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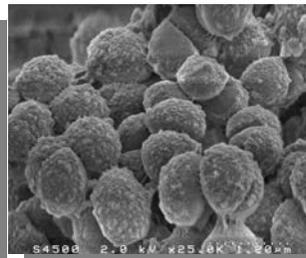
The human intestinal microbiota

- ✓ 50 trillions microorganisms ;
 - ✓ As many microorganisms as human cells (*Sender et al, Cell 2016*)
 - ✓ Hundreds of different species often **not yet cultured** (~70% of species);
 - ✓ a few dozen species conserved between individuals (core); a stable community.
 - ✓ A key organ, interacting with food (fermentation,...); interacting with our cells (Immune & nervous systems,...); protecting against pathogens (barrier function);...
 - ✓ A true organ, revealed as playing a role in several diseases
 - ✓ Thousands of metabolites/molecules with potential functional interest
- (*Blottière & Doré, médecine/science, 2016*)

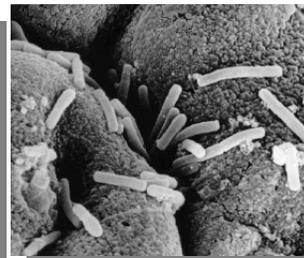


Faecalibacterium prausnitzii

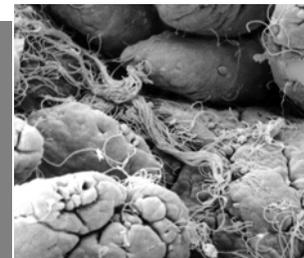
Photos INRA



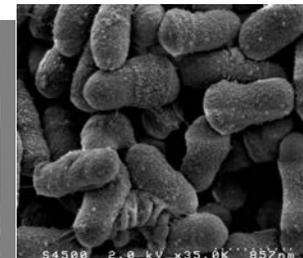
Ruminococcus spp



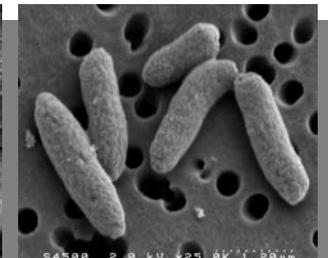
Clostridium difficile
From mice cecum



Bacteria anchored in a Peyer patch
Mouse intestine

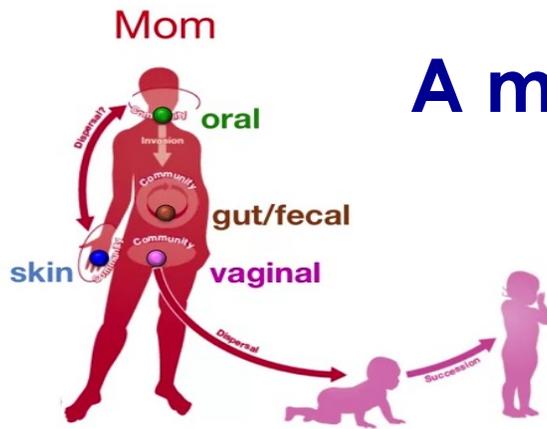


Bacteroides dorei



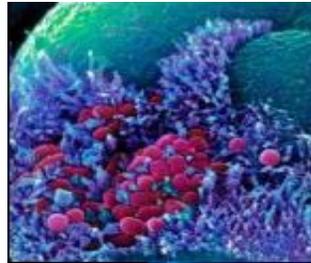
Escherichia coli

A man-microbe mutualism that starts at birth



adapted from Gonzalez et al. 2011, EMBO reports

Intestinal & immune
Maturation



Development
of the microbiota

'unique' symbiosis :
microbiota being
recognized
as an integral part of
the whole organism

Holobiont

Maintained symbiosis :
health and well-being

Disruption of
ecological balance :
loss of barrier function
& risk of infection

Disruption of tolerance :
risk of immune-mediated
diseases

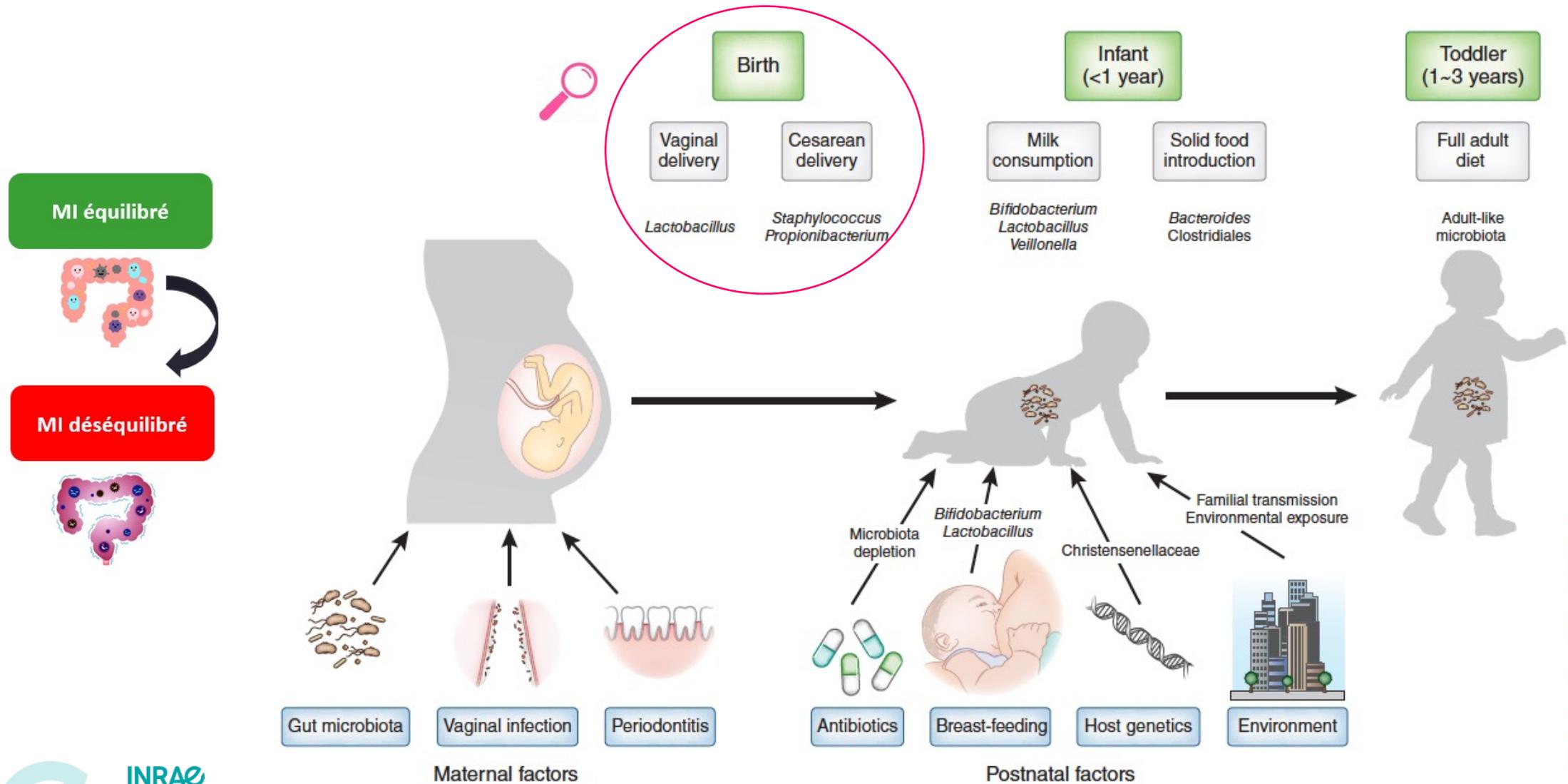
Prevention & Therapy of
the Holobiont : evaluation,
monitoring and treatment

Sterile *in utero*, the intestine is colonized at birth

- colonization is affected by :
 - Mode of delivery (vaginal delivery or caesarean section)
 - Hygiene of neonatal environment
 - Drugs administration (antibiotic, PPI, ...)
 - Maternal nutrition and maternal microbiome
 - Mode of feeding (breast milk versus bottled milk; probiotics)
 - Weaning
- early colonization, hygiene hypothesis and DOHaD
Impact on the microbiota-host symbiosis and therefore on biology and health?

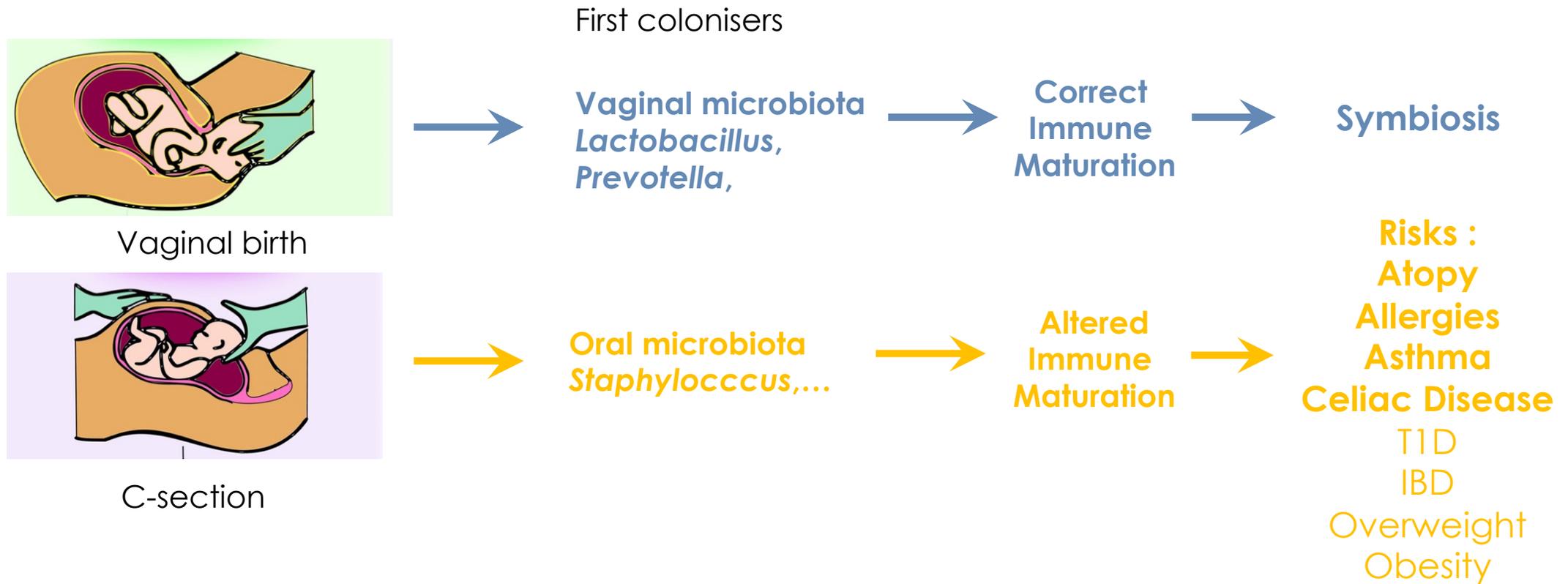


Factors affecting intestine colonization



Alteration of colonisation by mode of birth

C- section increases the risk of infection and the risk of future pathologies



Aquisition of Microbiota : impact of mode of delivery

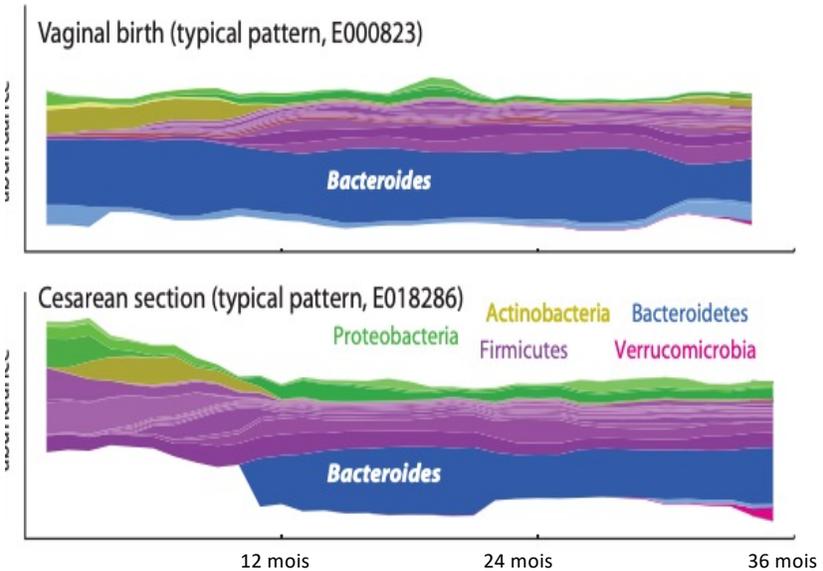
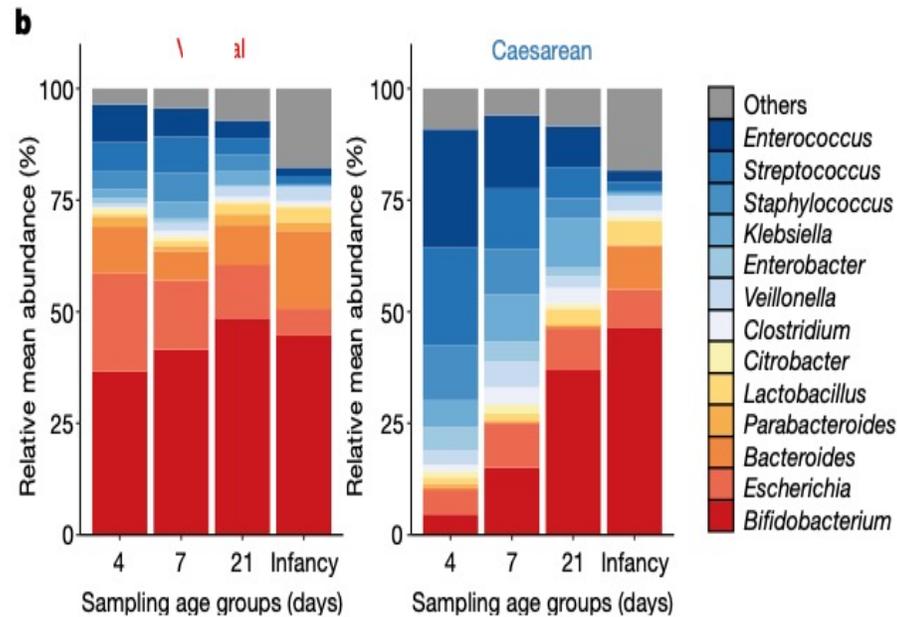
LETTER

