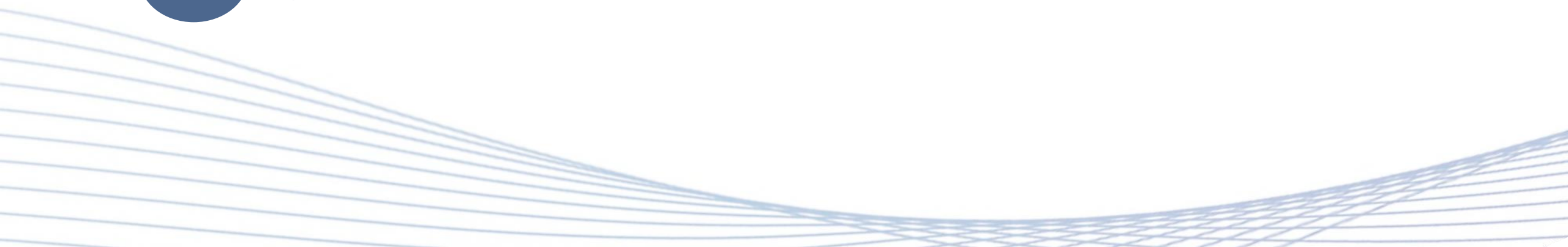# Impact of commonly used drugs on the composition and metabolic function of the gut microbiota

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Supervisor: Prof. Christopher K.C. LAI
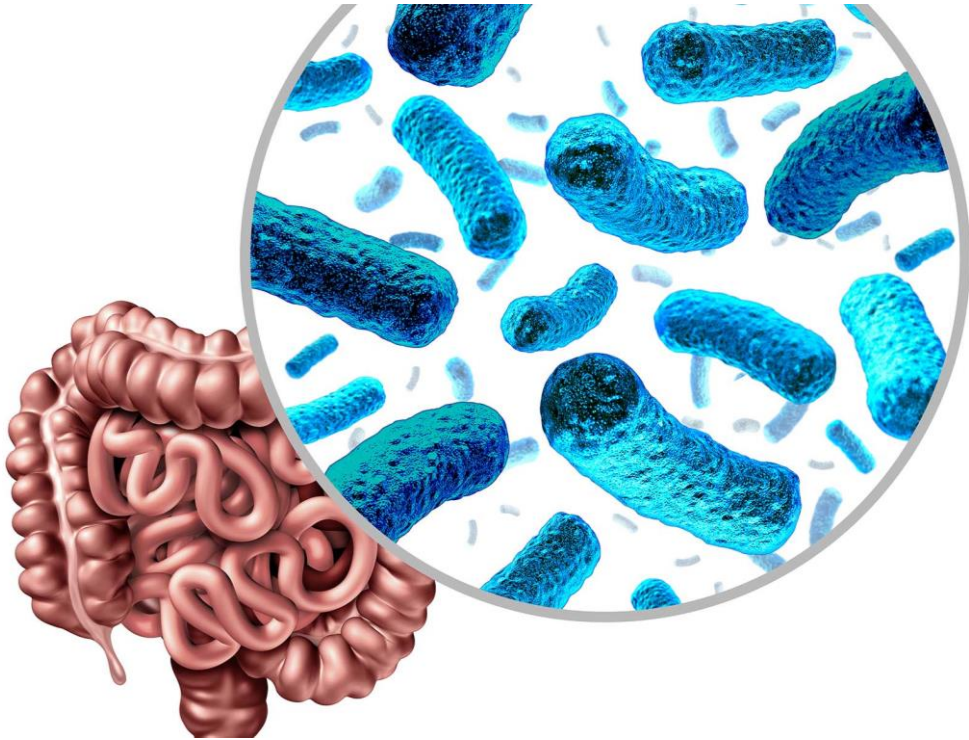
24 Nov 2023

Outline

Background

Introduction to gut microbiota

Gut microbiota:
- refers to the complex community of microorganisms that reside in the gastrointestinal tract, particularly the colon (large intestine)
- **10** times more abundant than somatic cells and germ line cells of our body
- Microbiome is **150** times bigger than human genome
- "a metabolic organ"

Diseases associated with the changes in the gut microbiota:
- Obesity
- Diabetes
- Liver diseases
- Neurodegenerative diseases

Atanu Adak, *et al*. Cellular and Molecular Life Sciences. 2019

Role of gut microbiota in diseases

Gut microbiota metabolizes the diet ingested by the host into a series of metabolites:

- short chain fatty acids
- secondary bile acids
- branched-chain amino acids
- Trimethylamine-N-oxide
- ......

