk between epigenome and gut microbiota in shaping offspring health in response to maternal diet.

Association versus causation

An important consideration in gut microbiome studies is the **distinction between association and causation**. These can usually be distinguished using **forward and reverse microbiome approaches**.

Causality is more complex to determine in pregnancy studies.

For example, maternal dietary patterns affect the composition of gut microbiota populations in the adult offspring of primates and mice.

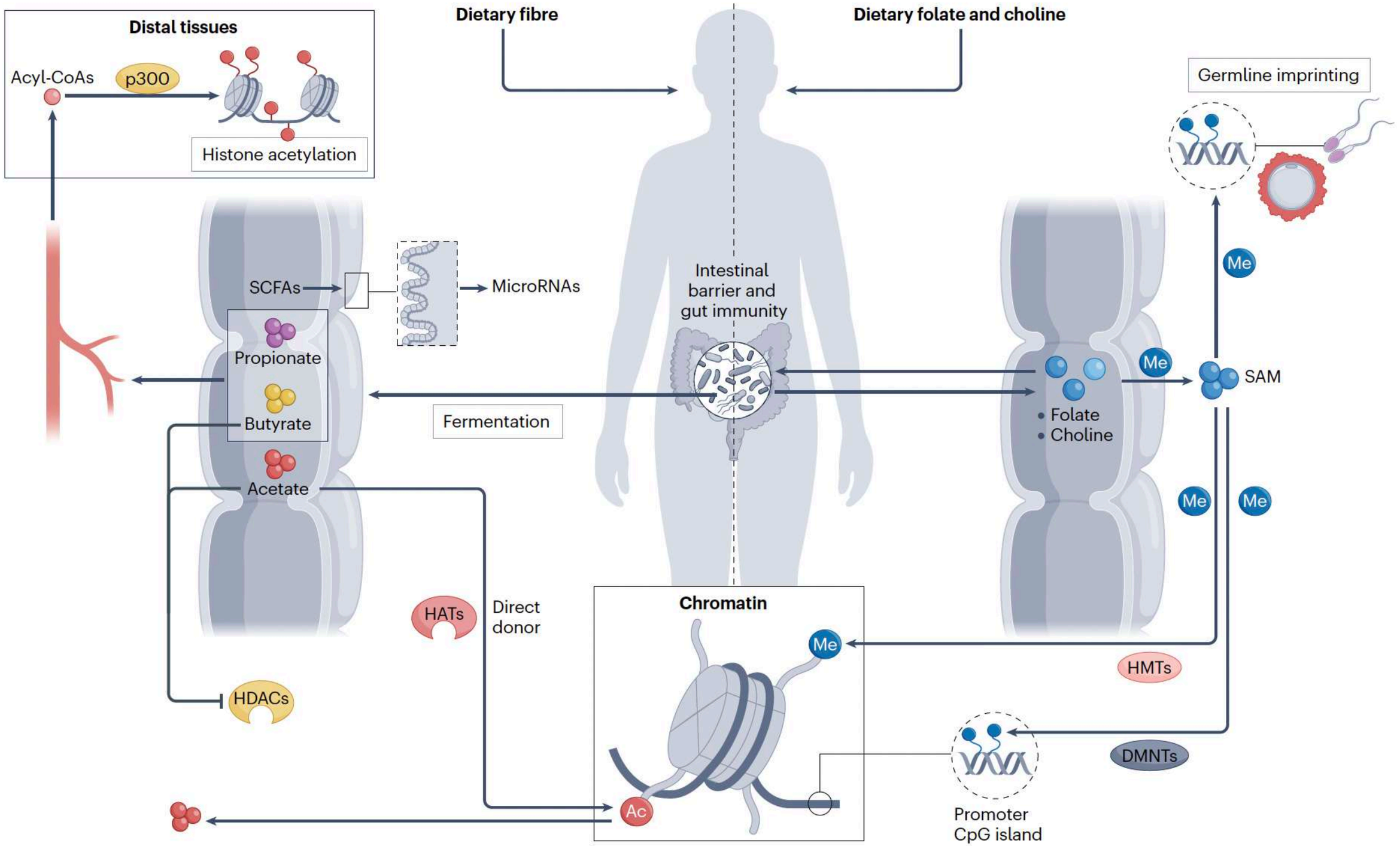
It is less clear whether health-related phenotypes observed in the offspring are due to in utero epigenetic modifications or to the passage of the microbiota from the mother to the offspring at birth.

To distinguish between these possibilities, studies usually leverage caesarean sections with cross-fostering, germ-free animals, or antibiotics during pregnancy (albeit many antibiotics are not safe for the fetus) and can evaluate the difference between interventions during pregnancy and interventions during breastfeeding.

