

# Exploring drug-microbiota interactions in the era of metagenomics

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university of  
groningen

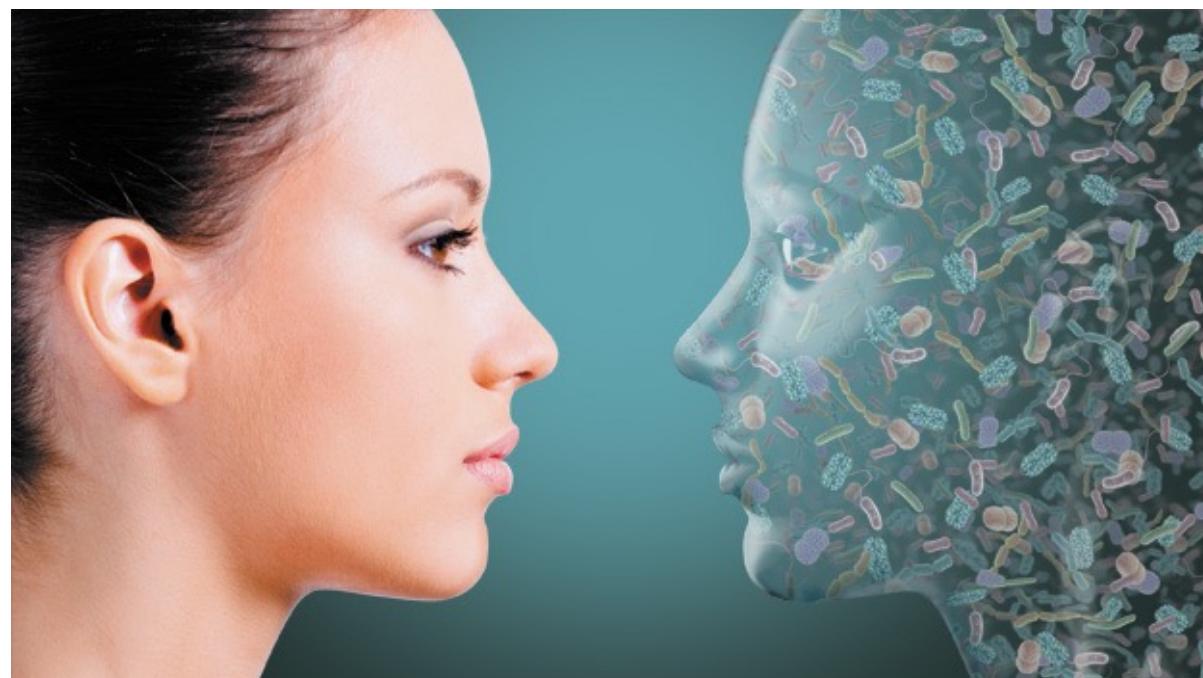


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# Microbiome: our second genome

From pharmacogenetics to *pharmacomicobiomics*?

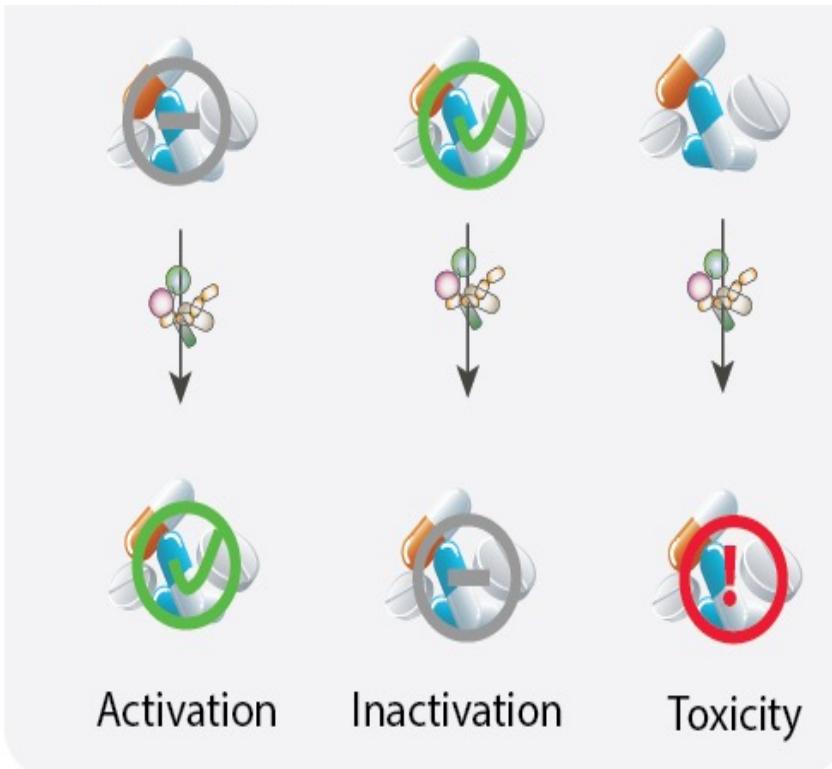
Microbiome can be modulated: improve drug efficacy?