Patrice D Cani. Gut. 2018
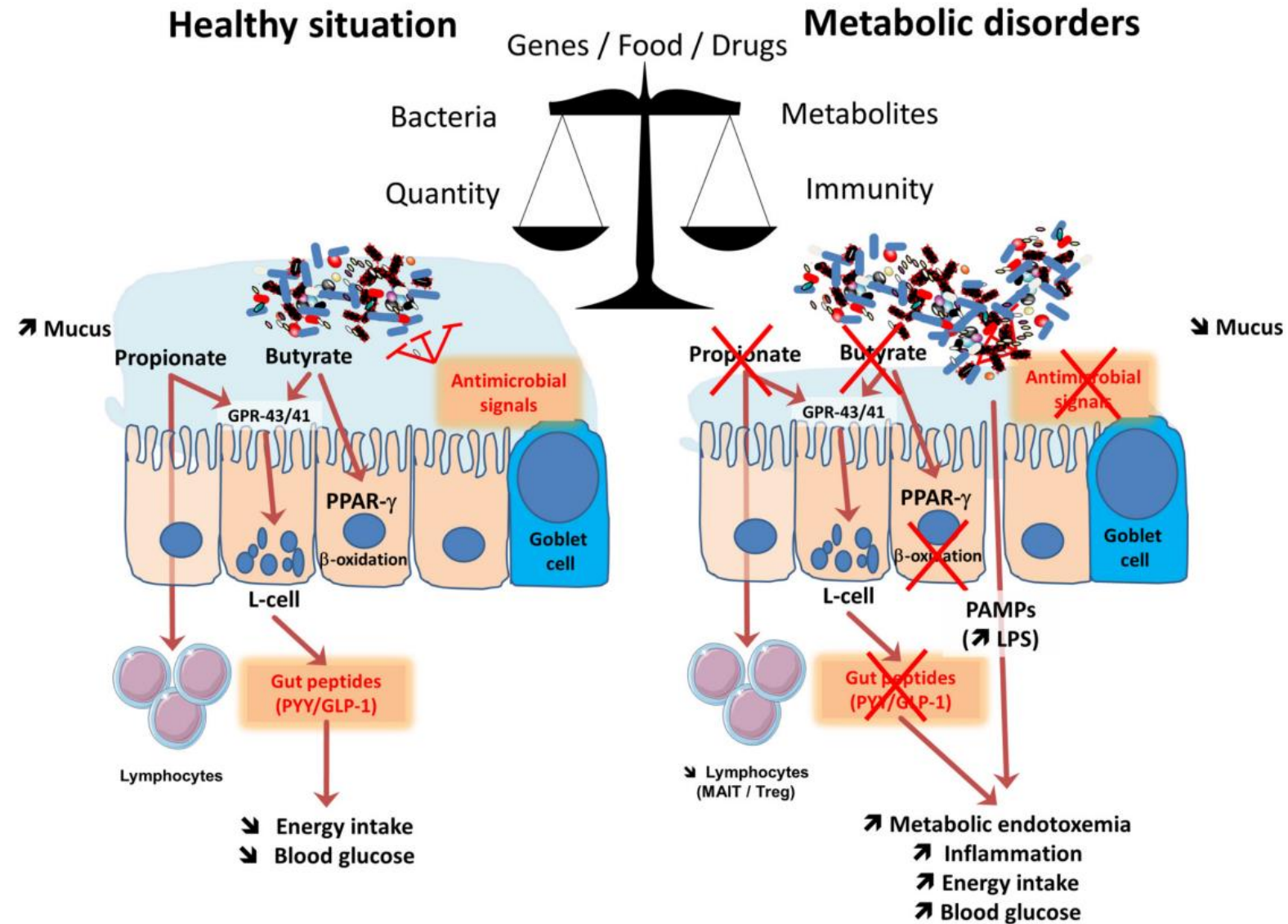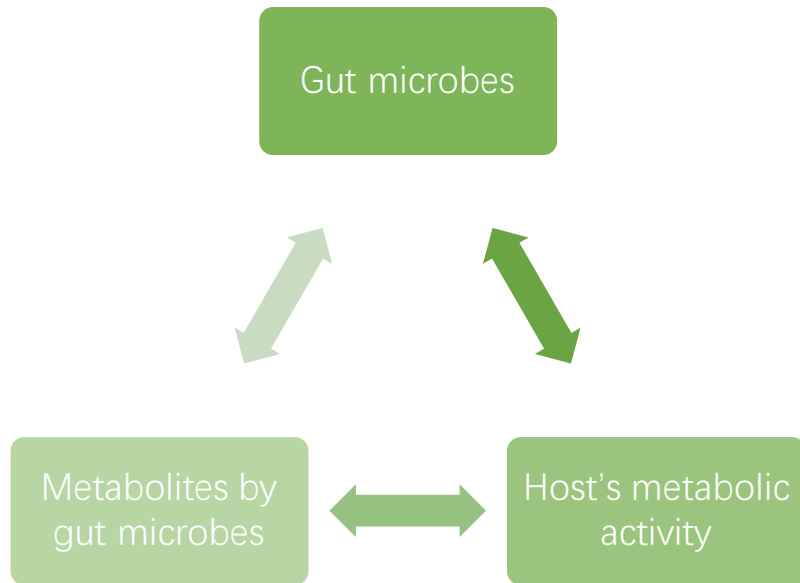
Role of gut microbiota in diseases

Intrinsic and extrinsic factors influencing gut microbiota

Only a minority of gut microbes are shared across the majority of individuals

- In a European data set of **3000** samples, only **17** bacteria were identified as a core microbiome present in **>95%** of all samples.
- Of the **639** species identified in a population study of **1135** Dutch individuals, **469 (73%)** were present in fewer than **10** individuals.

a Intrinsic factors

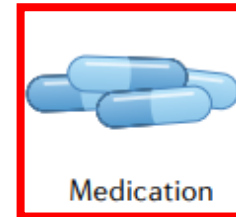Host gastrointestinal physiology   Sex   Age   Host genetics