<https://doi.org/10.1038/s41586-019-1560-1>

Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth

Yan Shao¹, Samuel C. Forster^{1,2,3}, Evdokia Tsaliki⁴, Kevin Vervier¹, Angela Strang⁴, Nandi Simpson⁴, Nitin Kumar¹, Mark D. Stares¹, Alison Rodger⁴, Peter Brocklehurst³, Nigel Field^{4*} & Trevor D. Lawley^{1*}

Differences in gut microbiota composition still observed at 3 years

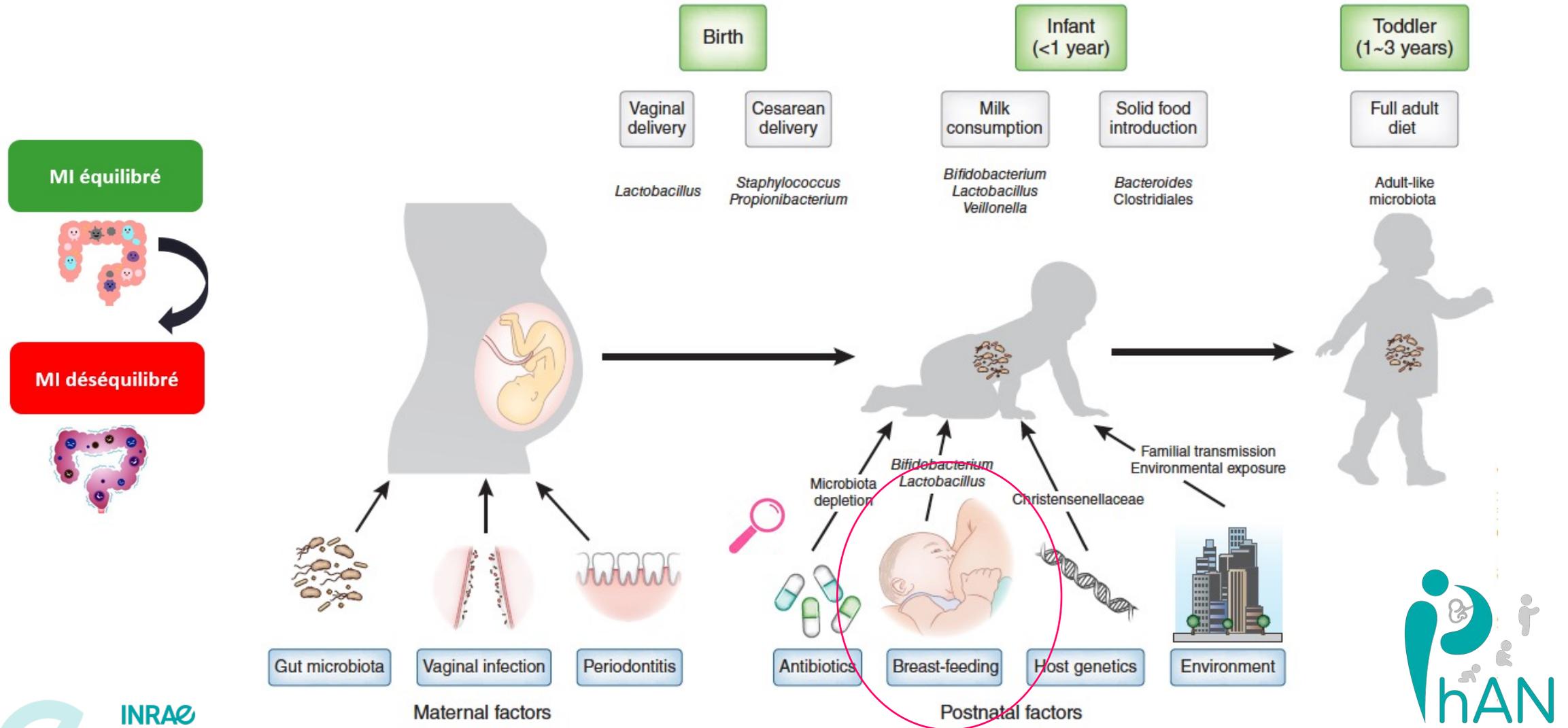


Low richness More pathobionts

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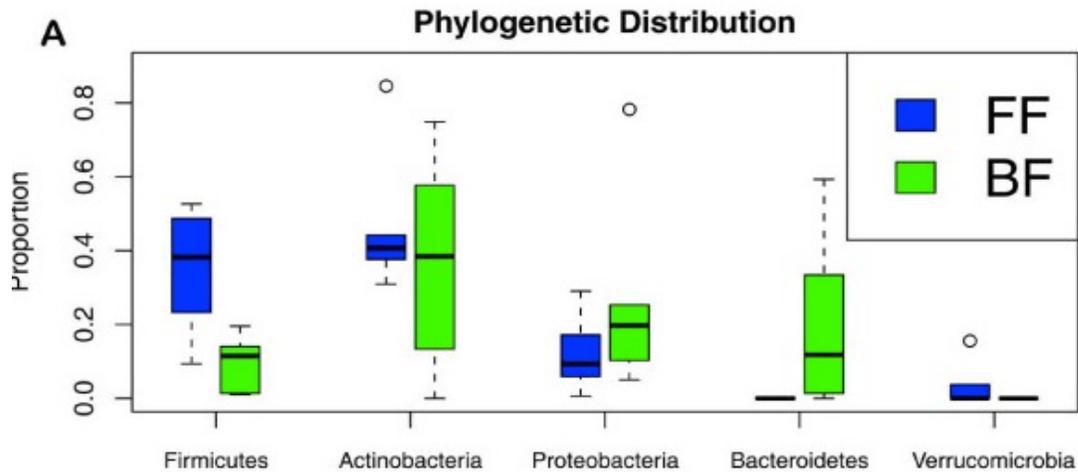
Shao et al, Nature, 2019

Factors affecting intestine colonization



Tamburini et al., Nat Medicine 2016

Factors affecting intestine colonization : Mother milk vs formula



LETTER

OPEN

<https://doi.org/10.1038/s41586-018-0617-x>

Temporal development of the gut microbiome in early childhood from the TEDDY study

Christopher J. Stewart^{1,2,18*}, Nadim J. Ajami^{1,18}, Jacqueline L. O'Brien¹, Diane S. Hutchinson¹, Daniel P. Smith¹, Matthew C. Wong³, Matthew C. Ross³, Richard E. Lloyd¹, HarshaVardhan Doddapaneni³, Ginger A. Metcalf³, Donna Muzny³, Richard A. Gibbs³, Tommi Vatanen⁴, Curtis Huttenhower⁴, Ramnik J. Xavier⁴, Marian Rewers⁵, William Hagopian⁶, Jorma Toppari^{7,8}, Anette-G. Ziegler^{9,10,11}, Jin-Xiong She¹², Beena Akolkar¹³, Ake Lernmark¹⁴, Heikki Hyoty^{15,16}, Kendra Vehik¹⁷, Jeffrey P. Krischer¹⁷ & Joseph F. Petrosino^{1*}

The contribution of breast milk, exclusive or partial, is the most important factor.

Breastfeeding = increased abundance of *Bifidobacterium* (*B. breve* and *B. bifidum*)

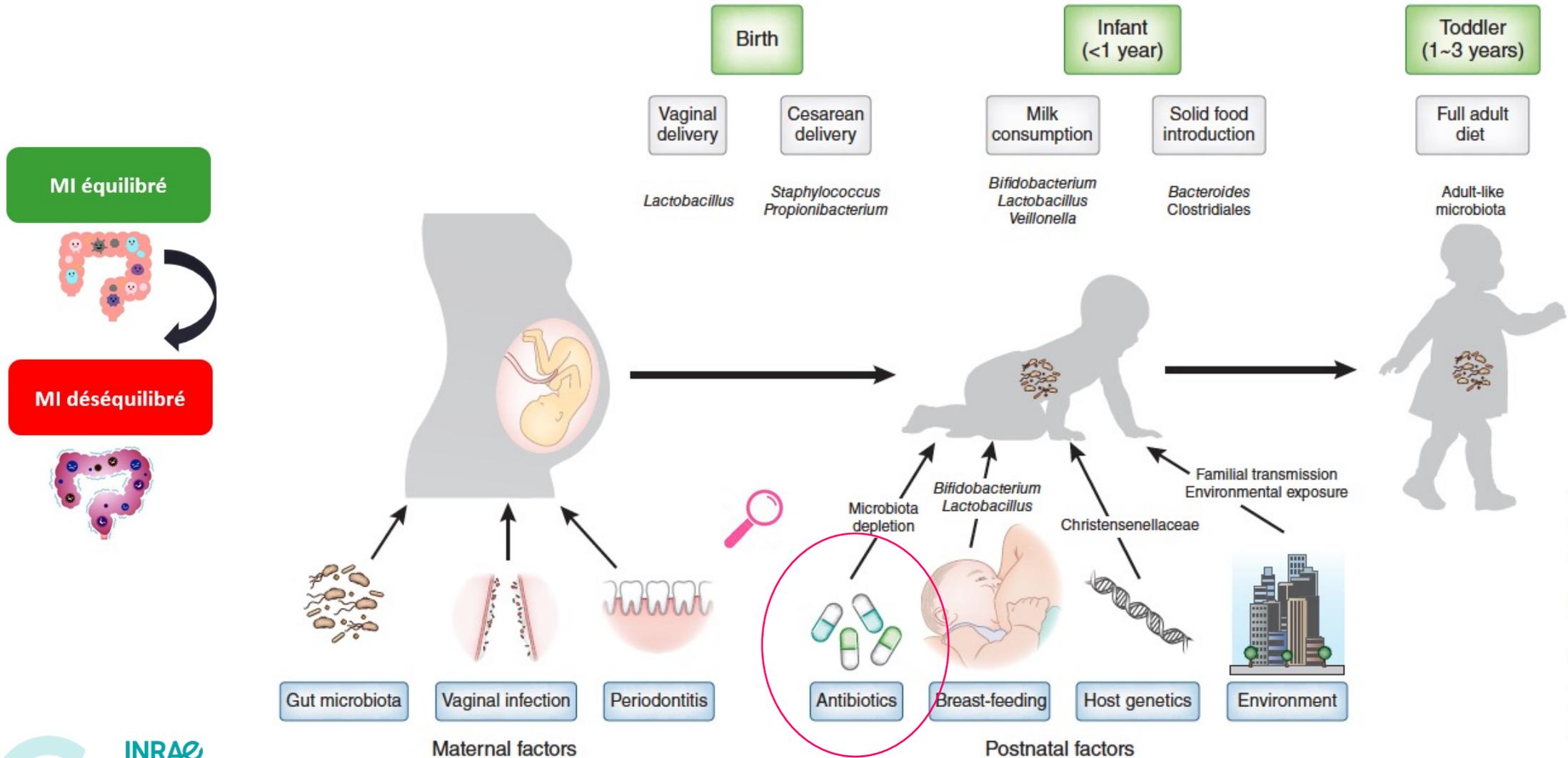
Importance of HMO and milk microbiota

Discontinuation of breast milk leads to rapid maturation of the intestinal microbiome, increase in Firmicutes