# Pharmacomicobiomics: a bi-directional relation

The drug-microbiota relation is complex and bi-directional

Scenario 1: Microbiota impacts drug efficacy and safety

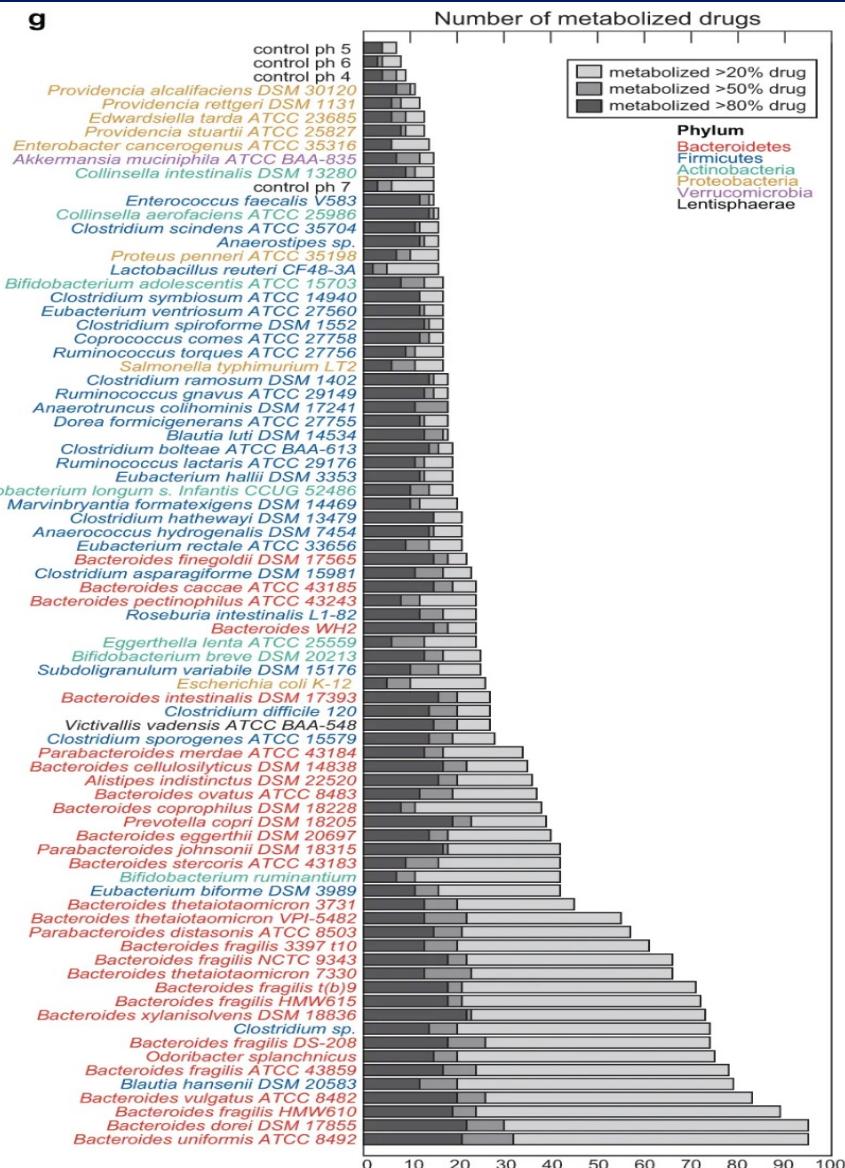


Doestzada et  