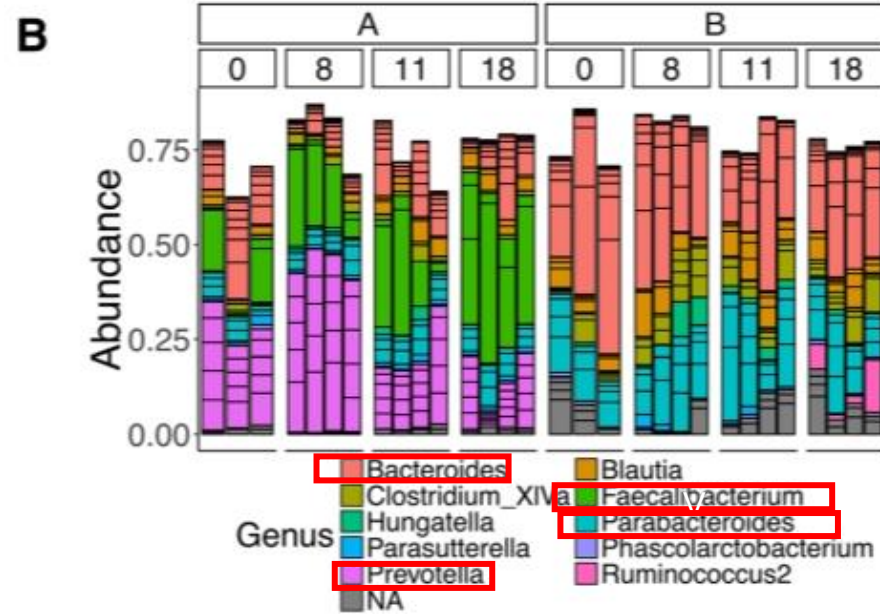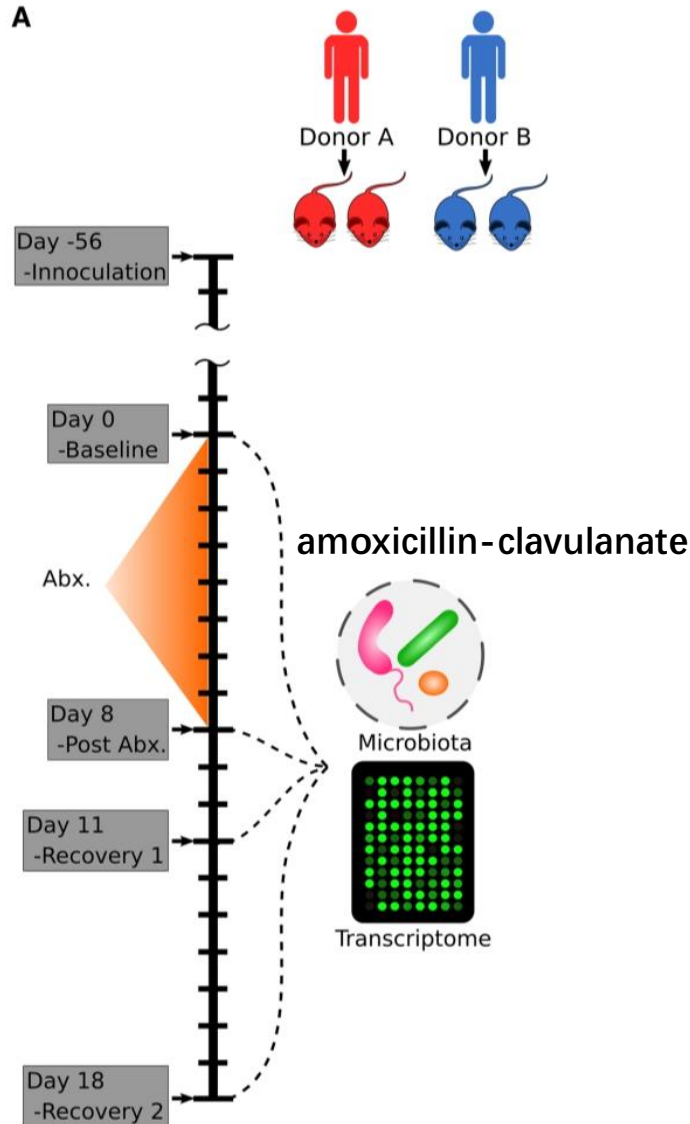**b Extrinsic factors**

Alcohol intake   Medication   Diet   Environmental factors

Lindell AE, *et al*. Nat Rev Microbiol. 2022

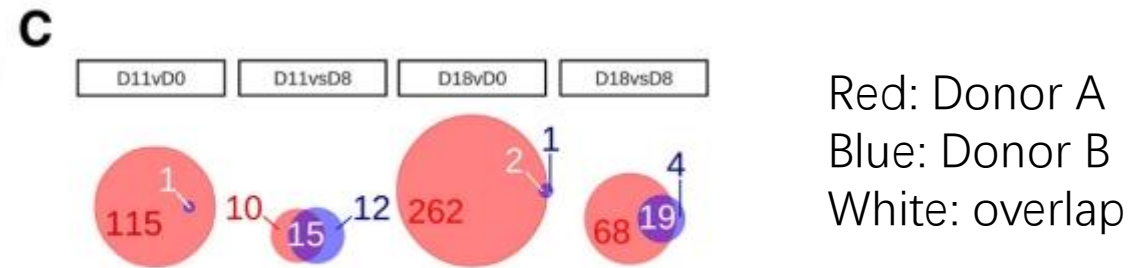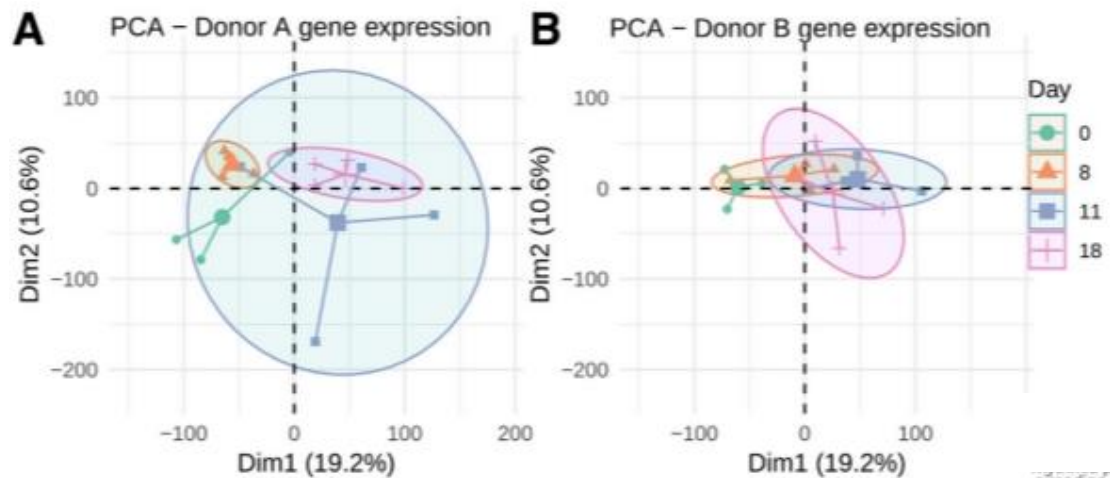# Commonly used drugs influencing gut microbiota