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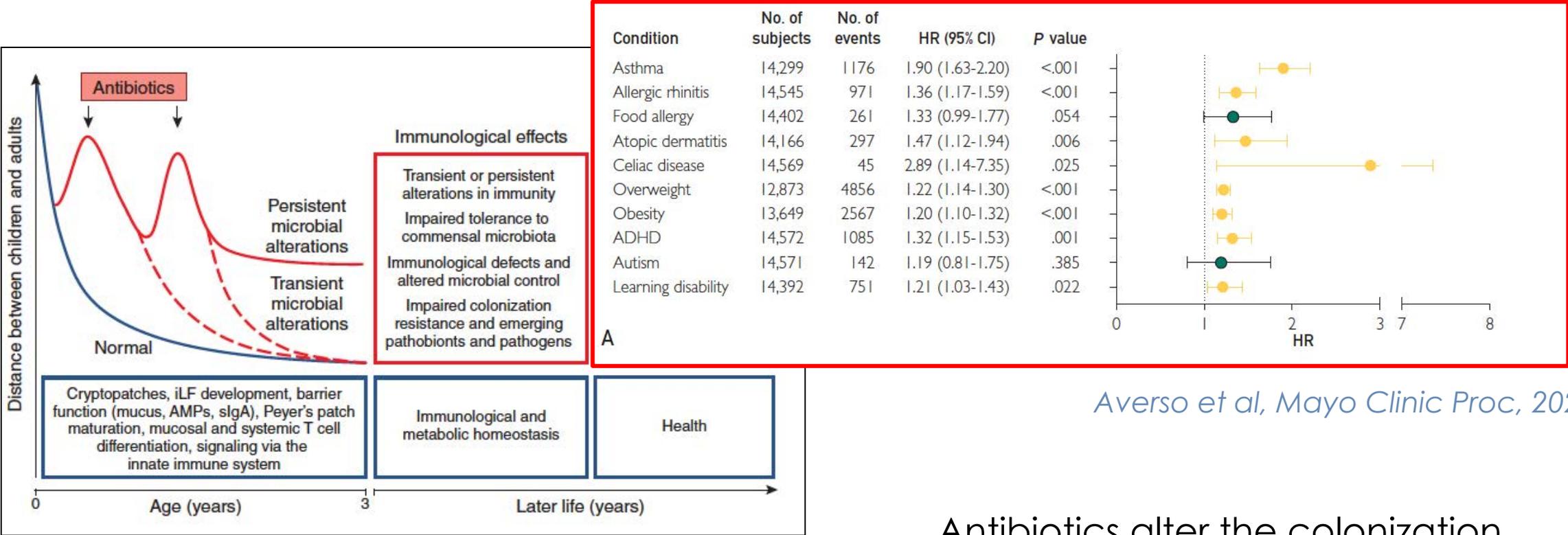
Factors affecting intestine colonization



Tamburini et al., Nat Medicine 2016

Factors affecting intestine colonization : Impact of Antibiotics

Clinical consequences



Averso et al, Mayo Clinic Proc, 2021

Antibiotics alter the colonization process for at least 2 years

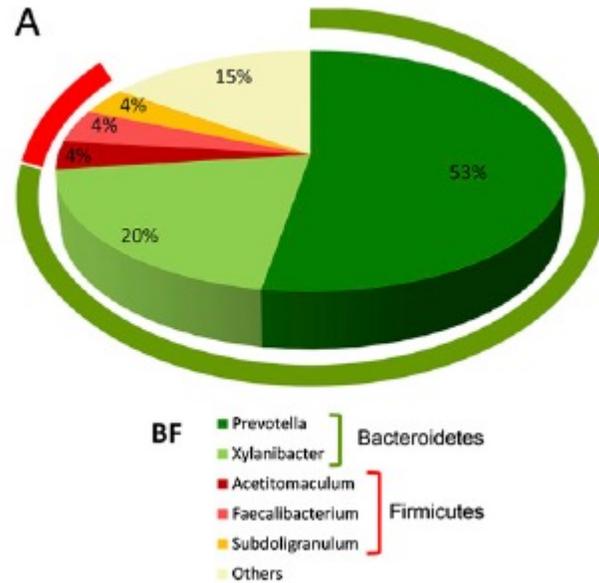


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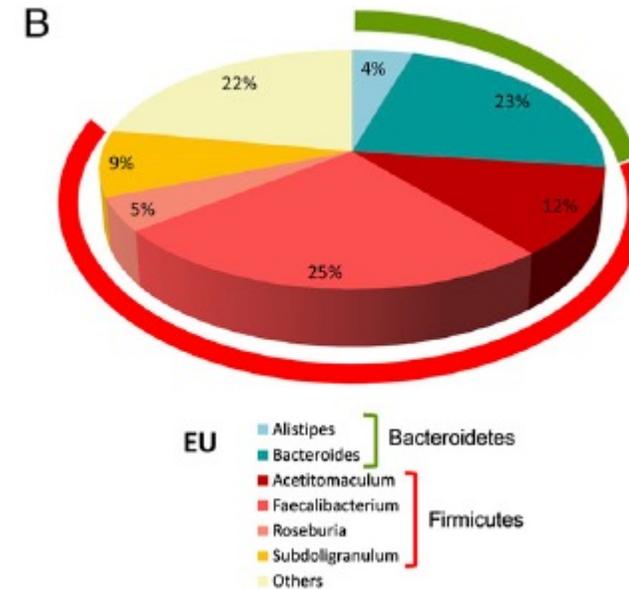
Zeissig, Nature Immunol, 2014

After weaning, importance of dietary habits

Children from Burkina Faso
Little calories, lots of fibres

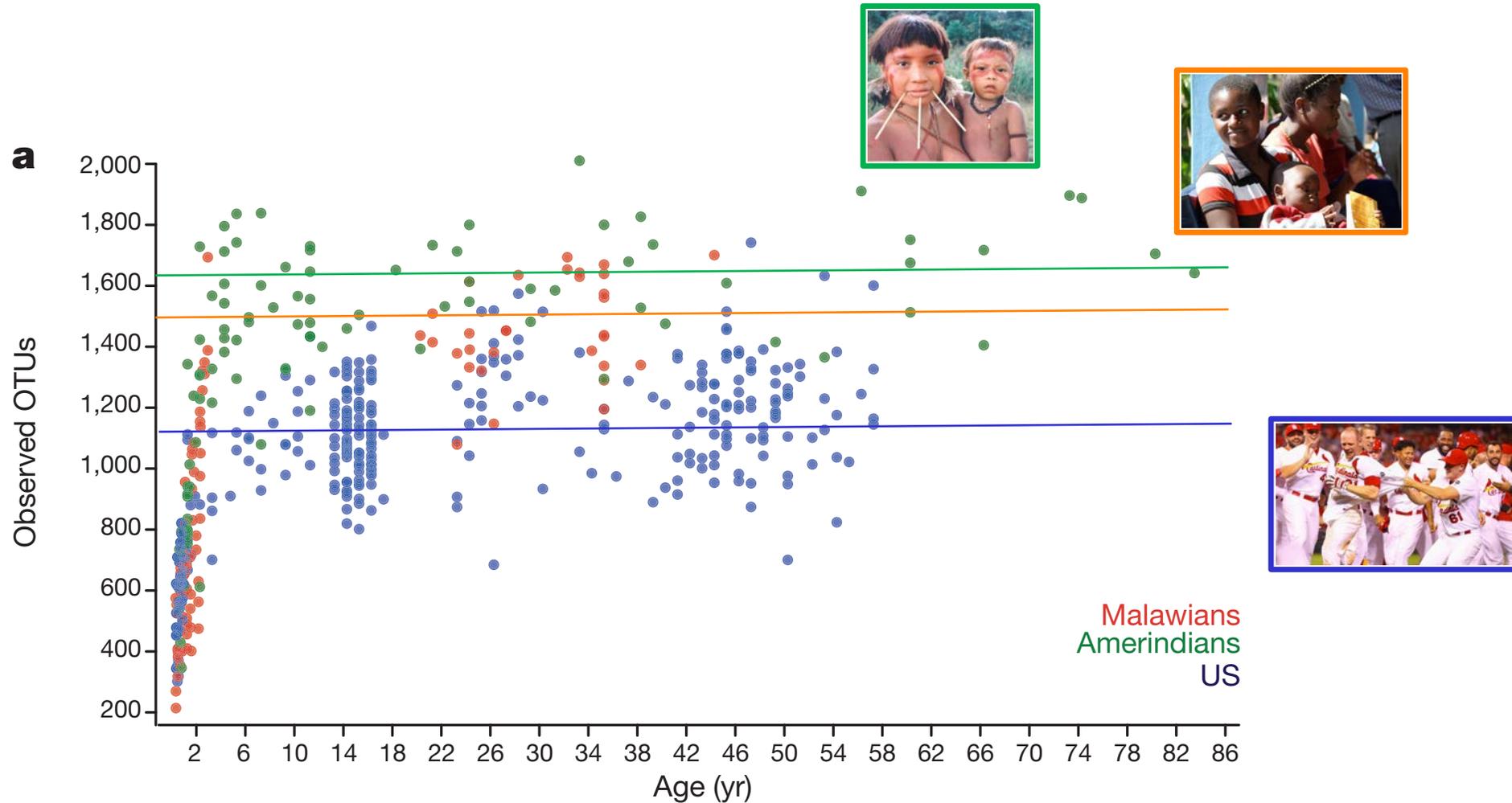


European children
Lots of de calories, few fibres



Different dietary habits results in different gut microbiota

Evolution of intestinal microbiota through aging



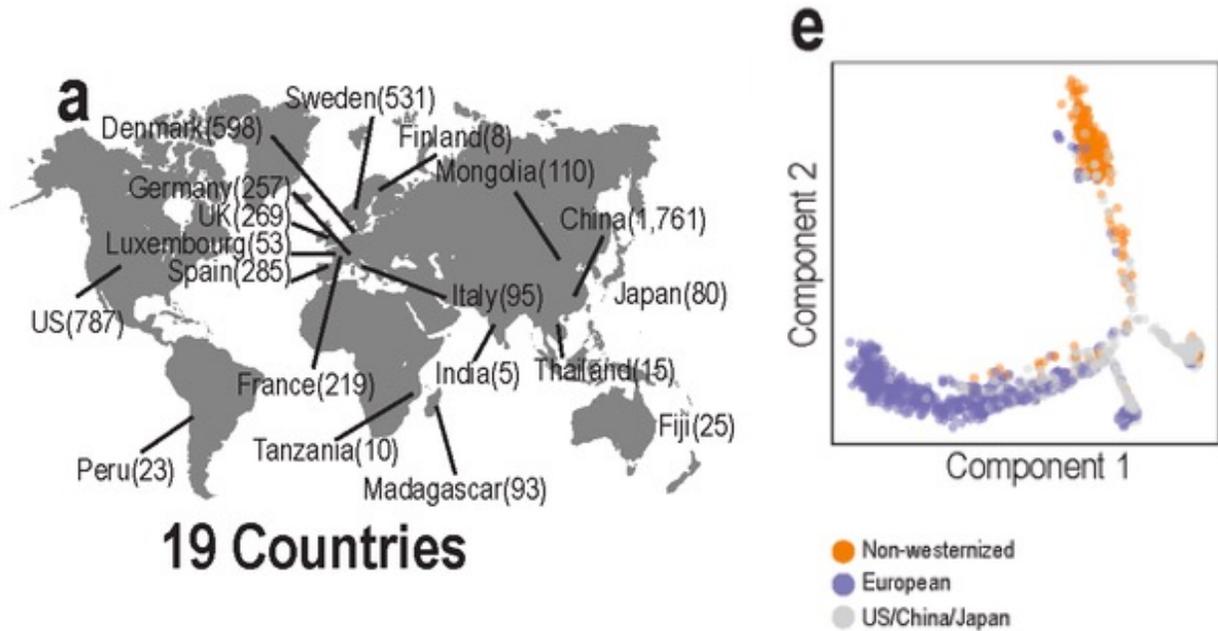
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Yatsunenko et al, Nature 2012

What is symbiosis ? Can we define IT ?

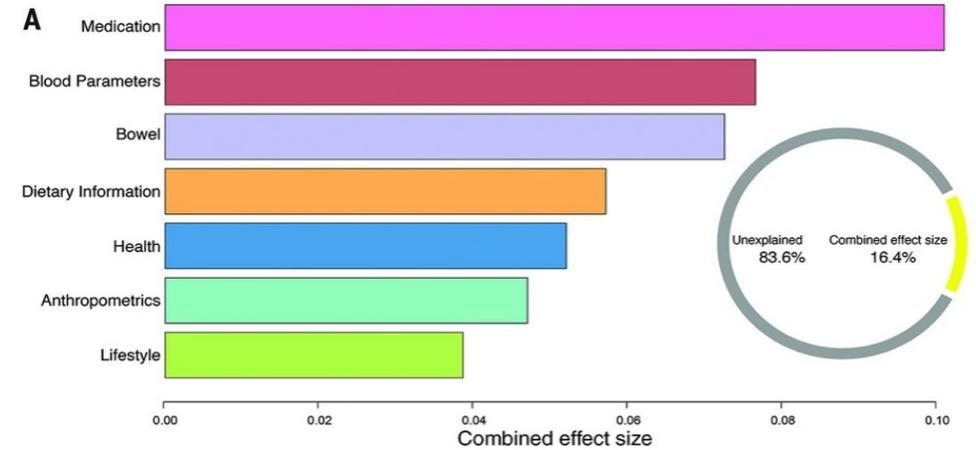
Population-level analysis of gut microbiome variation