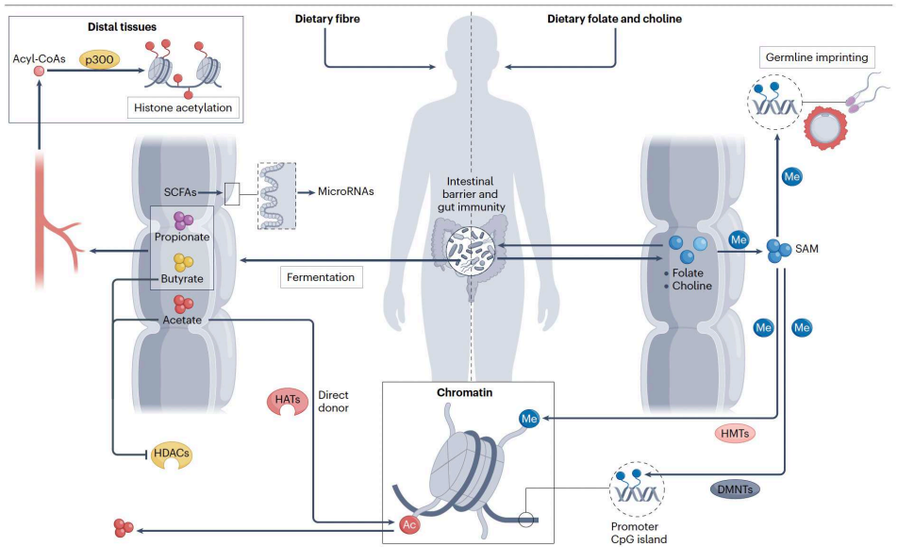
Studies need to distinguish the effects of diet in preconception, prenatal and postnatal end points and how these shift and interact with the parental gut microbiome.