1. Antibiotics

amoxicillin-clavulanate

- **Donor A** mice demonstrated an **increase** in *Prevotella* sequences from **D0** (mean 27.4% (SD 5.9%)) to **D8** (mean 44.9% (SD 3.7%)) with a significant **reduction** in this genus by late recovery (mean 13.9% (SD 7.7%))
- There is an **increase** in *Faecalibacterium* at these time points (**D0**—mean 13.1% (SD 10.5%), **D8**—mean 21.3% (SD 5%), **D11** (day 11)—mean 23.6% (SD 13%), **D18** (day 18)—mean 38.5% (SD 7.4%);

- *Bacteroides* **decreased** throughout the study in the **donor B** group, although this did not reach significance at any time point (D0—49.3% (SD 17.5%), D8—40.9% (SD 9.7%), D11—31.9% (SD 12%), D18—32.2% (SD 4%))
- *Parabacteroides* remained largely **stable** throughout the study.

Lavelle *et al*. Microbiome. 2019

Commonly used drugs influencing gut microbiota

1. Antibiotics

A PCA – Donor A gene expression

B PCA – Donor B gene expression

Day
- 0
- 8
- 11
- 18

C

| D11vD0 | D11vsD8 | D18vD0 | D18vsD8 |

Red: Donor A
Blue: Donor B
White: overlap

- **More significantly differentially expressed genes were detected in donor A**

- **There was an overlap in the genes that were both differentially expressed by A and B**

Lavelle *et al*. Microbiome. 2019

Commonly used drugs influencing gut microbiota

1. Antibiotics

- Gene ontology (GO) analysis reveals marked covariance between the microbiota and GO pathways in donor A mice but not in donor B mice

- **Inter-individual variation in the gut microbiota induced by antibiotic may contribute to personalized host responses following microbiota perturbation**

Lavelle *et al*. Microbiome. 2019
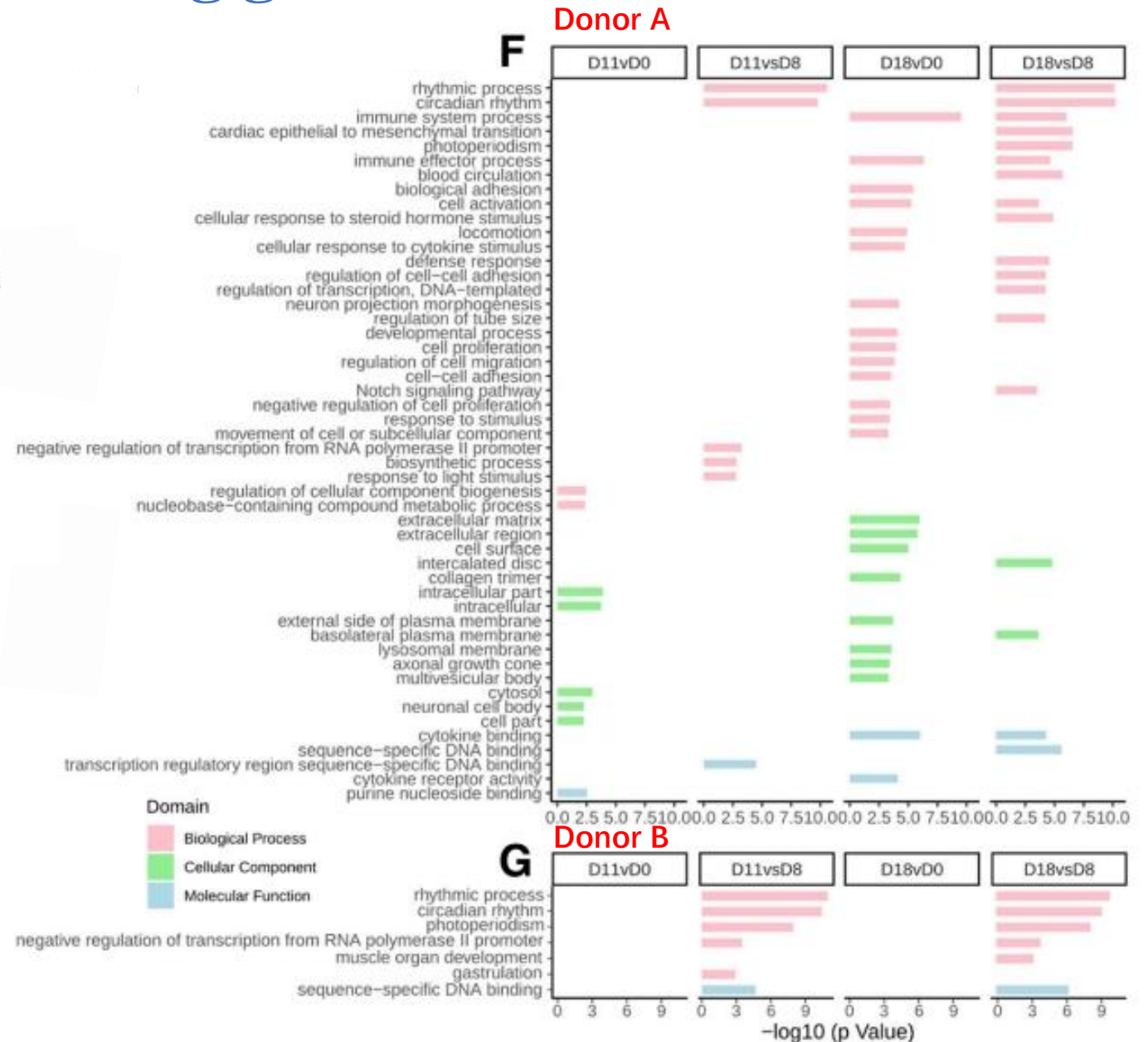
Commonly used drugs influencing gut microbiota

2. Proton pump inhibitors (PPI)

Commonly used PPIs:
- Pantoprazole
- Omeprazole
- Esomeprazole
- ......