Global human Gut Microbiome



19 Countries

Schoaie et al, preprint, 2021



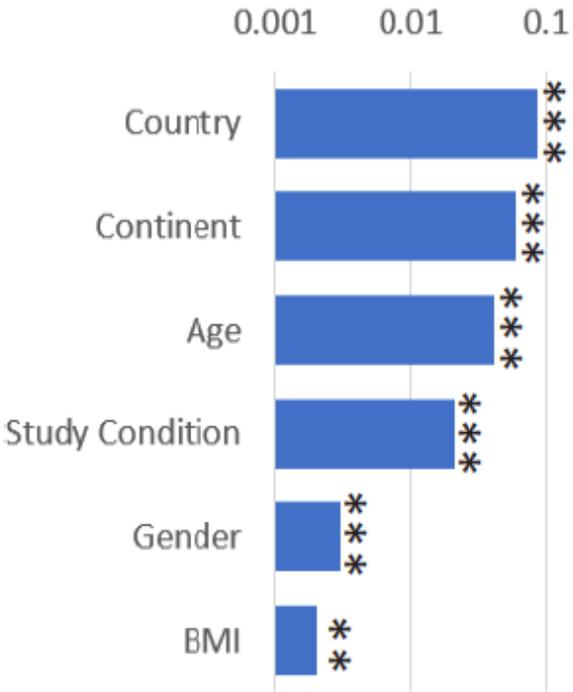
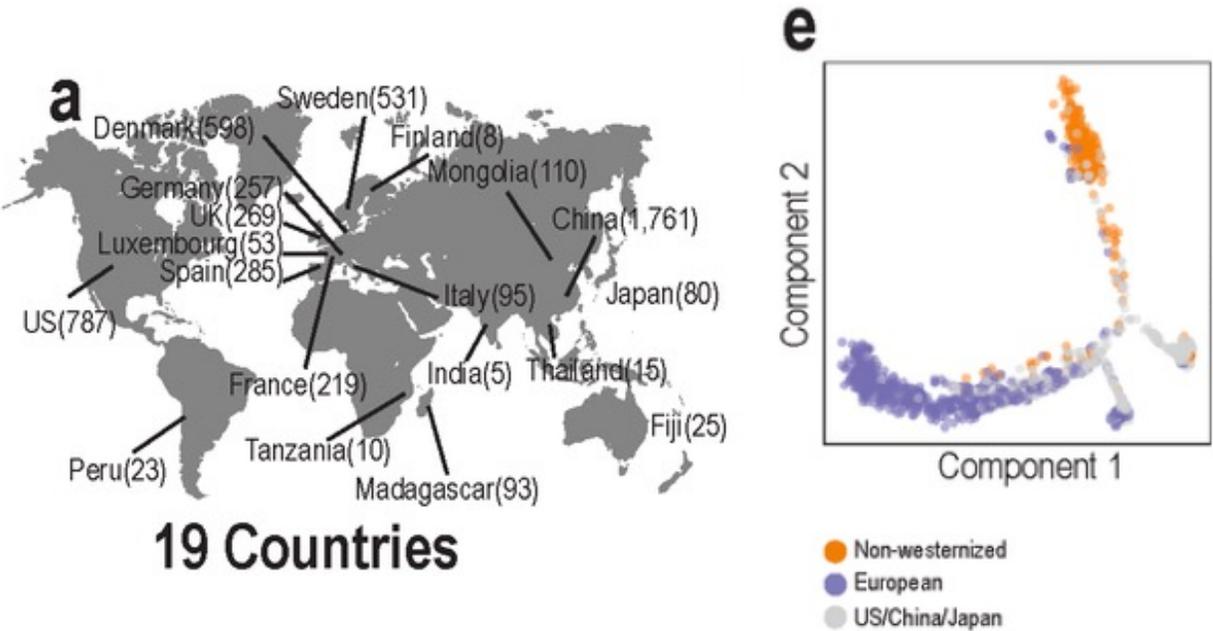
1 106 Belgium Flemish individuals
16 S sequencing (V4)

Medication explain 10 % of gut microbiota variation followed by blood parameters, bowel habits, health status, anthropometric features, and lifestyle.

What is symbiosis ? Can we define IT ?

Population-level analysis of gut microbiome variation

Global human Gut Microbiome



Schoaie et al, preprint, 2021

Age is also an important factor to consider

Introducing Enterotypes

All individuals studied today (n>1000) are clustered in 3 « Entérotypes », each characterized by an ecological context dominated by *Bacteroides*, *Prevotella*, *Ruminococcus*/*Methanobrevibacter*

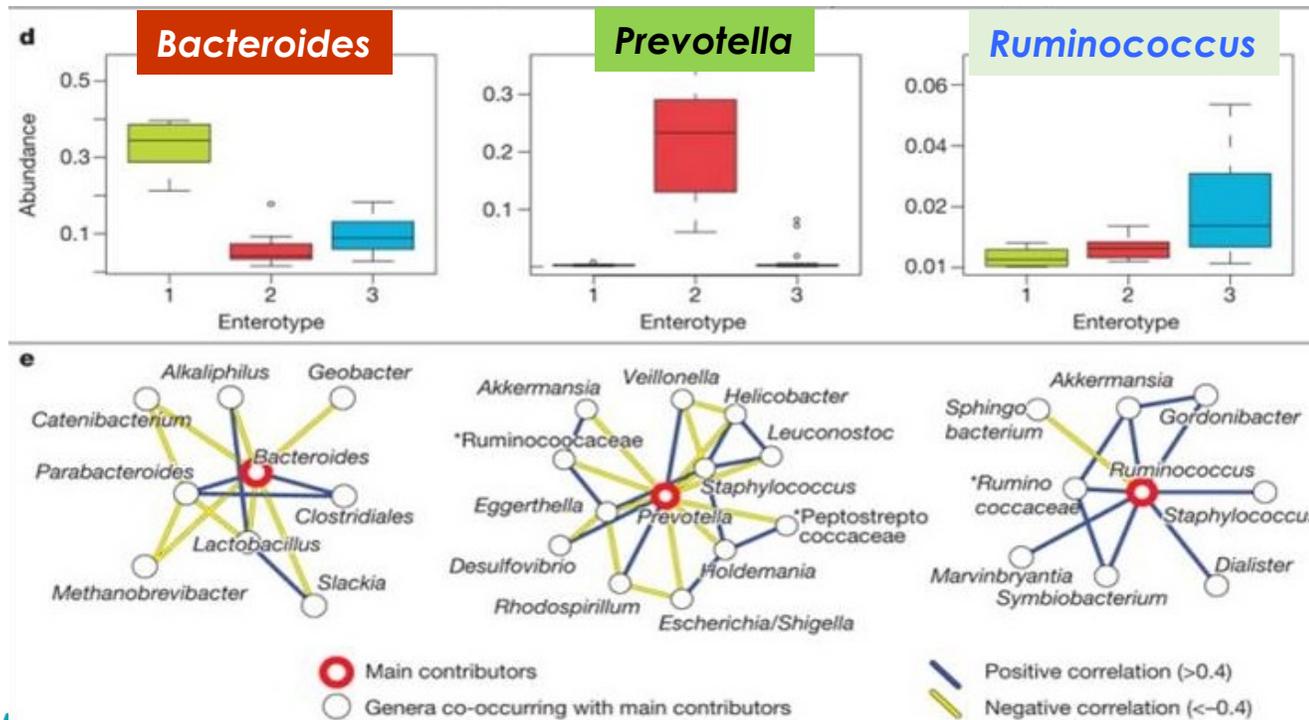
ARTICLE

doi:10.1038/nature09944

Enterotypes of the human gut microbiome

Manimozhayan Arumugam^{1*}, Jeroen Raes^{1,2*}, Eric Pelletier^{3,4,5}, Denis Le Paslier^{3,4,5}, Takuji Yamada¹, Daniel R. Mende¹, Gabriel R. Fernandes^{1,6}, Julien Tap^{1,7}, Thomas Bruls^{3,4,5}, Jean-Michel Batto⁷, Marcelo Bertalan⁸, Natalia Borruel⁹, Francesc Casellas⁹, Leyden Fernandez¹⁰, Laurent Gautier⁸, Torben Hansen^{11,12}, Masahira Hattori¹³, Tetsuya Hayashi¹⁴, Michiel Kleerebezem¹⁵, Ken Kurokawa¹⁶, Marion Leclerc⁷, Florence Levenez⁷, Chaysavanh Manichanh⁹, H. Bjorn Nielsen⁸, Trine Nielsen¹¹, Nicolas Pons⁷, Julie Poulain³, Junjie Qin¹⁷, Thomas Sicheritz-Ponten^{8,18}, Sebastian Tims¹⁵, David Torrents^{10,19}, Edgardo Ugarte³, Erwin G. Zoetendal¹⁵, Jun Wang^{17,20}, Francisco Guarner⁹, Oluf Pedersen^{11,21,22,23}, Willem M. de Vos^{15,24}, Soren Brunak⁸, Joel Doré⁷, MetaHIT Consortium†, Jean Weissenbach^{3,4,5}, S. Dusko Ehrlich⁷ & Peer Bork^{1,25}

→ Link with food habits



Ecology underlying enterotypes should be better understood



Enterotypes

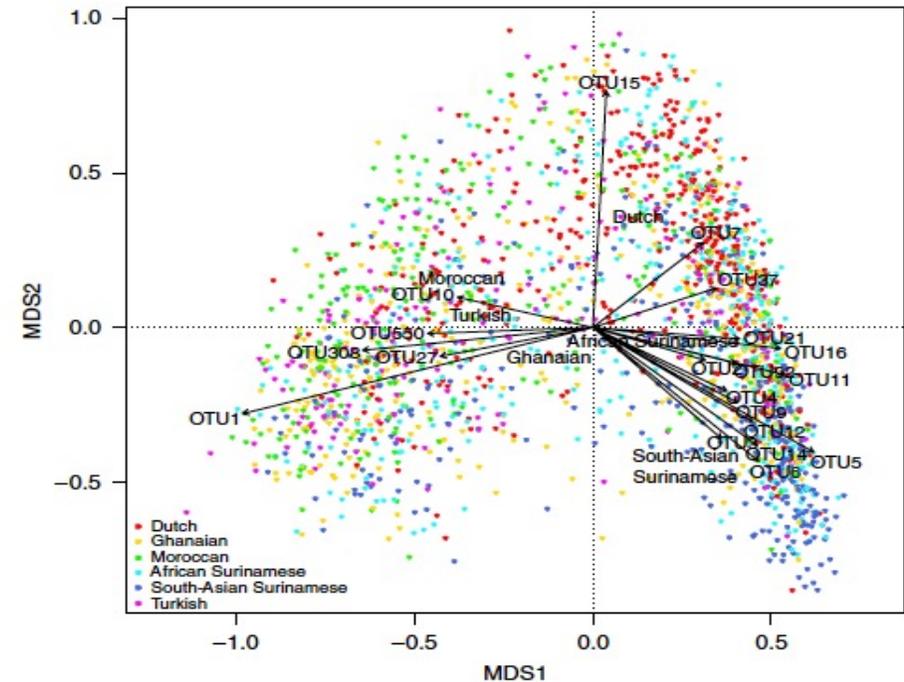
nature medicine LETTERS
<https://doi.org/10.1038/s41591-018-0160-1>

Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography

Mélanie Deschasaux^{1*}, Kristien E. Bouter², Andrei Prodan², Evgeni Levin², Albert K. Groen², Hilde Herrema², Valentina Tremaroli³, Guido J. Bakker⁴, Ilias Attaye⁴, Sara-Joan Pinto-Sietsma^{1,4}, Daniel H. van Raalte², Marieke B. Snijder^{1,5}, Mary Nicolaou⁵, Ron Peters⁶, Aeilko H. Zwinderman¹, Fredrik Bäckhed^{3,7} and Max Nieuwdorp^{2,3,4*}

Ethnicity explain the interindividual dissimilarities in gut microbiota composition, with three main poles primarily characterized by *Prevotella* (Moroccans, Turks, Ghanaians), *Bacteroides* (African Surinamese, South-Asian Surinamese), and *Clostridiales* (Dutch).

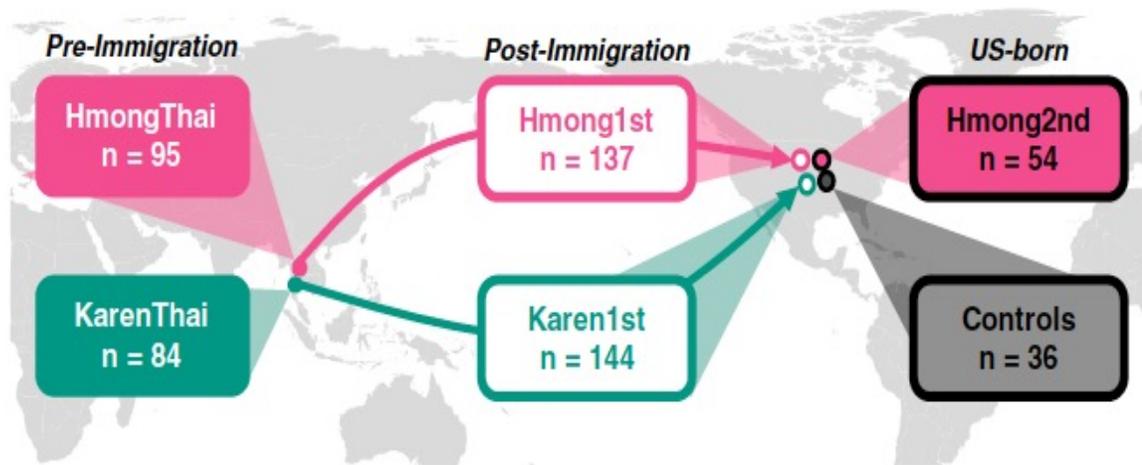
Despite sharing the same environment for a long period, our participants showed ethnic-specific gut microbiota profiles, probably reflecting the composition they acquired before migration (94% arrived in adulthood)