Yang et al., 2025

Effects of the gut microbiome on epigenetic modifications



Yang et al., 2025



Effects of the gut microbiome on epigenetic modifications

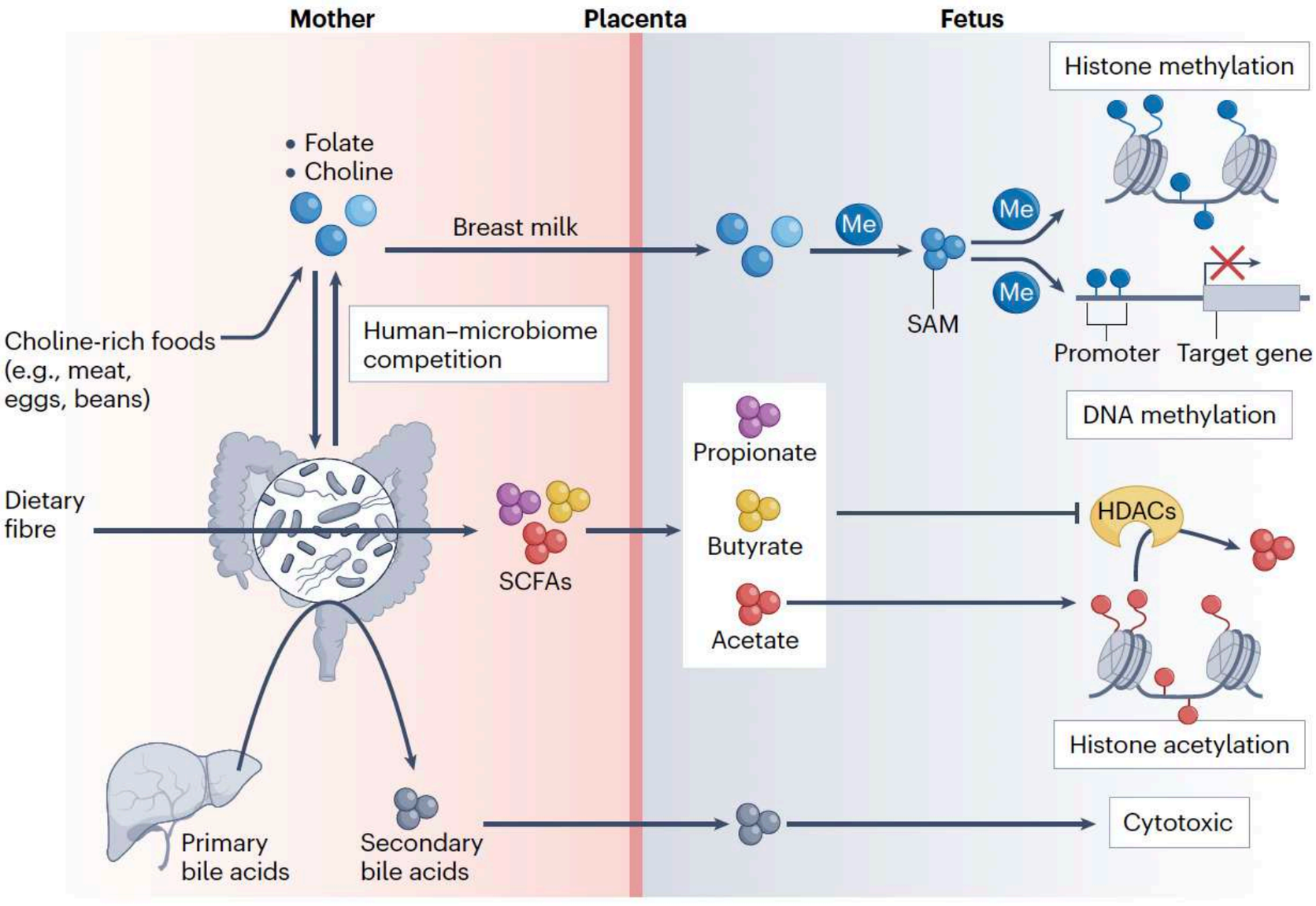
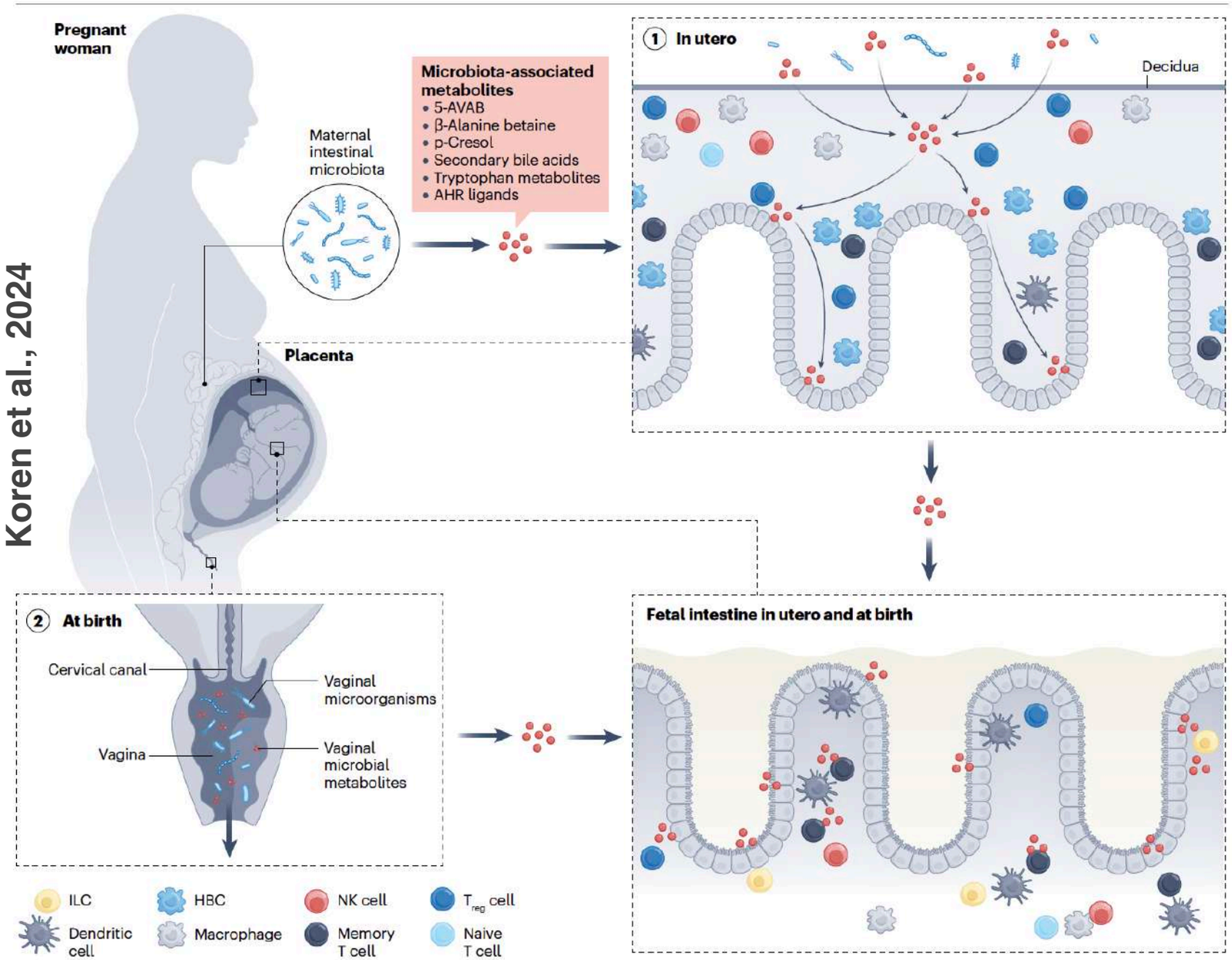


Fig. 3 | Epigenetic effects of maternal dietary intake. Choline and folate, obtained from dietary sources such as meat, eggs and beans, or breast milk, could be metabolized by both the host and the gut microbiota, with competition and dynamics between the two. Choline and folate can penetrate the placental barrier and affect the synthesis of *S*-adenosylmethionine (SAM) via one-carbon metabolism in the fetus. Affected SAM production could alter the fetus DNA and histone methylation processes. Dietary fibres are fermented by the gut microbiota to produce short-chain fatty acids (SCFAs), including acetate, propionate and butyrate. These SCFAs could also penetrate the placental barrier and affect epigenetic regulation by inhibiting histone deacetylases (HDACs), promoting histone acetylation. Furthermore, primary bile acids, produced by the liver, are transformed into secondary bile acids by the gut microbiota. Secondary bile acids penetrating the placental barrier can affect fetal development because secondary bile acids in high concentrations are cytotoxic. Me, methyl.