Indications of PPIs:
- Peptic ulcers
- Gastro-esophageal reflux
- Dyspepsia
- Gastroduodenal disorders and bleeding caused by NSAIDs

Being associated with an increased risk of enteric infections (C. *difficile*, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp)

Floris Imhann, *et al*. Gut. 2016

Commonly used drugs influencing gut microbiota

2. Proton pump inhibitors

**3 independent cohorts comprising 1815 fecal samples** → **16S rRNA gene analysis** → **Heat map** →

- Cohort 1: general population
- Cohort 2: patients with IBD
- Cohort 3: IBS case-control cohort

some increased bacteria in PPI users are typically found in the oral microbiome ← There are 92 (up to 20%) significantly **increased** or **decreased** bacterial taxa in the gut microbiome of PPI users compared with non-users (FDR<0.05) ←

- *Rothia dentocariosa*
- *Rothia mucilaginosa*
- The genera *Scardovia* and *Actinomyces*
- the family *Micrococcaceae*

Floris Imhann, *et al*. Gut. 2016
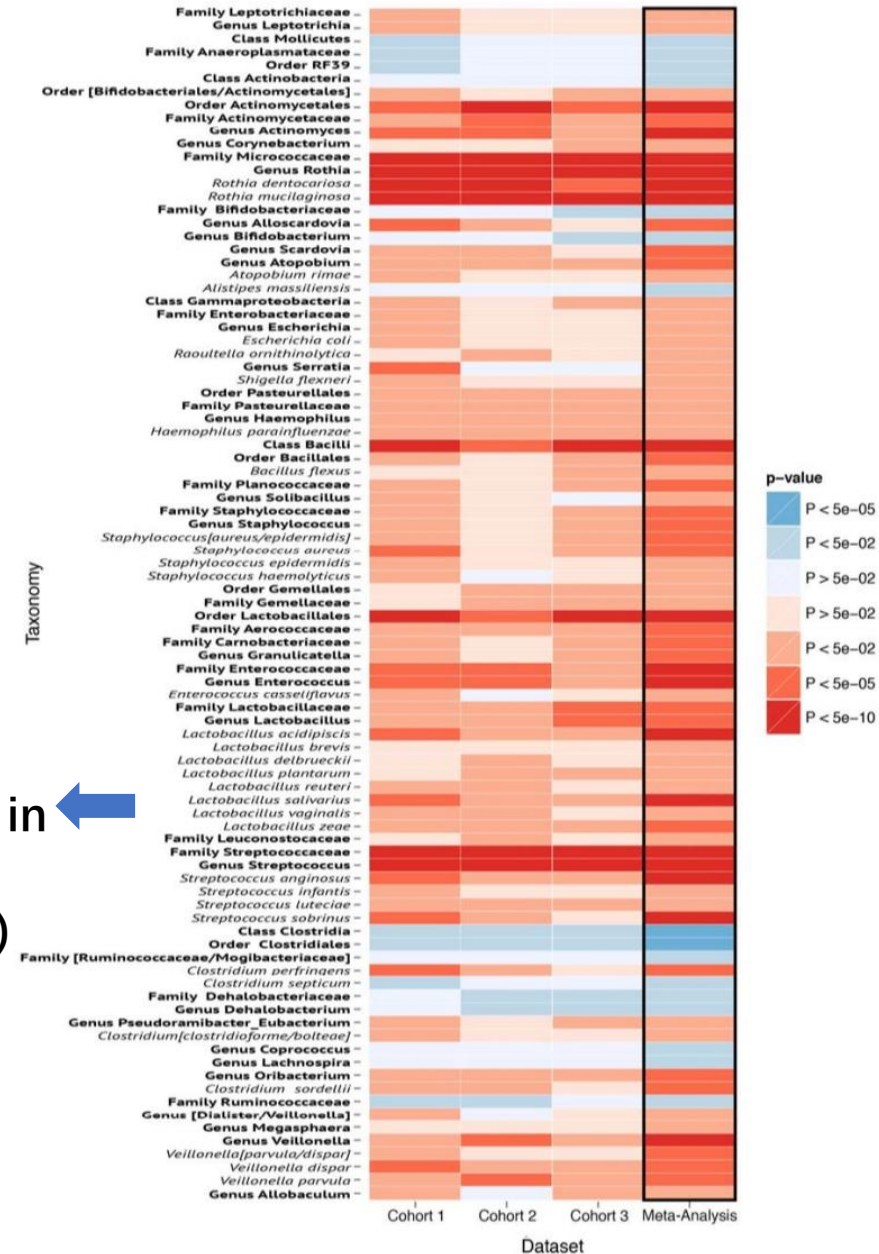
2. Proton pump inhibitors