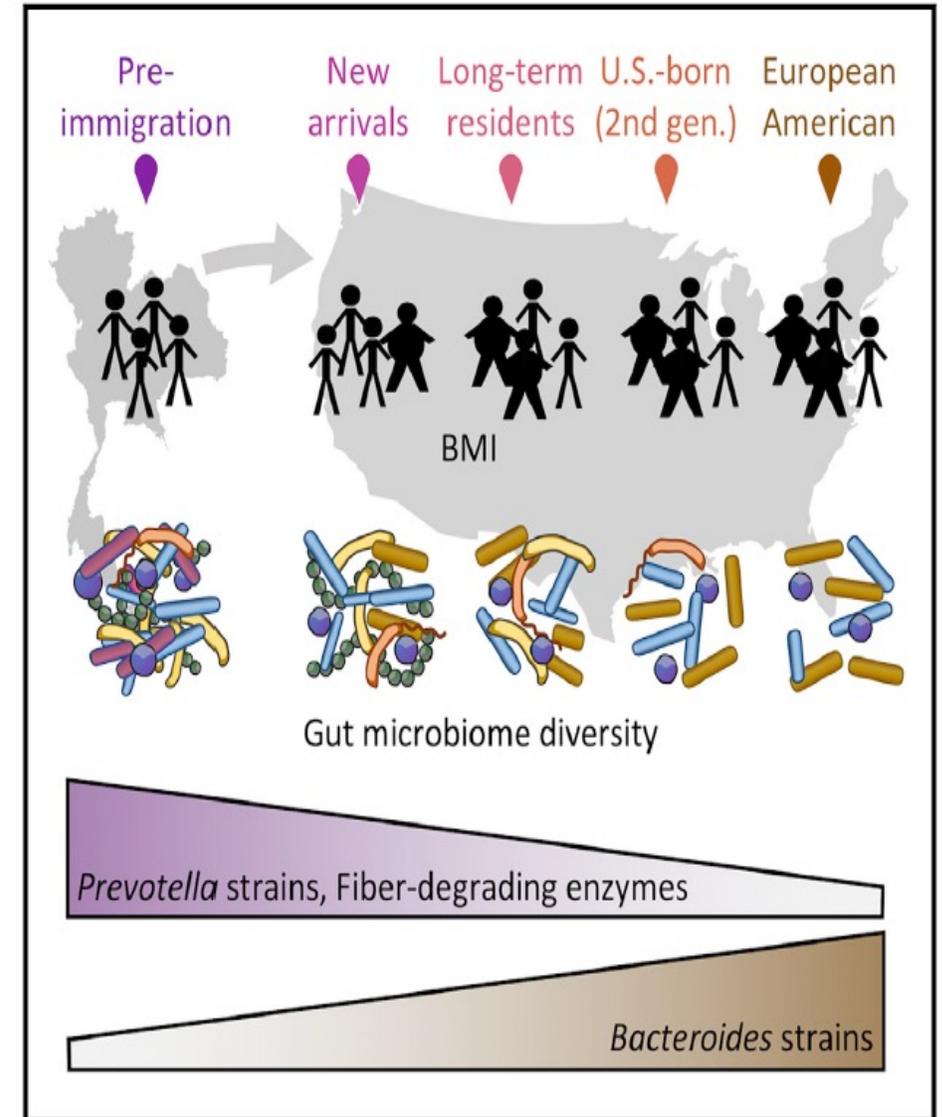
2084 individuals Helius study
16 S sequencing (V2)

What is symbiosis ? Can we define IT ?

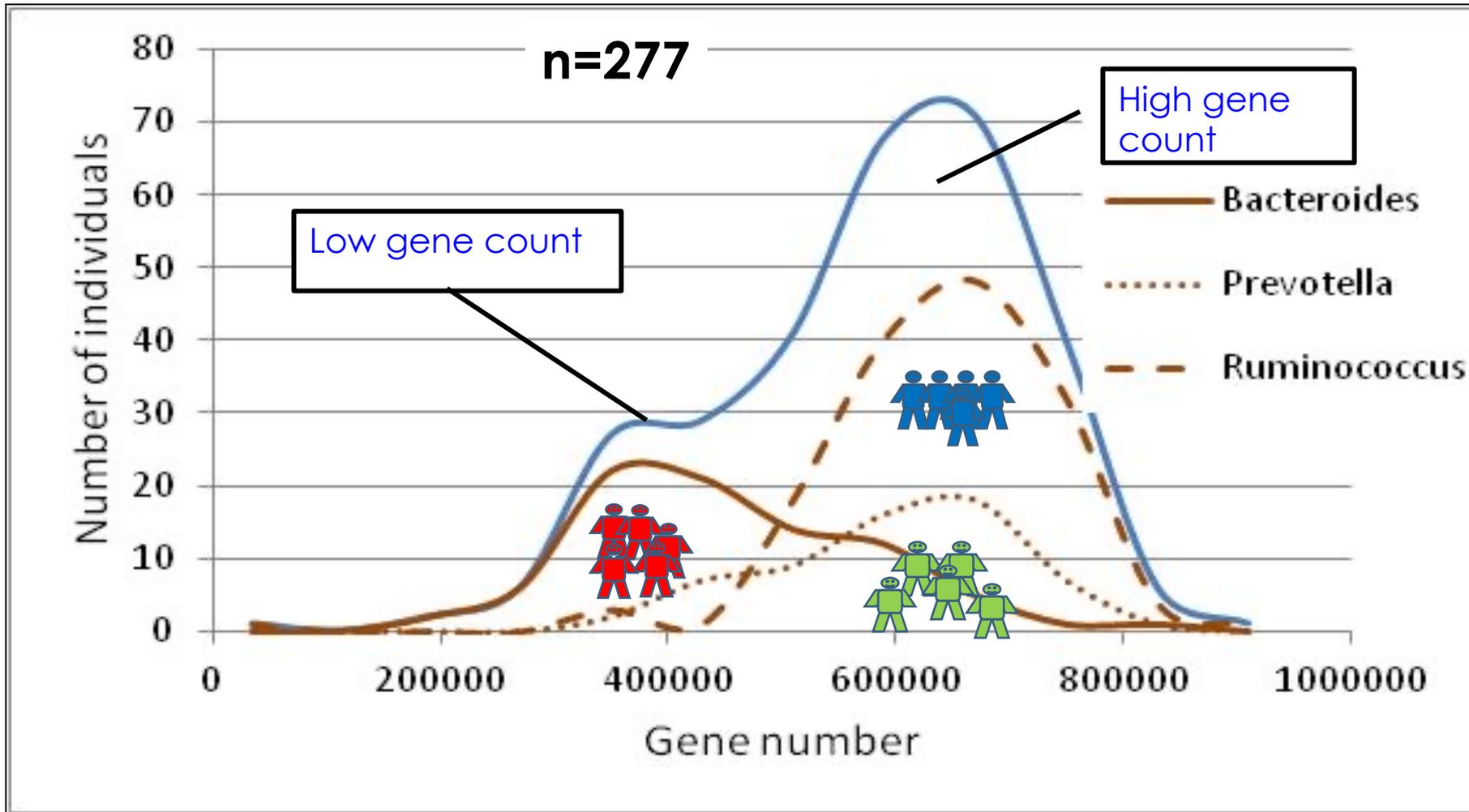
US Immigration Westernizes
the Human Gut Microbiome



550 Thai individuals
16 S sequencing (V4)
+ shotgun



Human gut microbiomes differ on gene (and species) richness



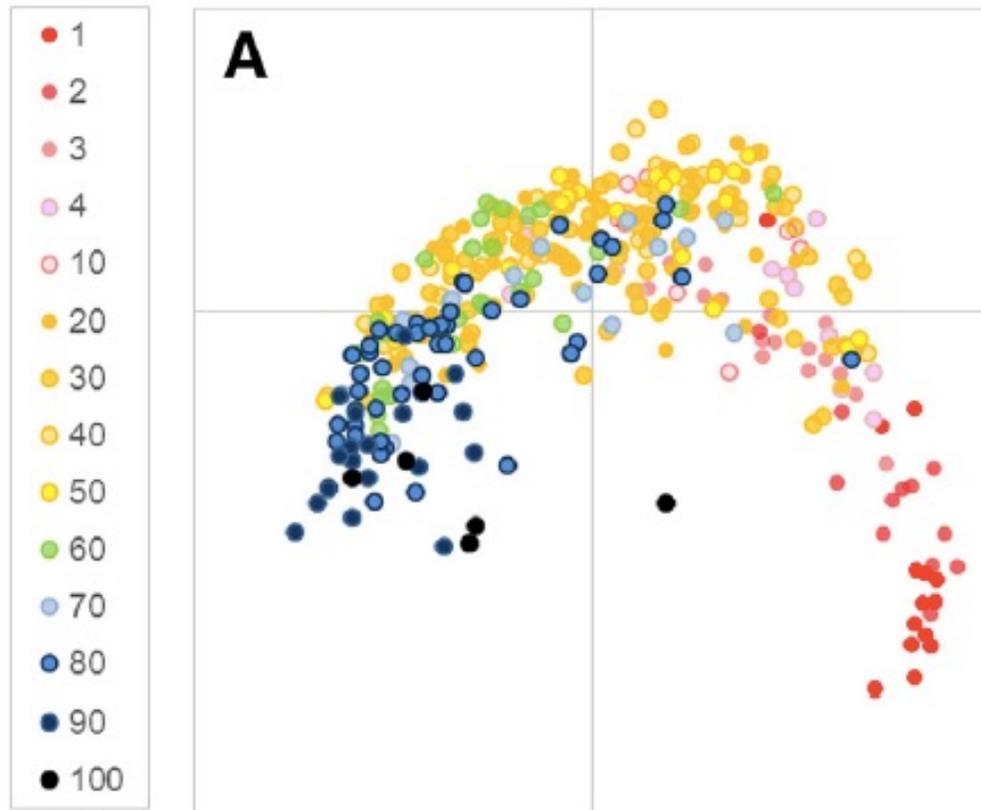
LGC
≈ 15 % of lean
individuals

≈ 40%
Overweight-
moderate obese

≈ 75%
Morbid obese
before bypass
surgery

58 « species » significantly linked to gene count

Age-related changes in gut microbiota composition from newborn to centenarian



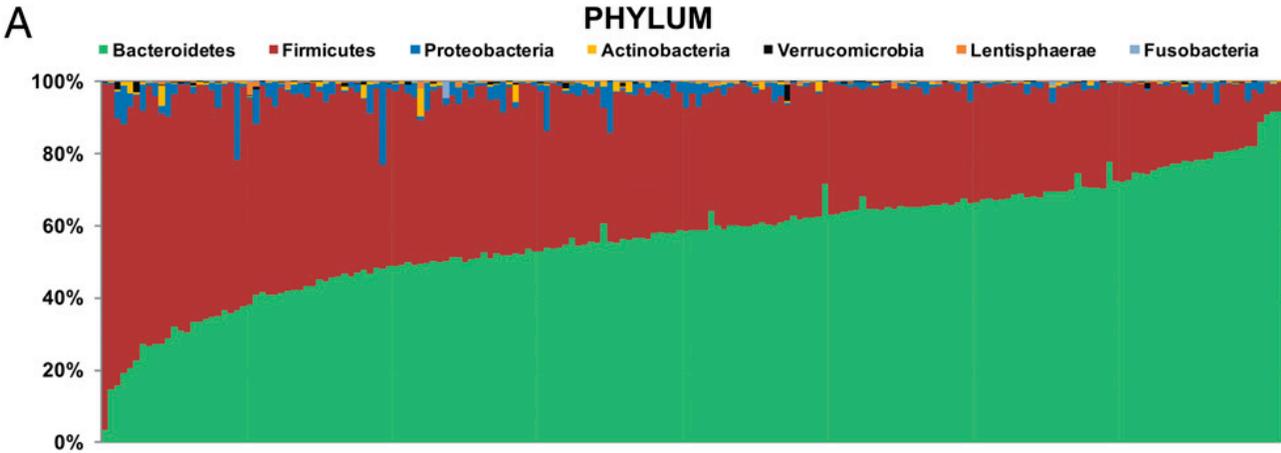
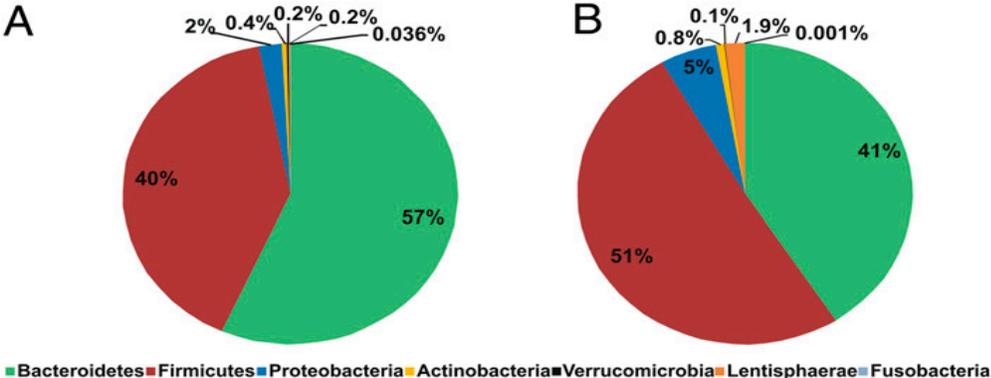
367 healthy Japanese subjects 0 and 104 y.o.