Yang et al., 2025

Microbial metabolites from the maternal microbiome contribute to fetal and neonatal immune development



Koren et al., 2024

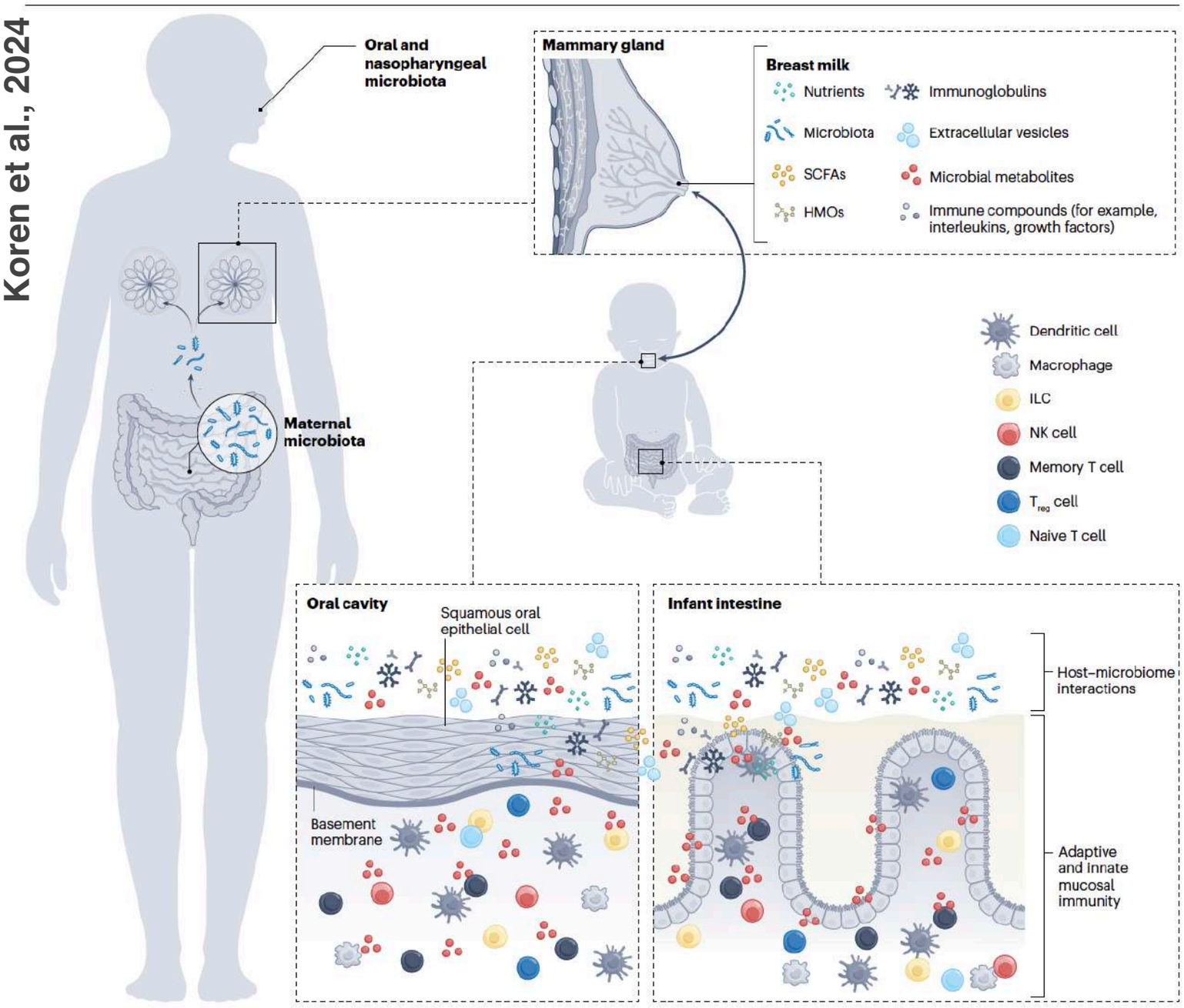
1) Maternal intestinal microbiota derived metabolites influence immune development in the placenta and fetal intestine in utero

2) The vaginal microbiome and microbial metabolites contribute to intestinal immune development at birth

5-AVAB, 5-aminovaleric acid betaine; AHR, aryl hydrocarbon receptor; HBC, Hoffbauer cell; ILC, innate lymphoid cell; NK, natural killer; Treg cell, regulatory