Gut microbiome of PPI users shifts towards the oral microbiome in the first coordinate
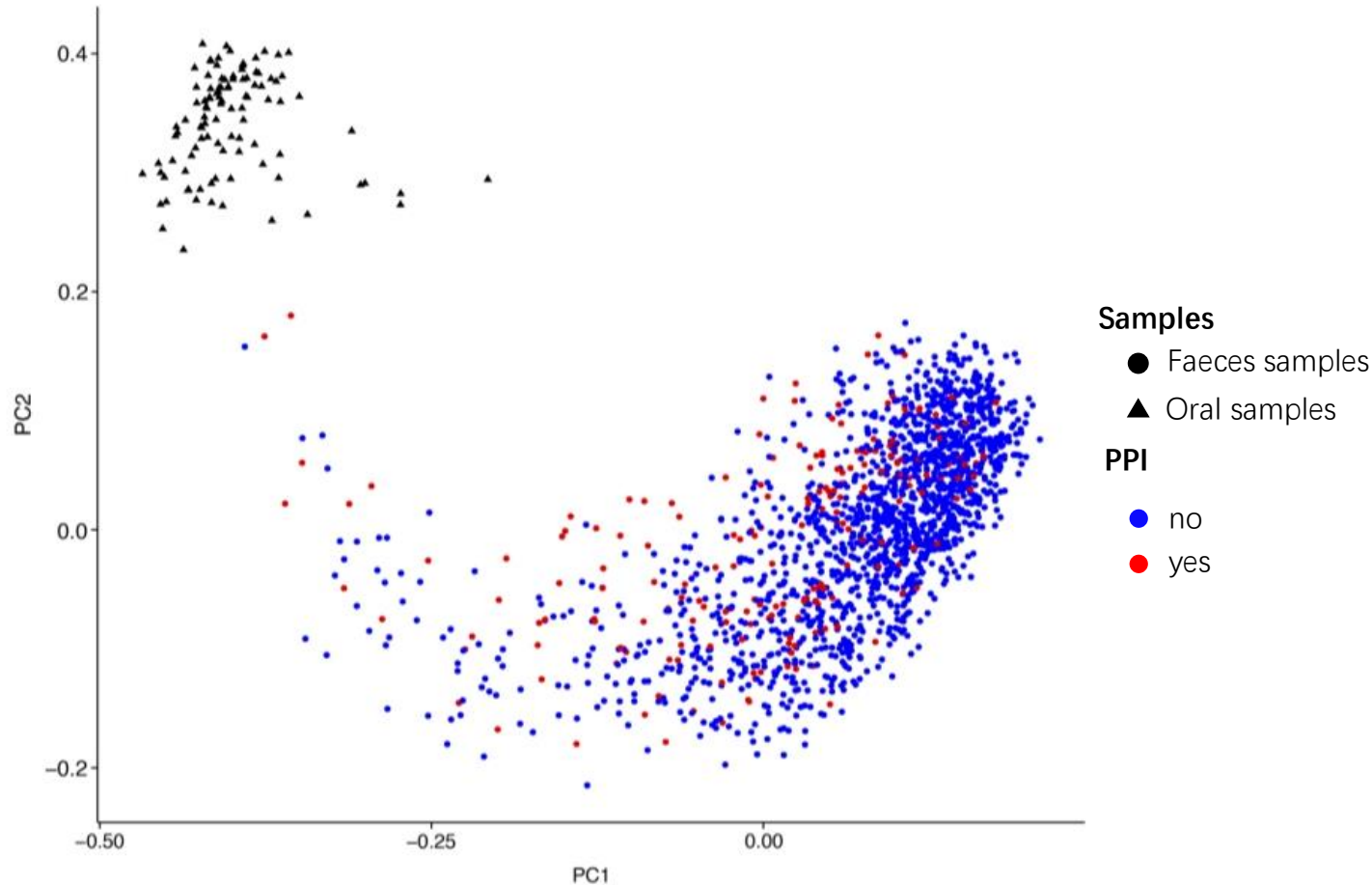

Figure. 1. Principal coordinate analysis of 1815 gut microbiome samples and 116 oral microbiome samples

PPI use

⬇

Reduced acidity of the stomach

⬇

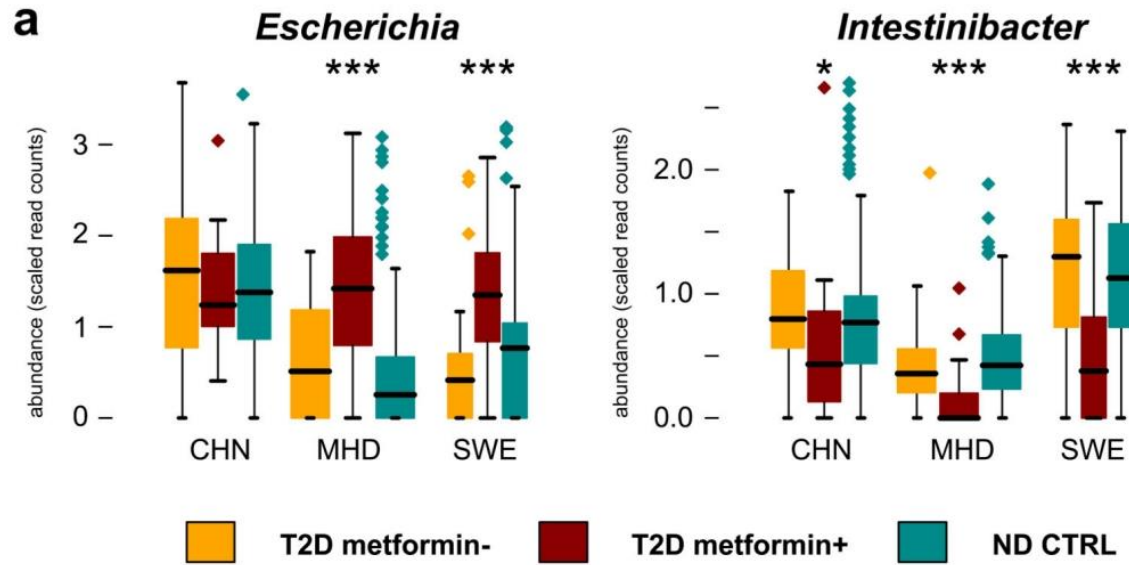Subsequent survival of more bacteria that are ingested with food and oral mucus