al. 2018  
*Protein cell*

# Scenario 2: gut microbes metabolize drugs

271 oral administrated drugs vs 76 gut bacterial strains

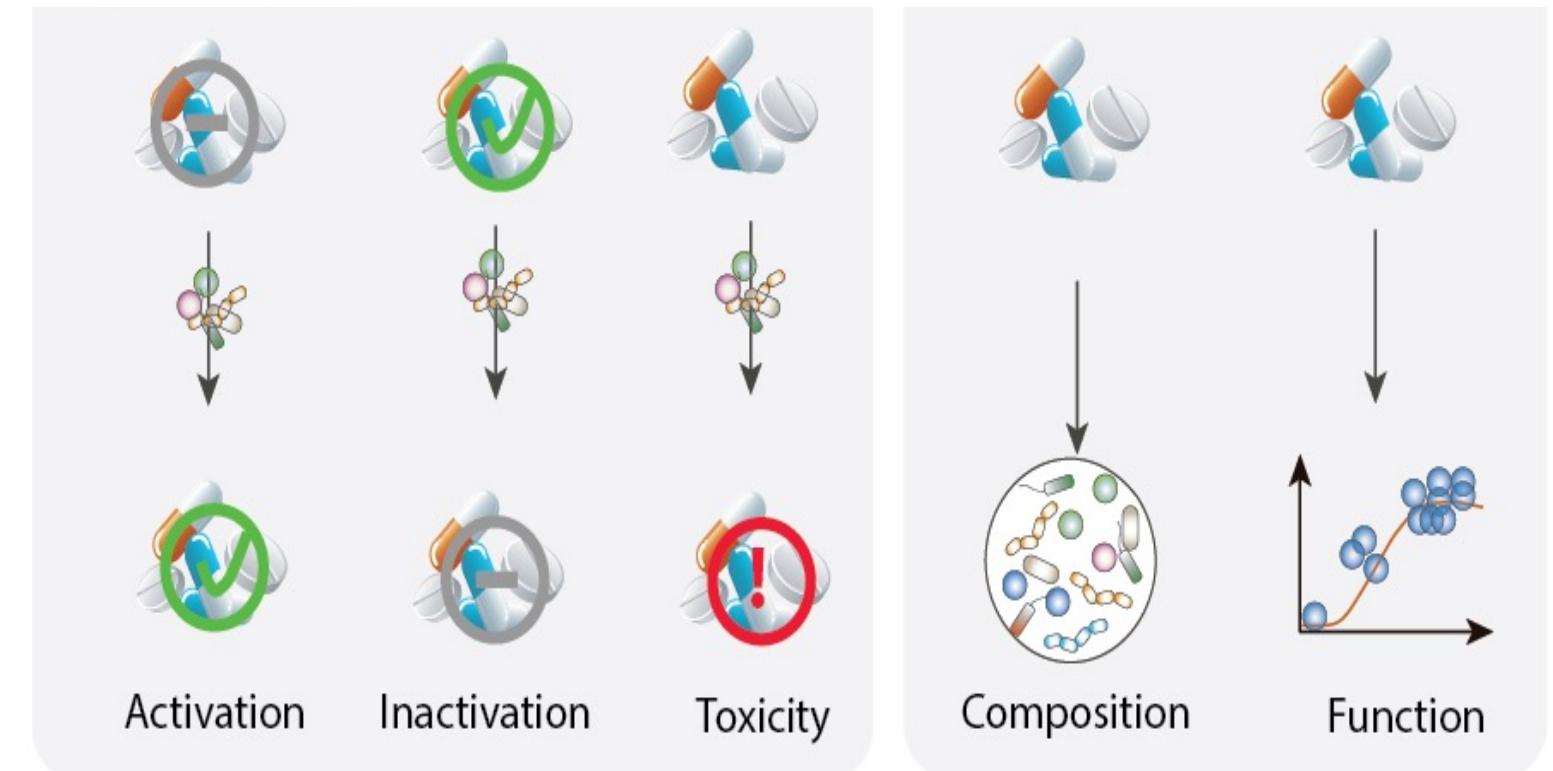
2/3 of drugs could be metabolized by at >1 bacterial strain