Human milk microorganisms and their metabolites support the gut microbiome and immune system in the offspring

Koren et al., 2024



Breast milk composition is complex and unique

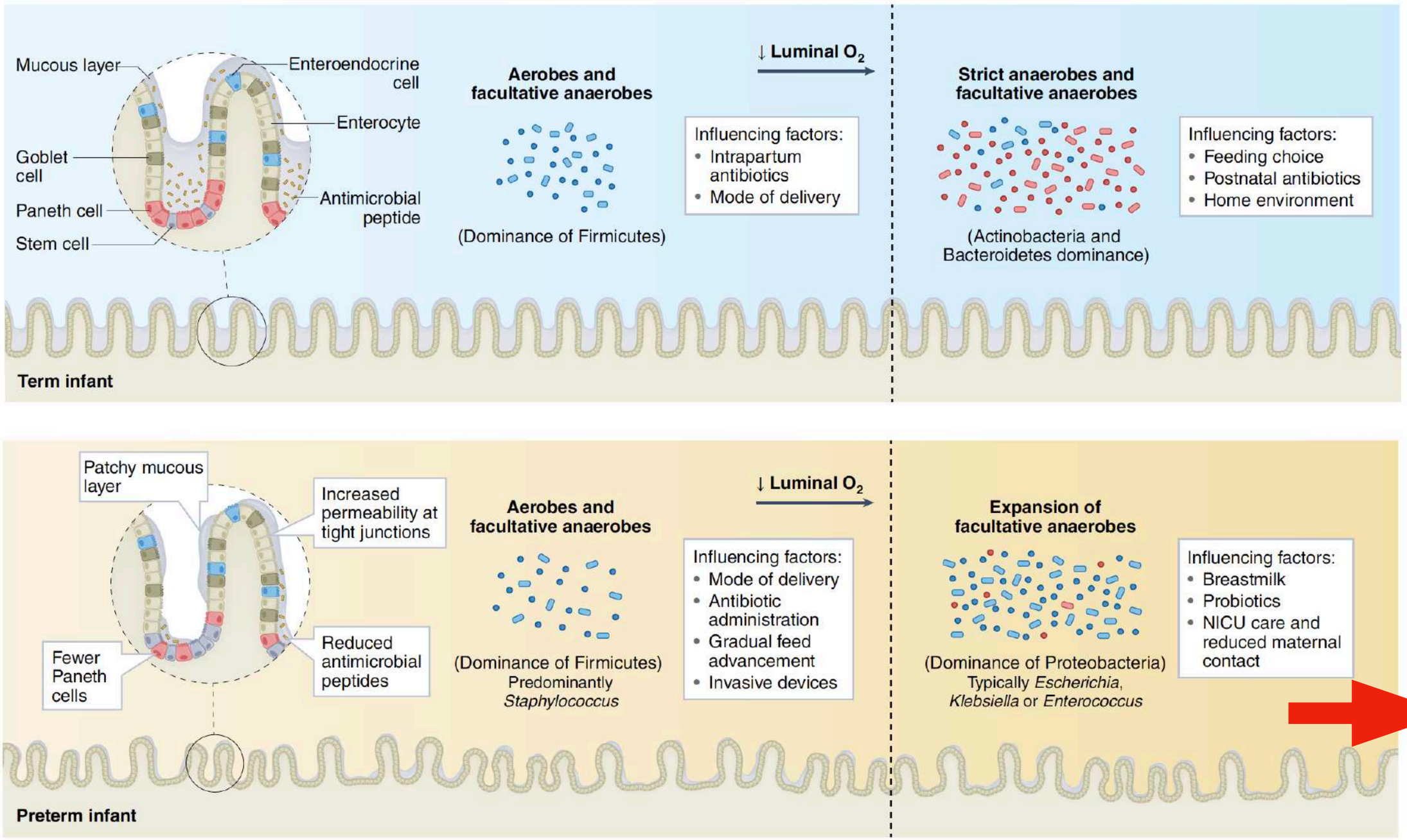
Milk contains nutrients and specific bioactive compounds:

- microbiota & metabolites (including SCFAs)
- microorganism-derived products (cell walls, membrane, DNA, specific secreted proteins, and other fragments or structures)
- human milk oligosaccharides (HMOs)
- immune-related compounds (secretory IgA, immunoglobulins, lactoferrin and lysozyme)
- CD14 T cells, cytokines, growth factors, defensins
- extracellular vesicles, which can cargo microRNAs, long non-coding RNAs, proteins and lipids, as well as maternal cells, including leukocytes and stem cells

This complexity is key to adaptive and innate mucosal immunity in the neonate and to support neonatal microbial assembly by interacting closely with intestinal epithelial cells and intestinal receptors signalling to the immune system (modulating the adaptive immune response via a T helper cell response and stimulating regulatory T (Treg) cells and regulatory B cells) and generating immune tolerance