⬇

increased risk of enteric infections

Floris Imhann, *et al*. Gut. 2016

3. Metformin

Gut microbial shifts under metformin treatment

- CHN: Chinese cohort
- MHD: cohort from MetaHIT project in Denmark
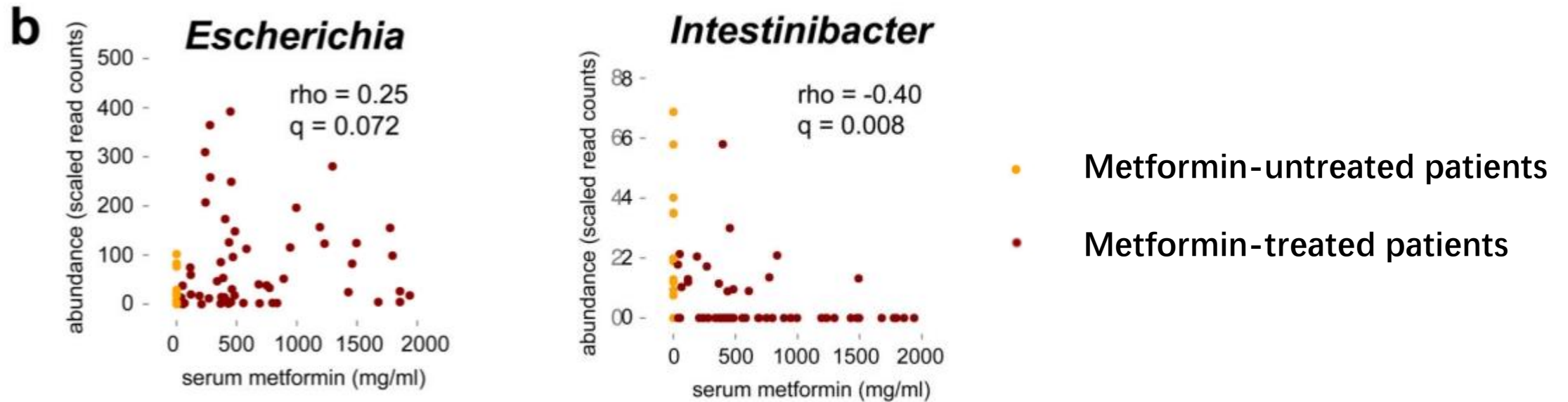- SWE: Swedish cohort

Indirect metformin treatment effects
- reduced intestinal lipid absorption
- lipopolysaccharide (LPS)-triggered local inflammation

The increase of E.coli may contribute to side effects such as diarrhea

Messori S, *et al*. Vet. Microbiol. 2013

Kristoffer Forslund, *et al*. Nature. 2015

3. Metformin

Gut microbial shifts under metformin treatment

b

Escherichia

rho = 0.25
q = 0.072

abundance (scaled read counts)

500 —
400 —
300 —
200 —
100 —
0 —

0   500 1000 1500 2000

serum metformin (mg/ml)

Intestinibacter

rho = -0.40
q = 0.008

abundance (scaled read counts)

88 —
66 —
44 —
22 —
00 —

0   500 1000 1500 2000

serum metformin (mg/ml)

• Metformin-untreated patients
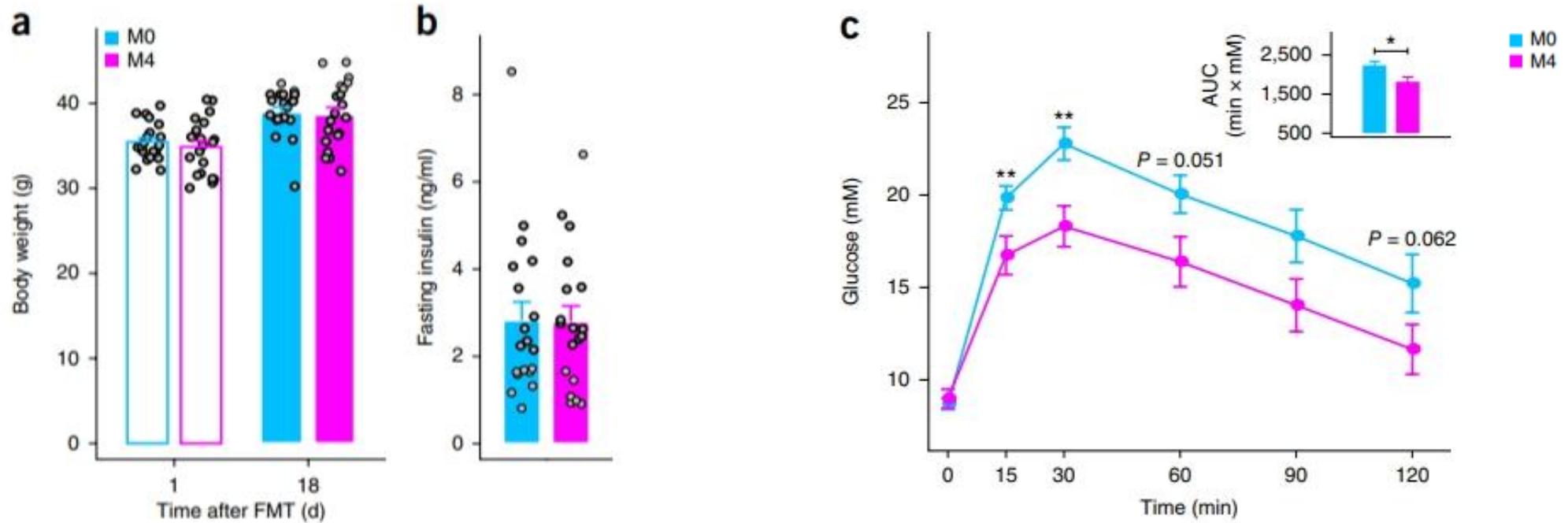
• Metformin-treated patients

The level of serum metformin is positively correlated with the abundance of *E. coli*, and in negative correlation with the abundance of *Intestinibacter*