# Pharmacomicobiomics: a bi-directional relation

The drug-microbiota relation is complex and bi-directional

Scenario 2: impact of drugs on the gut microbiota



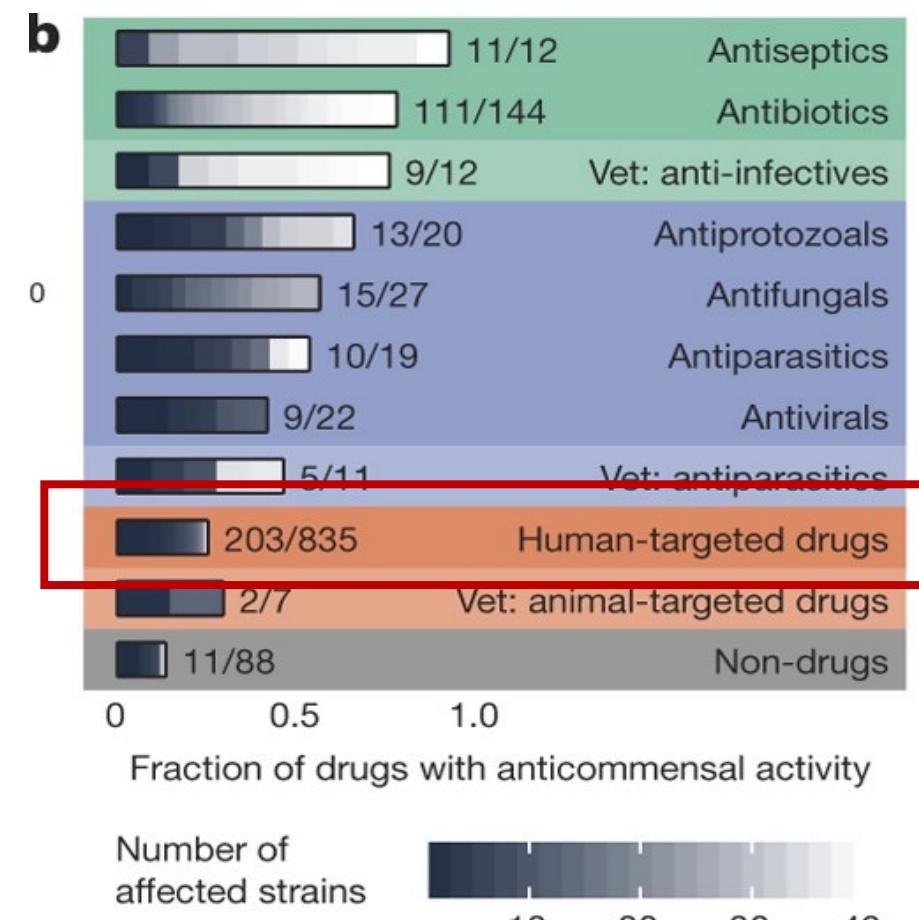
Doestzada et  
al. 2018  
*Protein cell*

# Scenario 1: Anti-commensal effect of non-antibiotic drugs

**Non-antibiotic drugs can impact bacterial grow**

**>1000 drugs vs 40 gut bacterial strains**

**24% of drugs with human targets inhibited the growth of at least 1 bacterial strain**

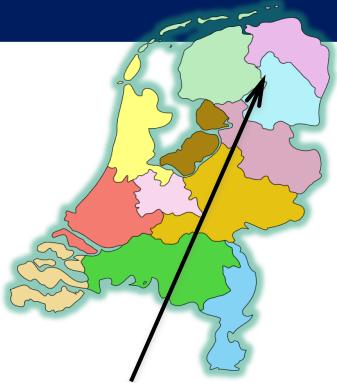


# **Microbiome-drug associations in population cohorts**

**Microbiome is a complex ecosystem:  
multiple bugs interact with each other**

**Human faecal metagenomics allows us to investigate drug-microbe  
associations unbiased and on a large scale**

# Microbiome-drug associations in population cohorts



## Lifelines



167,000 participants

3-generation design

>2000 phenotypes:

- Environment
- Lifestyle
- Social contacts
- Diet
- Medication
- Biological measurements

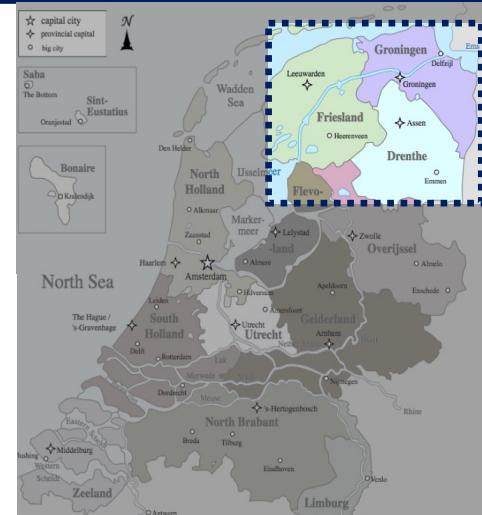
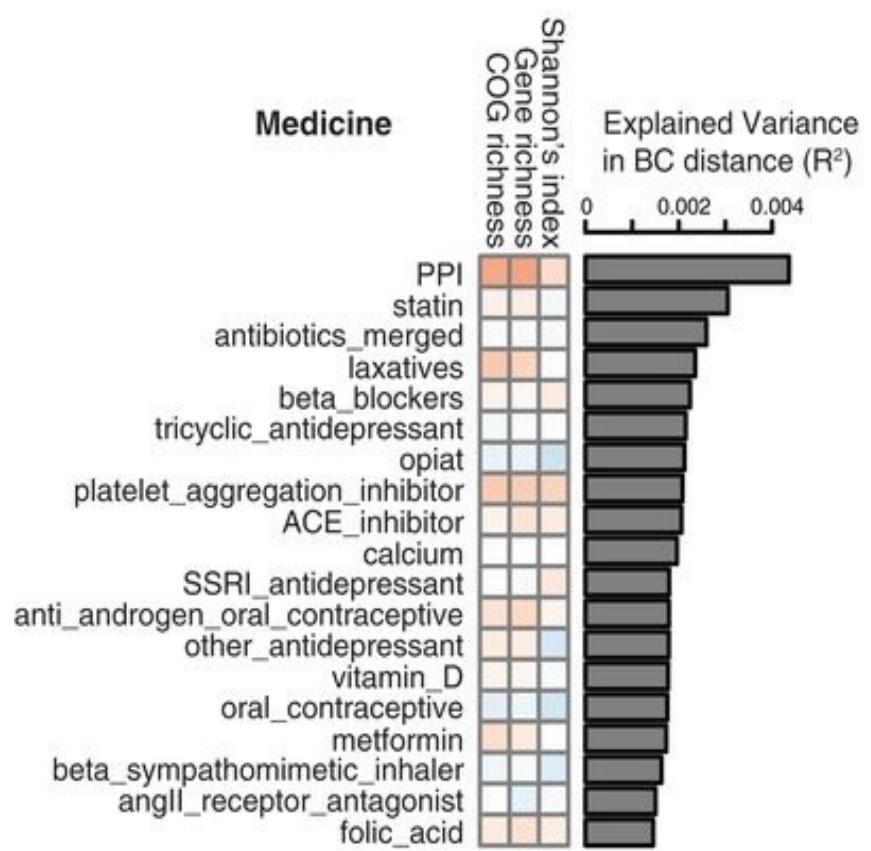
# Microbiome-drug associations in population cohorts