ILC, innate lymphoid cell; NK, natural killer

Term and Preterm infant



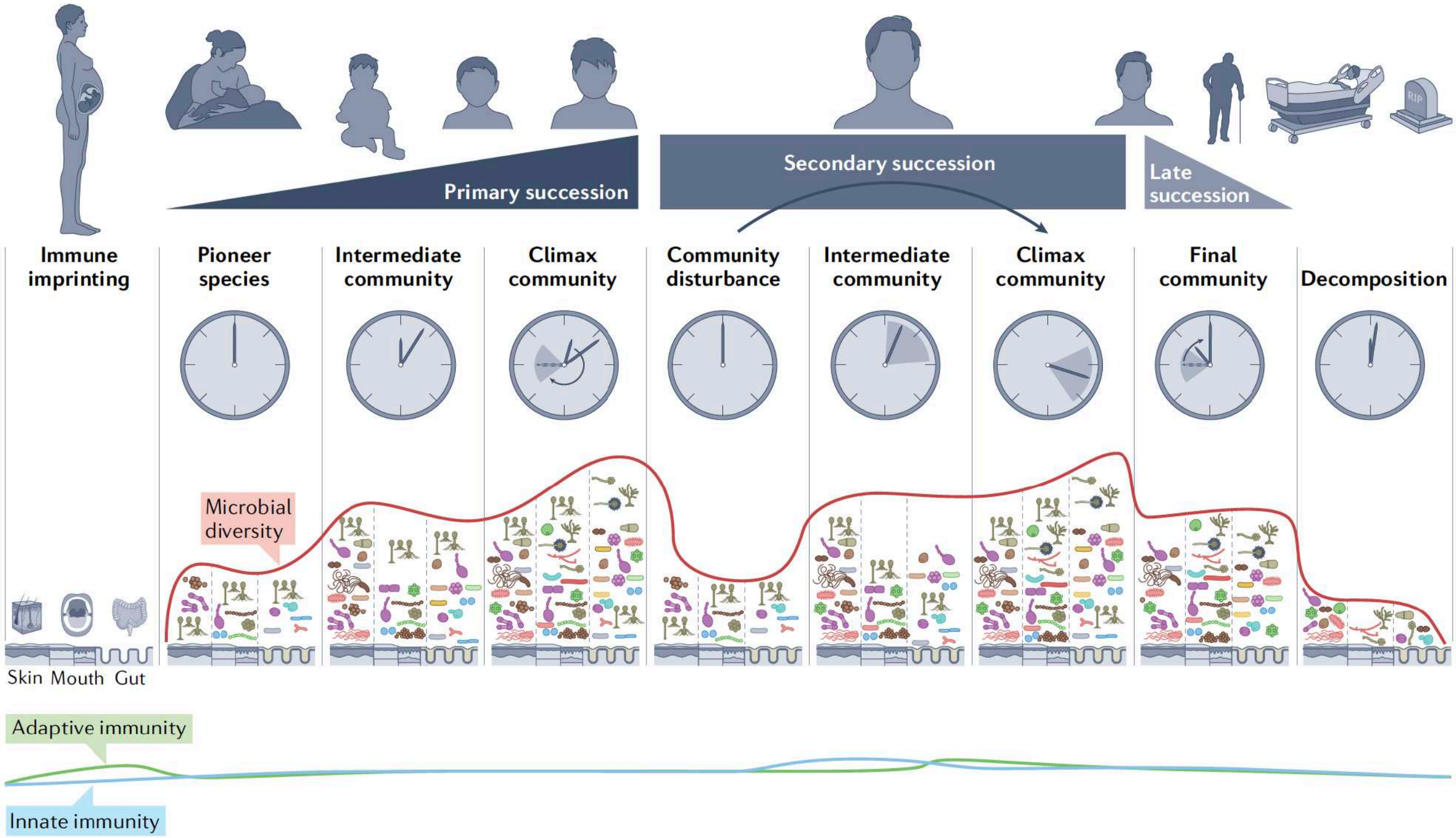
Healy et al., 2022

Anatomical differences, successional development of bacterial communities, and factors influencing microbiome establishment in term and preterm infants

The intestinal anatomy of the preterm infant is immature, with poor differentiation of epithelial cells leading to weakened gut-barrier defences

The initial colonizers of the gut are similar for term and preterm infants but, over time (hours to days) (represented by the vertical dashed line), various influencing factors and alterations in community dynamics lead to the establishment of considerably different populations of microbiota