Kristoffer Forslund, *et al*. Nature. 2015

3. Metformin

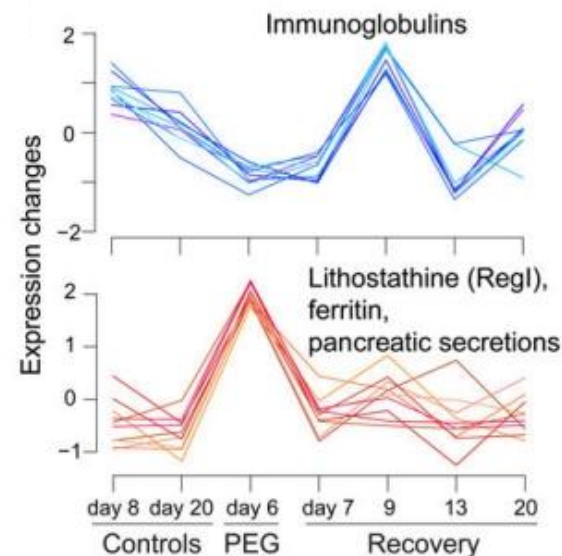Metformin-altered microbiota improves glucose tolerance
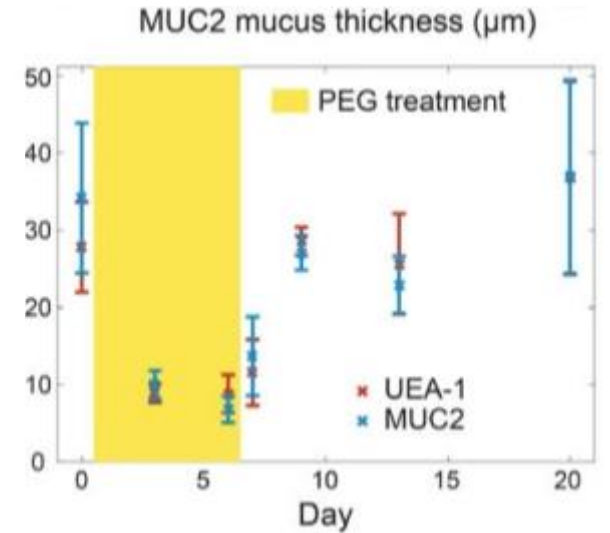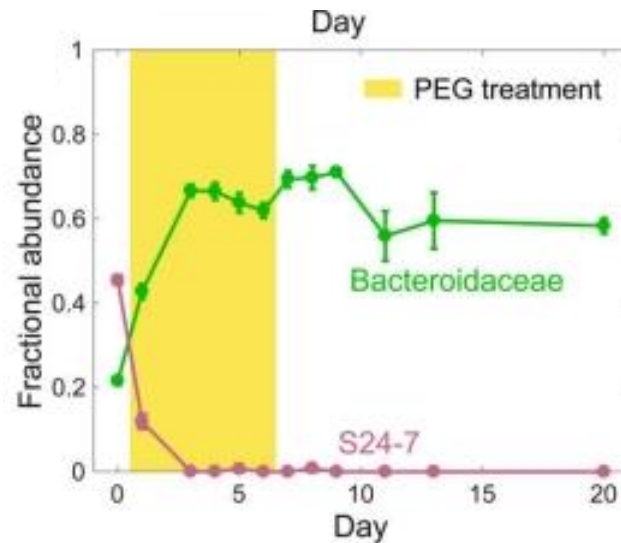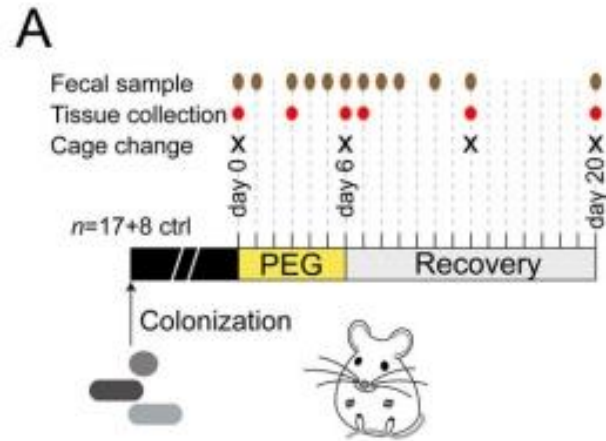

M0: before metformin treatment
M4: 4 months after metformin treatment

Commonly used drugs influencing gut microbiota

4. Laxatives

Mild and transient diarrhea induced by laxatives leads to long-term changes in the gut microbiome of mice

Carolina Tropini, *et al*. Cell. 2018
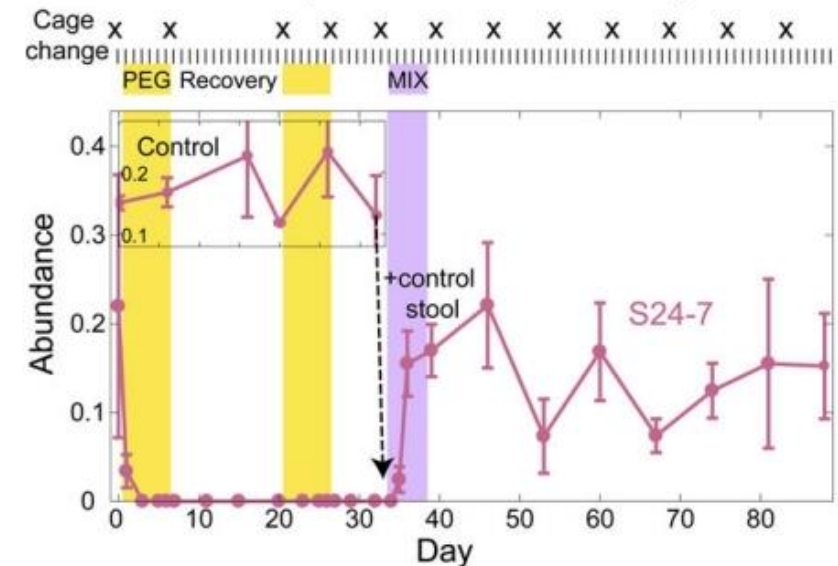
4. Other commonly used non-antibiotic drugs

Other commonly used non-antibiotic drugs:

- Statins
- Opioids
- Antidepressants
- ……

Factors should be taken into account:

- Intestinal transit time
- Stool consistency
- Bacterial quantities (e.g. microbial load per sample)
- ……

Conclusion

Studying commonly used drugs' impact on gut microbiota will:

- Better understand bi-directional interactions between drugs and microbiota

- Help explain part of the drug's therapeutic function, as well as some of its side effects

- Emphasize the need to rigorously control for confounders like drug use when performing microbiome studies looking at specific diseases or conditions

Reference

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