Evolution of intestinal microbiota through aging

Eldermet

187 fecal samples from elderly subjects

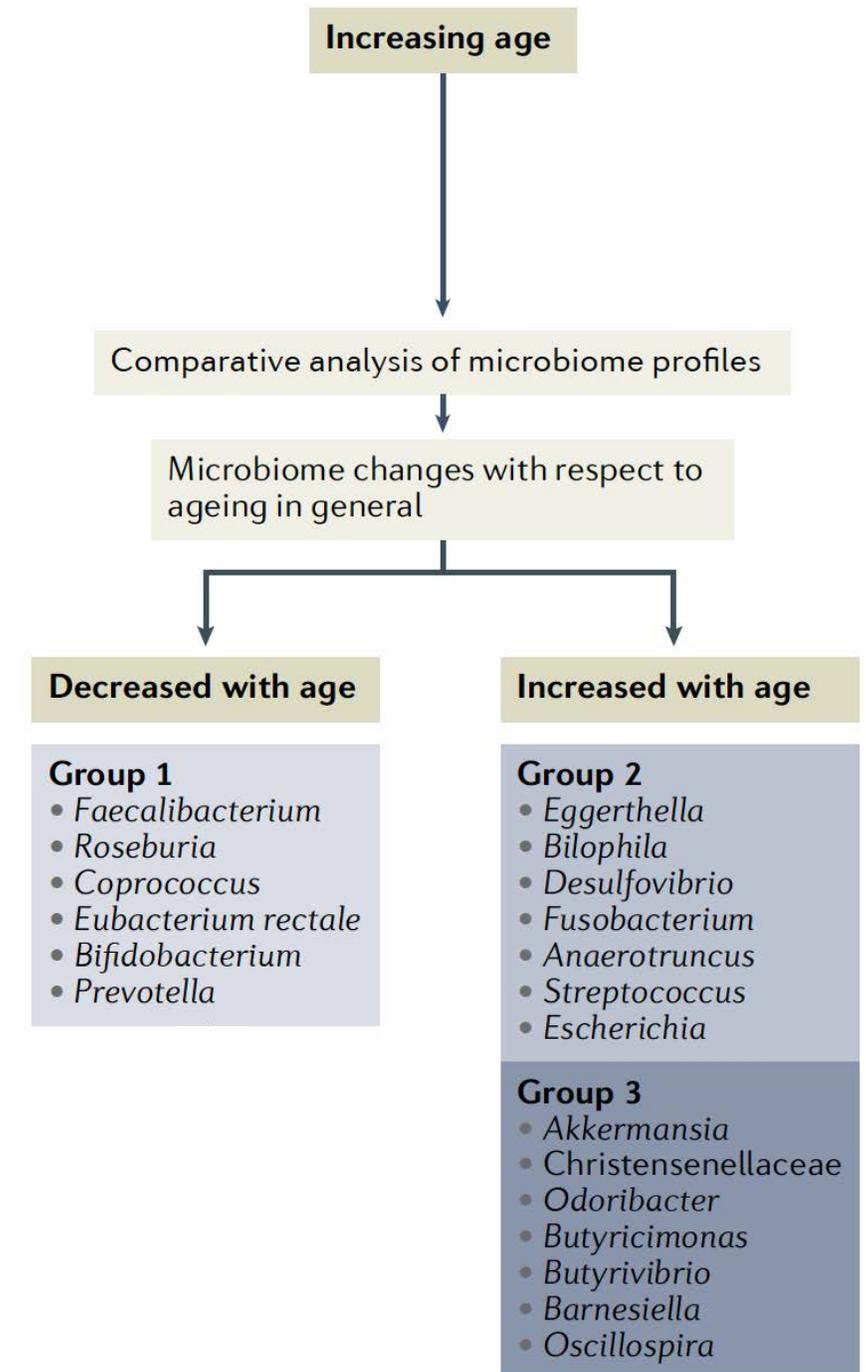
9 fecal samples from adults



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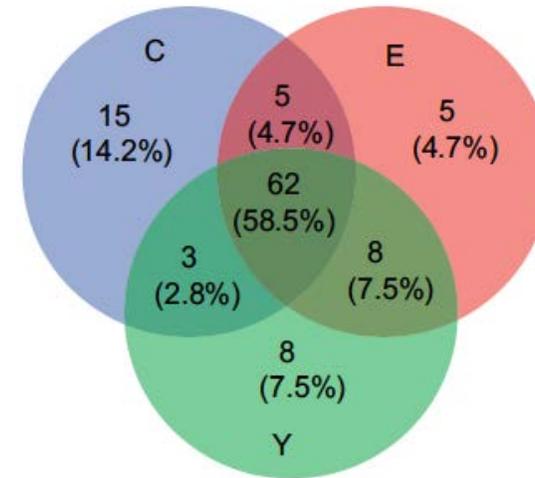
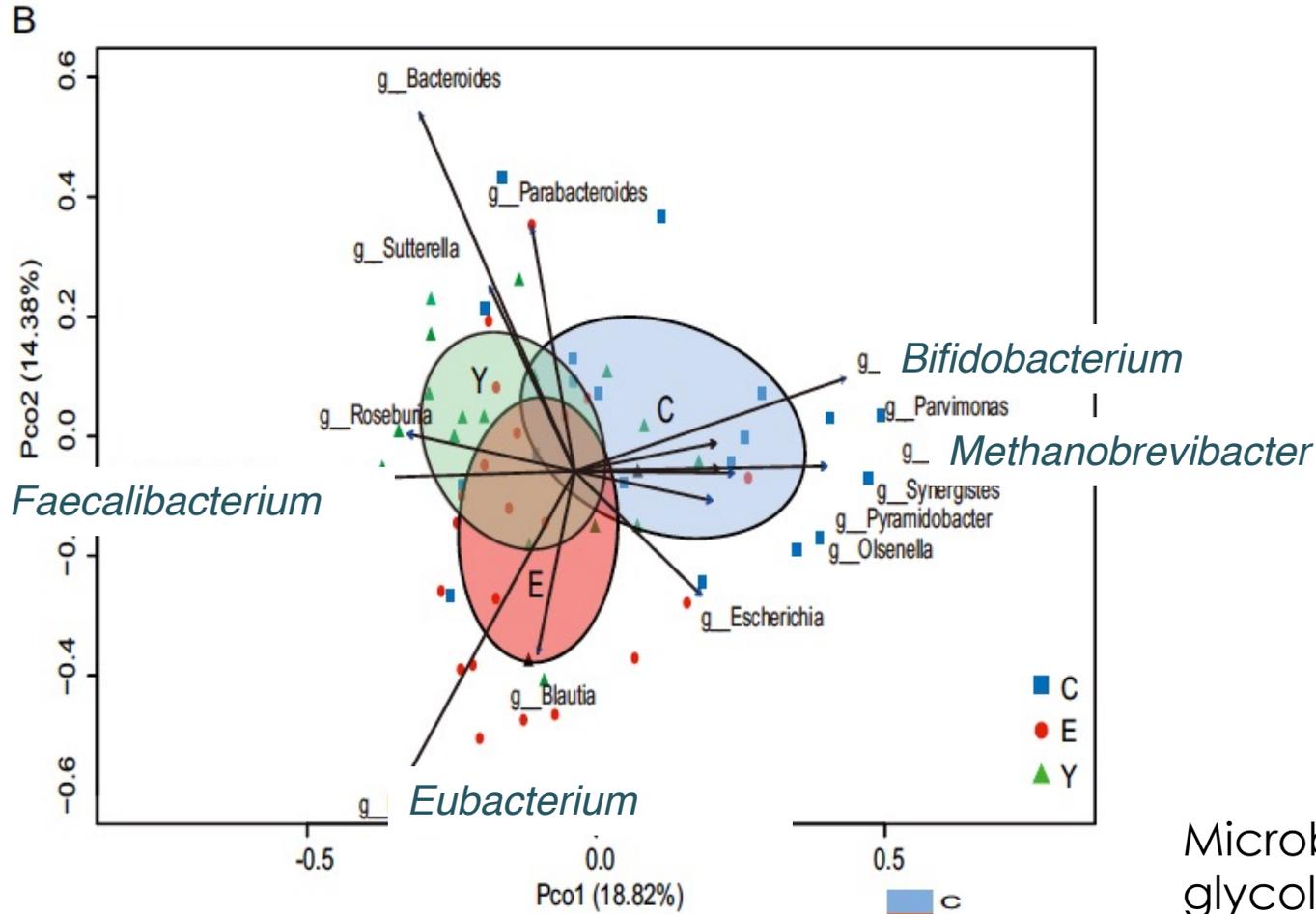
Claesson et al, PNAS USA, 2011

Individual age-related changes and the gut microbiome



Sardinian Centenarians

Depletion of *Faecalibacterium prausnitzii* and *Eubacterium rectale* and enriched for *Methanobrevibacter smithii* and *Bifidobacterium adolescentis* in Sardinian Centenarians.

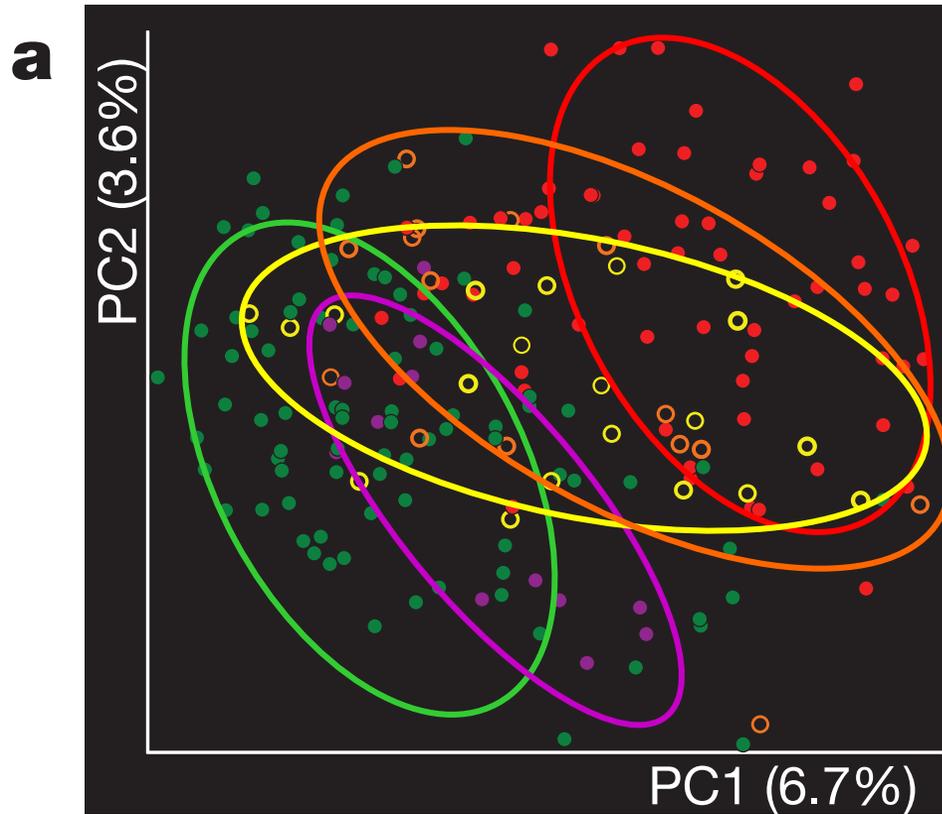


Microbiota in centenarians had high capacity for glycolysis and fermentation to SCFAs, although low in genes encoding enzymes involved in degradation of carbohydrates, including fibers and galactose.



Microbiota analysis separates elderly subjects based upon where they live in the community

Eldermet



Subject colour coding:

Green: community;

Yellow: day hospital;

Orange: rehabilitation;

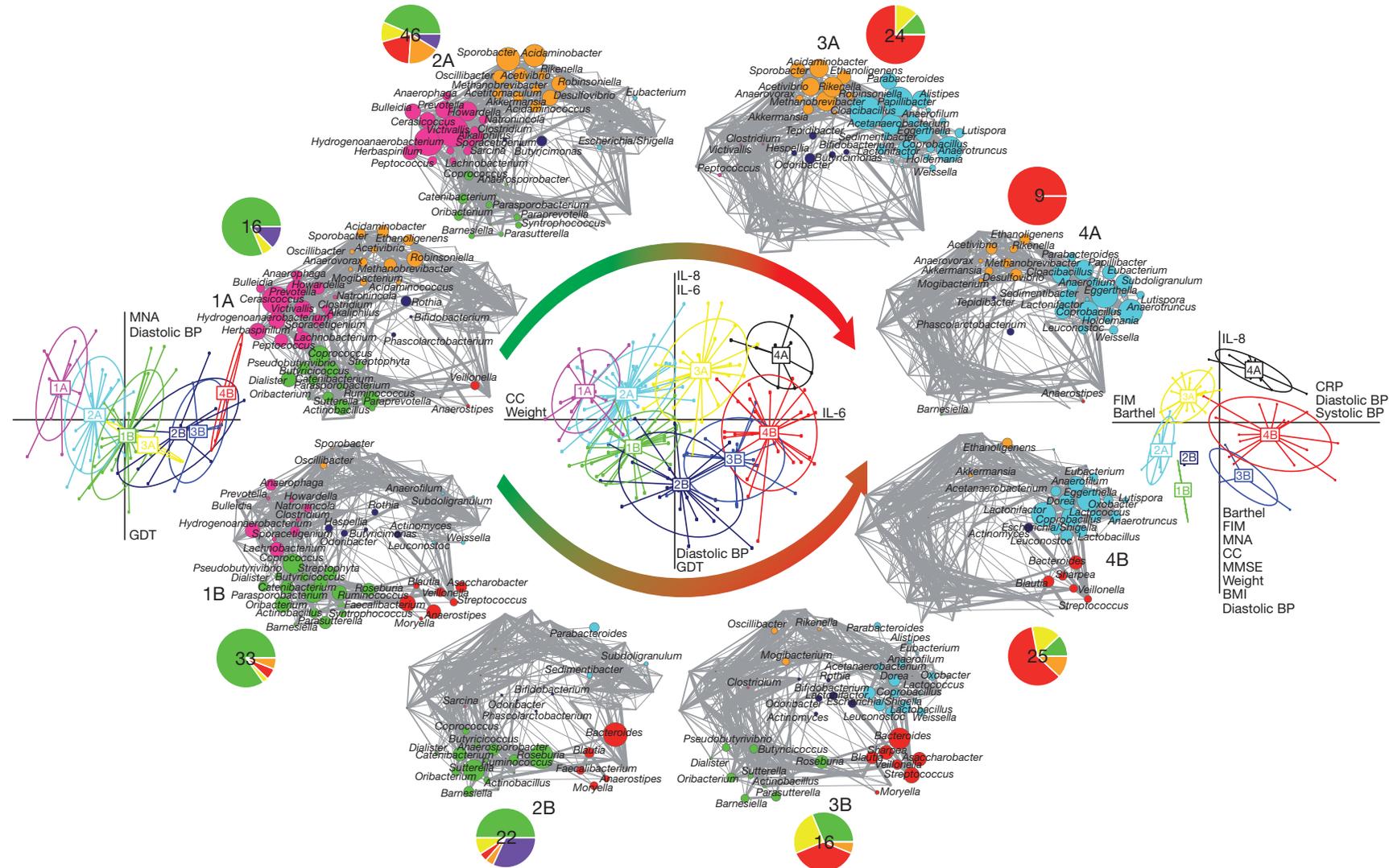
Red: long-stay;