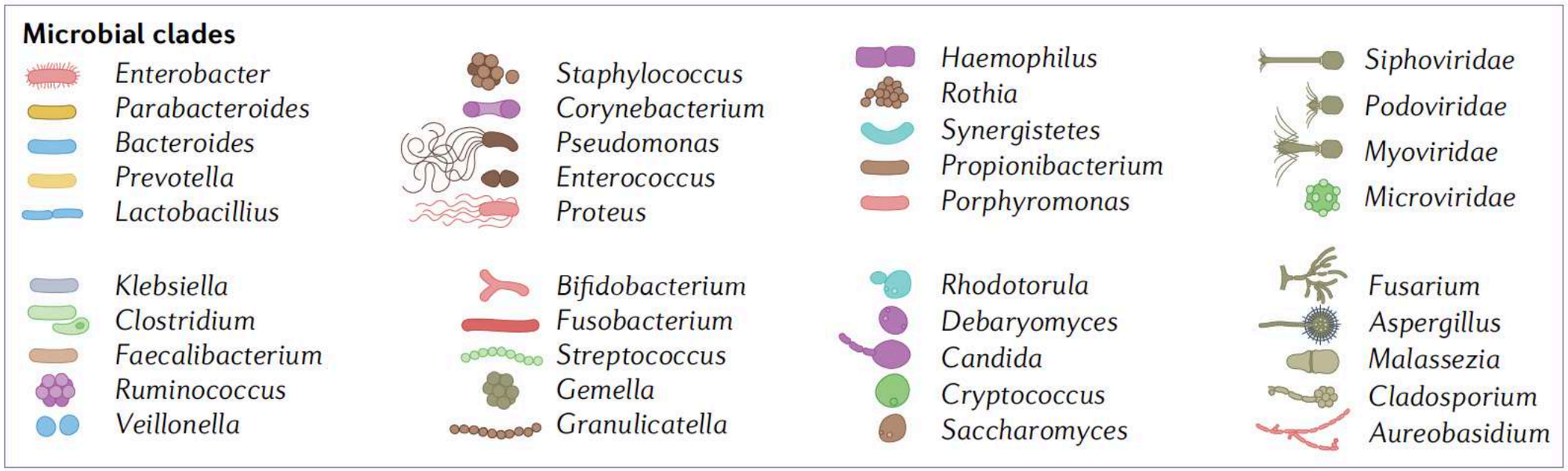
The succession of the human microbiota from conception to death