Purple: young healthy controls

191 fecal samples
from elderly subjects

Loss of diversity in the core microbiota is
associated with increased frailty

Transition in microbiota composition across residence location is mirrored by changes in health indices.

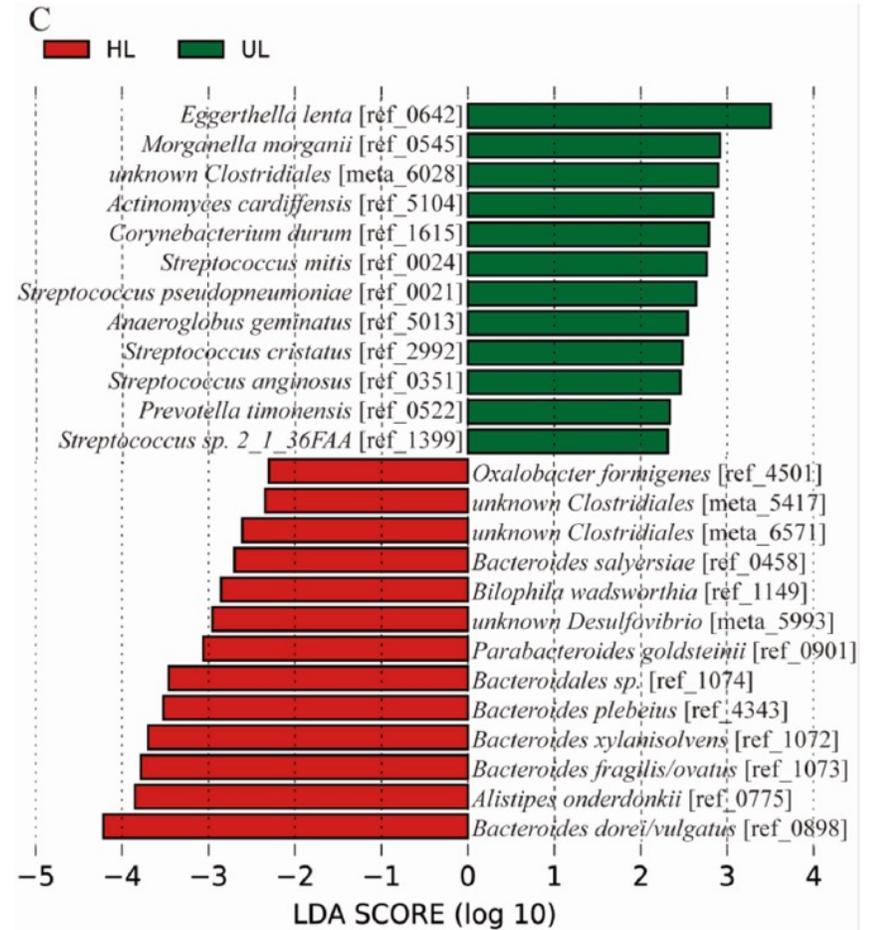
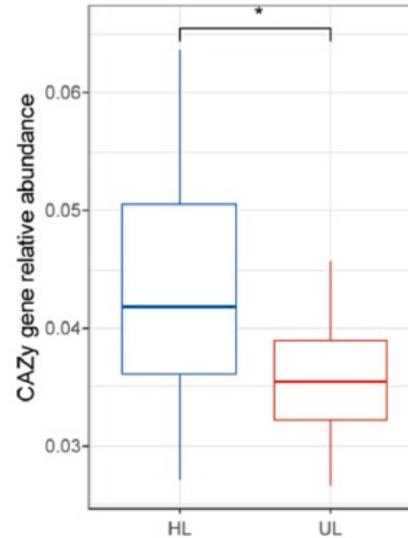
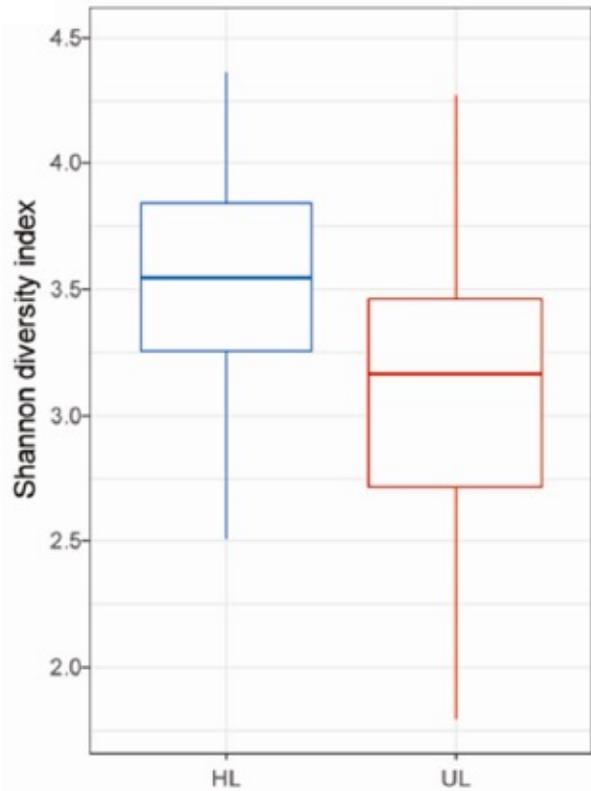


Difference in Microbiome between healthy and unhealthy ageing

> 90 y.o.

healthy long-living (n = 28)

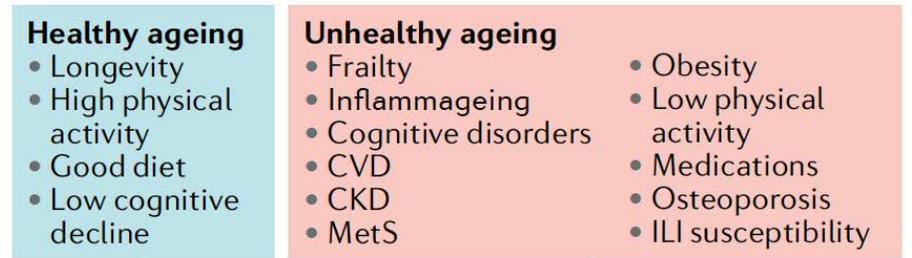
unhealthy long-living (n = 9)



Loss of diversity in unhealthy people

Increased Firmicutes & Actinobacteria and less Bacteroidetes in UnHealthy long-living

Individual age-related changes and the gut microbiome



Comparative analysis of microbiome profiles

Microbiome changes in unhealthy ageing (compared with healthy ageing)

Associated with healthy ageing

Associated with unhealthy ageing

Group 1

Group 3

Group 2

- *Eggerthella*
- *B. fragilis*
- *C. hathewayi*
- *C. bolteae*
- *C. clostridioforme*
- *C. cindens*
- *Ruminococcus torques*
- *R. gnavus*
- *Coprobacillus*
- *Streptococcus*
- *C. difficile*
- *Bilophila*
- *Actinomyces*
- *Desulfovibrio*
- *Campylobacter*
- *Atopobiaceae*
- *Veillonella*
- *Enterococcus*
- *Enterobacteriaceae*

Group 1

- *Faecalibacterium*
- *Roseburia*
- *Coprococcus*
- *Eubacterium rectale*
- *Bifidobacterium*
- *Prevotella*

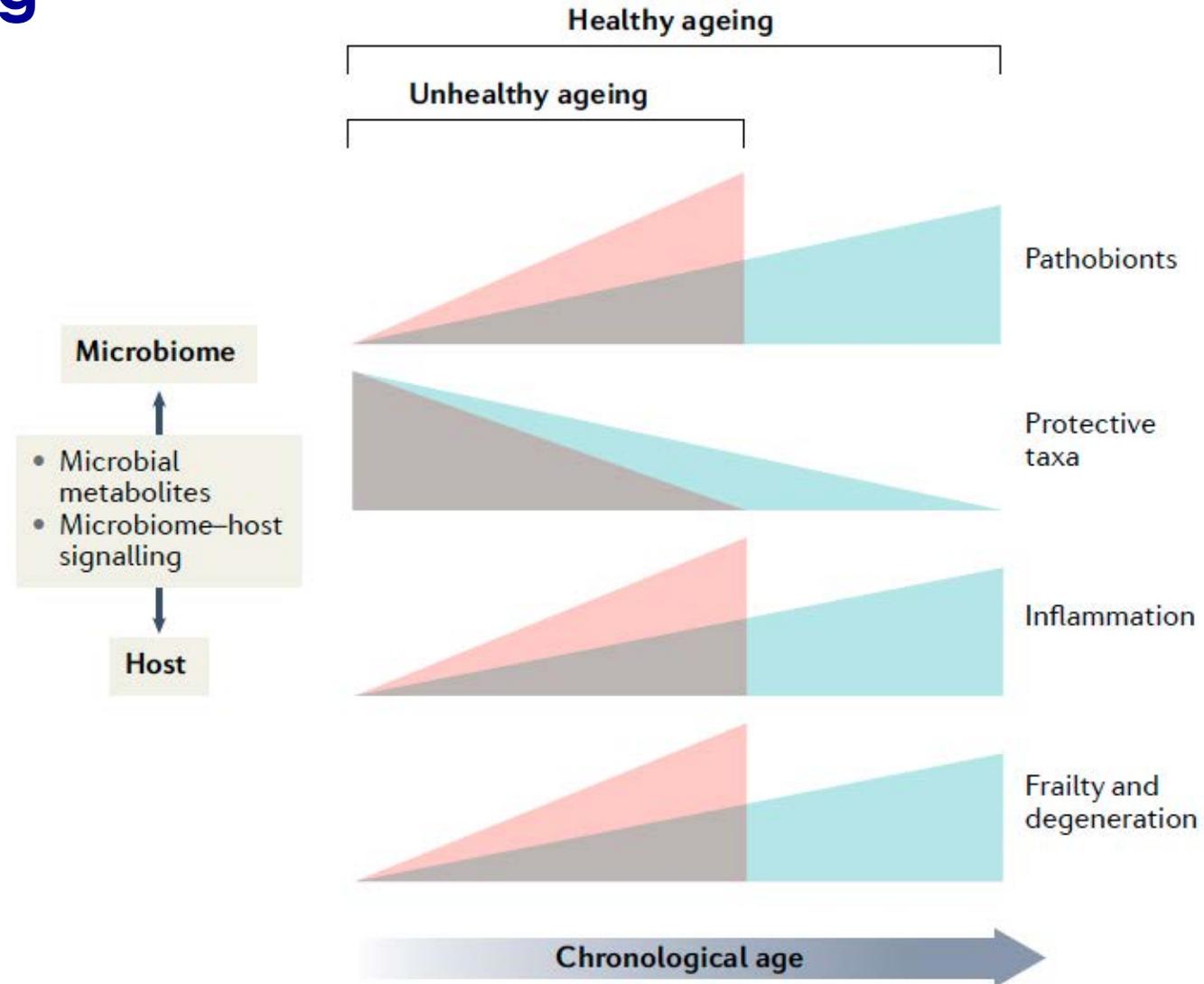
Group 3

- *Akkermansia*
- *Christensenellaceae*
- *Odoribacter*
- *Butyricimonas*
- *Butyrivibrio*
- *Barnesiella*
- *Oscillospira*