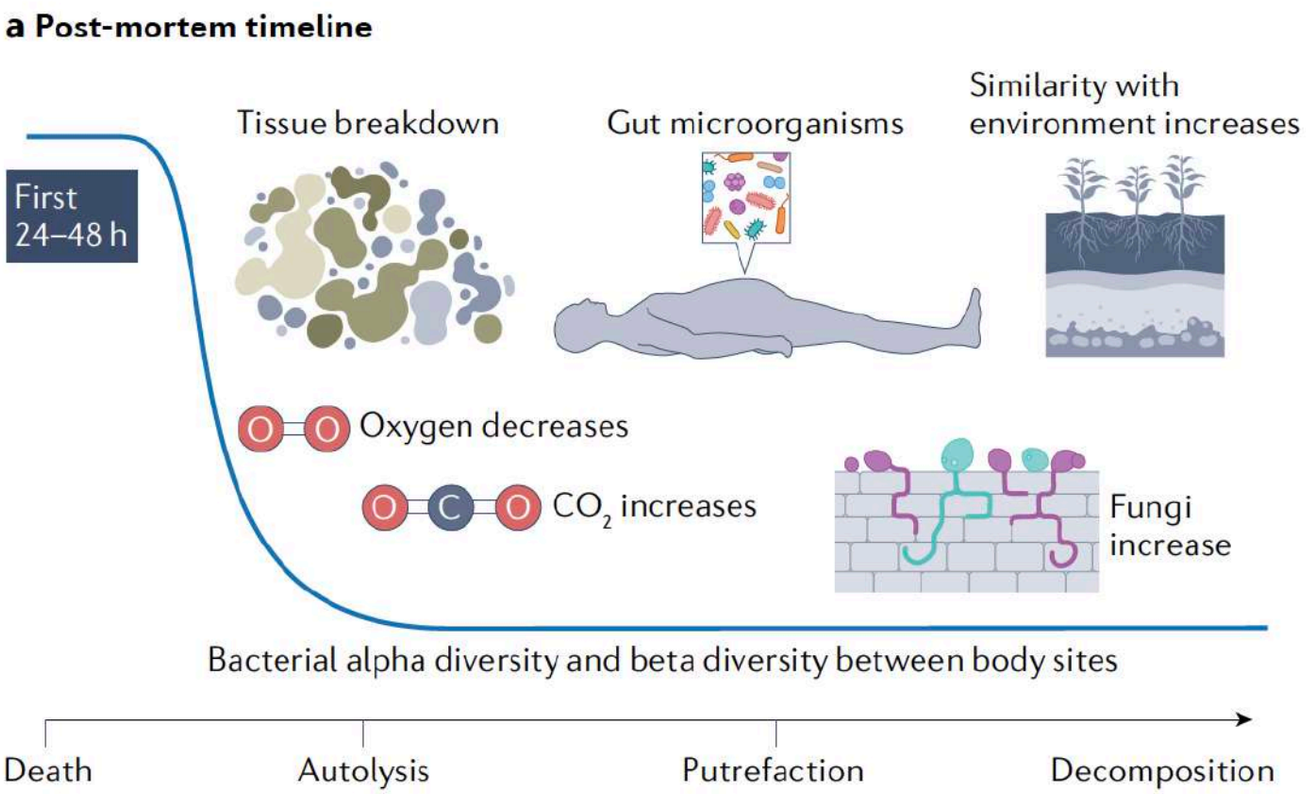
Martino et al., 2022

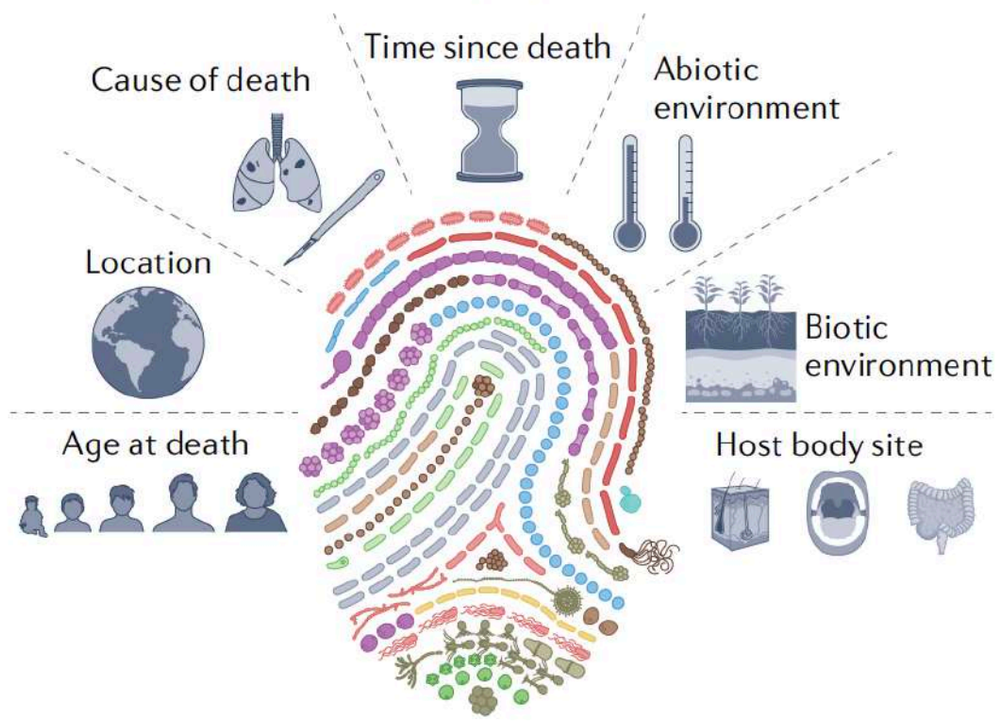
- **Immune imprinting begins before birth through the mother's microbiota and its metabolites**
- **Initial colonization of pioneer species begins at birth, and body site- specific microbial communities emerge**
- **These communities increase in complexity until they reach a relatively stable community structure**

Martino et al., 2022



The microbiota after death





Martino et al., 2022

- After death the microbiota is relatively stable in the first 24–48 h
- The tissue then begins to break down during autolysis, leading to bloom in the gastrointestinal microbiota and a decrease in alpha diversity and a decrease in beta diversity between body sites
- During putrefaction, the role of fungi increases, and the microbiota of the body becomes more similar to the microbiota of the surrounding environment
- The post- mortem microbiota is unique to each body and is distinct between bodies on the basis of the time since death, cause of death, environment, location and age at death, at the beginning, between body sites

In sum the roles of the microbes in the human ecosystem are:

1. Digestion and Metabolism

- Helps break down complex carbohydrates, fiber, and proteins that the human body cannot digest alone
- Produces essential **short-chain fatty acids (SCFAs)** like butyrate, acetate, and propionate, which provide energy to gut cells and regulate metabolism
- Aids in the synthesis of **vitamins** (*e.g.*, B vitamins, vitamin K)

2. Immune System Regulation

- Plays a crucial role in **training and modulating the immune system**, helping to distinguish between harmful and harmless microbes
- Prevents infections by **competing with pathogens** for nutrients and space (colonization resistance)
- Produces **anti-inflammatory** and immune-modulating compounds

3. Protection Against Pathogens (Defense Mechanism)

- Maintains gut barrier integrity by strengthening **tight junctions** between intestinal cells
- Produces antimicrobial substances to prevent pathogen overgrowth

4. Influence on Brain and Behavior (Gut-Brain Axis)

- Produces **neurotransmitters** like serotonin, dopamine, and GABA, which influence mood and cognitive functions
- Regulates the **gut-brain axis**, impacting mental health conditions like anxiety and depression

5. Role in Disease Prevention and Development

- **Dysbiosis (microbial imbalance)** is linked to diseases like **inflammatory bowel disease (IBD), obesity, type 2 diabetes, allergies, and even neurodegenerative disorders**
- **A healthy gut microbiome reduces inflammation and supports overall metabolic and immune balance**