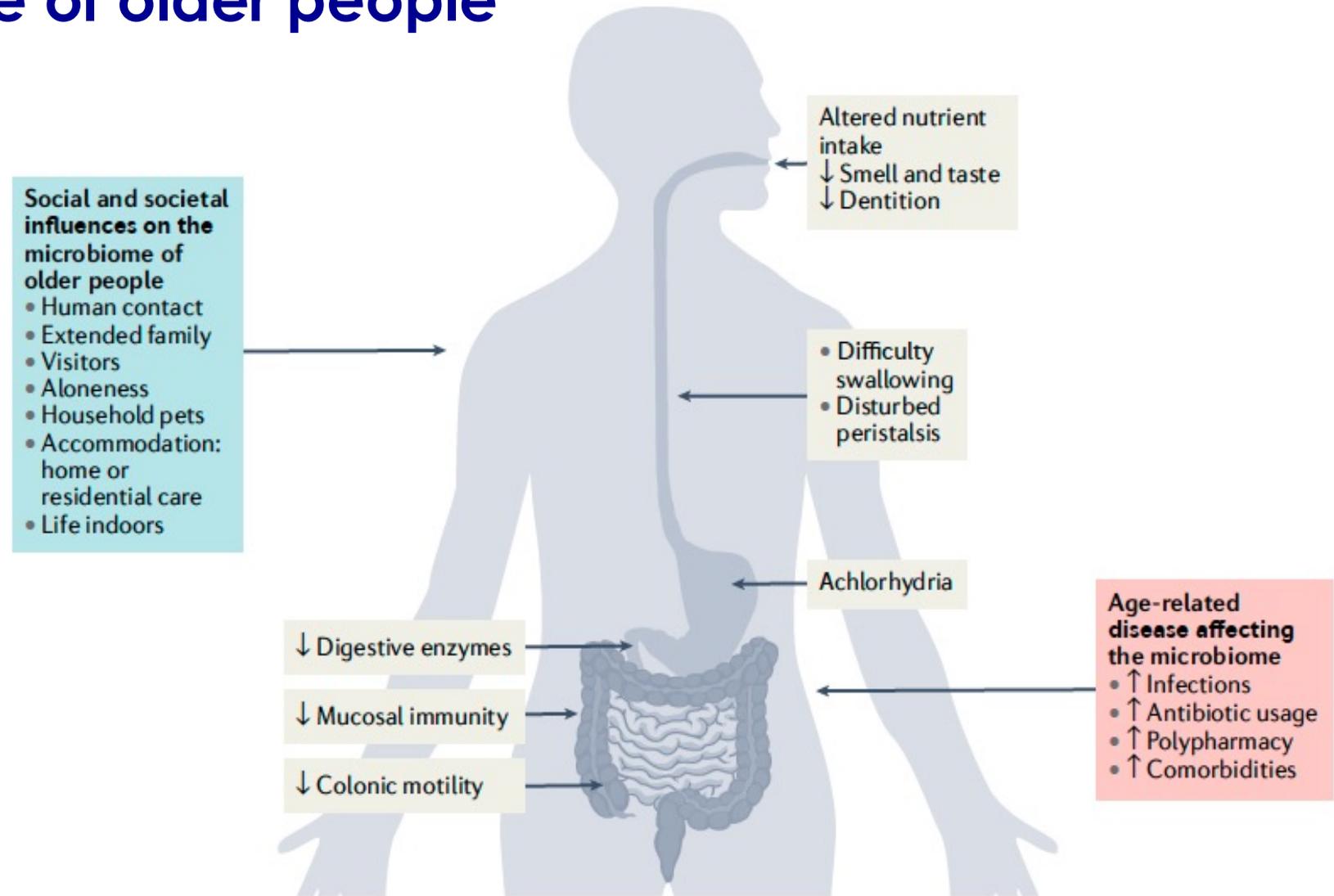


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Microorganism–host signalling as a contributor to healthy or unhealthy ageing



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

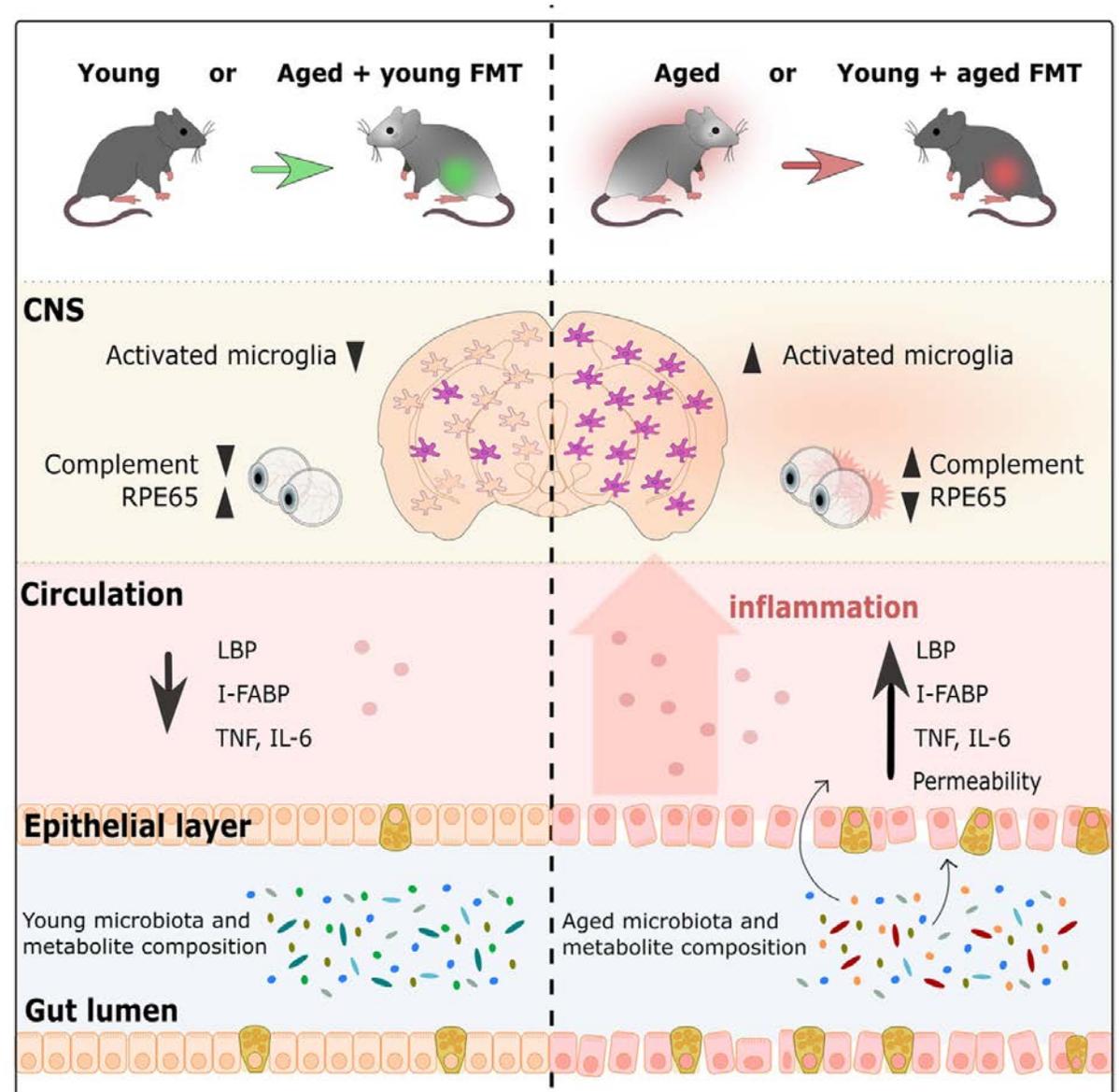
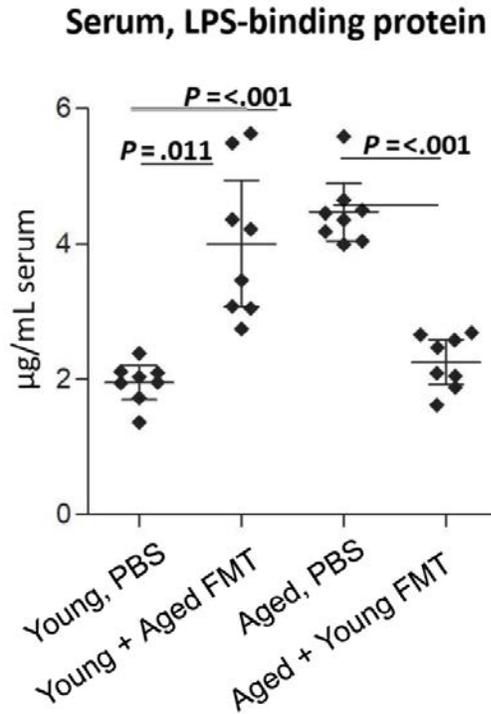


Metabolites associated with major microbiome gain/loss groups and ageing- associated conditions

Taxon groups	Metabolites	Linked disorder	Association	Refs
Group 2 (unhealthy ageing-associated pathobionts)	Trimethylamine	Cardiovascular disorders	Putatively causative	175-177
		Cognitive disorders		178,179
		Inflammation, oxidative stress		180
		Osteoporosis		180
		Colorectal cancer		181
		Chronic kidney disease		182
	Para-cresol	Inflammation, oxidative stress		183
		Cognitive disorders		184
		Chronic kidney disease		182
	Deoxycholic acid and lithocholic acid	Cognitive disorders		185
		Colorectal cancer		186,187
	Lipopolysaccharide	Metabolic syndrome		188
Inflammation, oxidative stress				
DNA-damaging toxins	Colorectal cancer		71-73	
Group 1 and Group 3 (commensals associated with younger age groups and healthy ageing)	Butyrate	Cognitive disorders	Preventive	77,78
		Insulin resistance		75,79
		Obesity		189,190
		Inflammation, impaired barrier function		191
	Acetate	Insulin resistance		192



Fecal microbiota transfer reverses hallmarks of aging



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Le microbiote français
Le French Gut

Ensemble faisons
avancer la science
du microbiote



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metagenopolis
mgps.eu

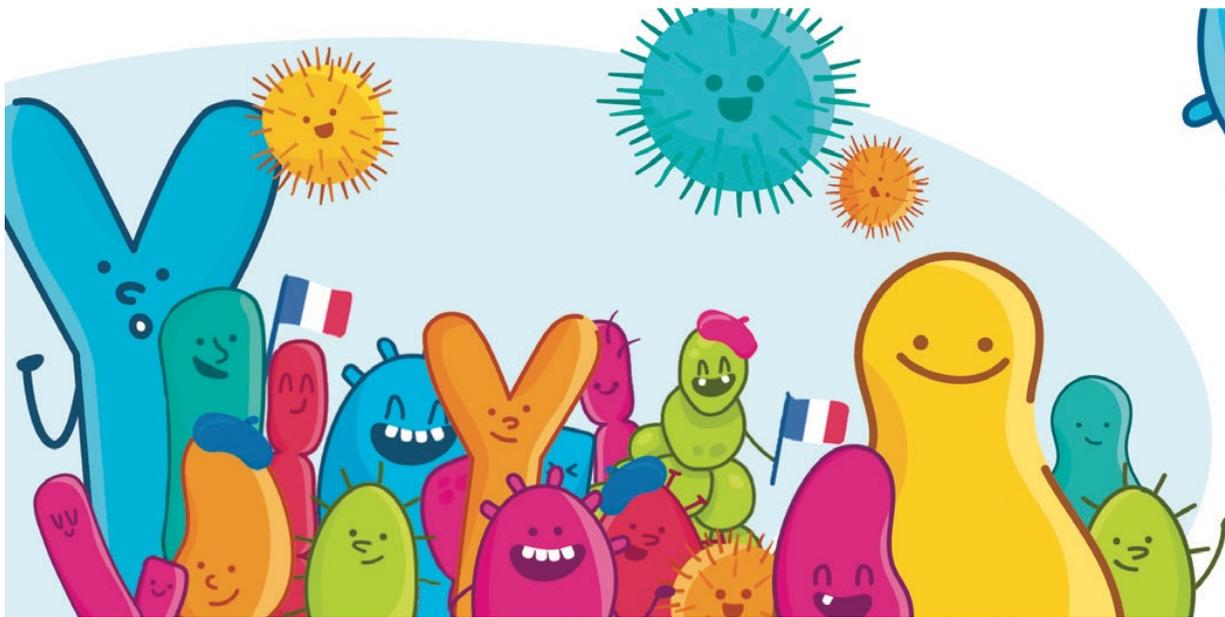
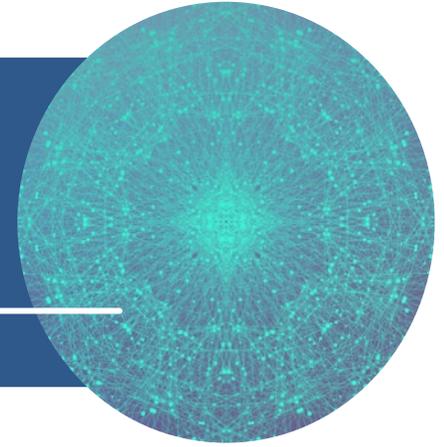


« Le » French Gut project

Part of the Million Microbiome of Humans Project (MMHP)

National citizen contribution to microbiome science with the ambition of defining the heterogeneity of healthy gut microbiomes within the French population, the environmental and lifestyle factors impacting them, as well as their deviations seen in chronic diseases

MGP participates to MMHP by bringing 100,000 French gut metagenomes



Le microbiote français
Le French Gut

UN PROJET
INRAE

metagenopolis
mgps.eu



INRAE

Le French Gut
(100,000 gut metagenomes)
INRAE is the project lead
Consortium INRAE with
public (APHP, INSERM) and private
institutions