LifeLines Deep

In a cohort of 1135 individuals

**19 out 42 drugs** were associated to the gut microbiota composition

**13 drug associations** were replicated in a Flemish population cohort  
(n=3000, 16S sequencing)

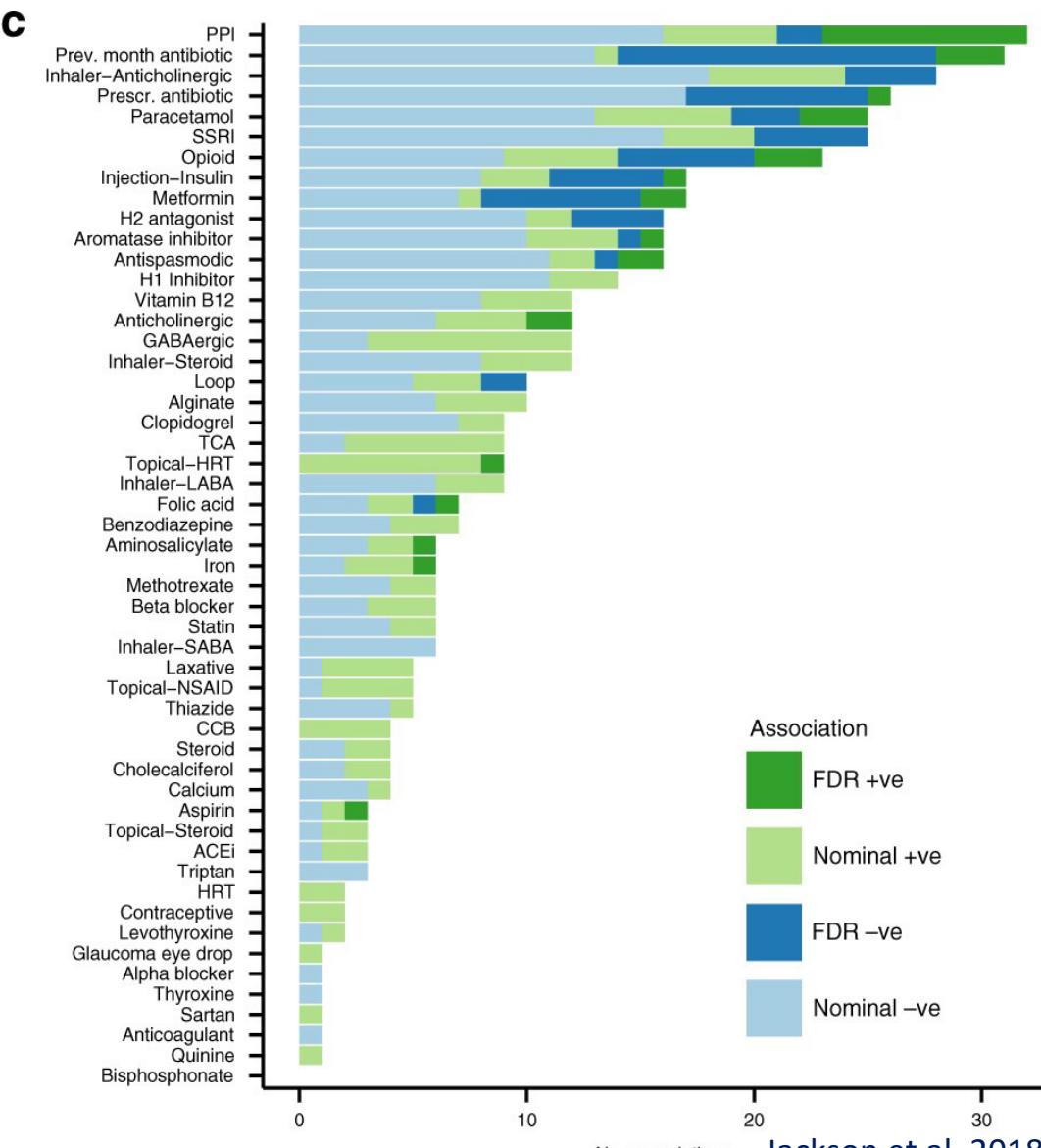


**lifelines**

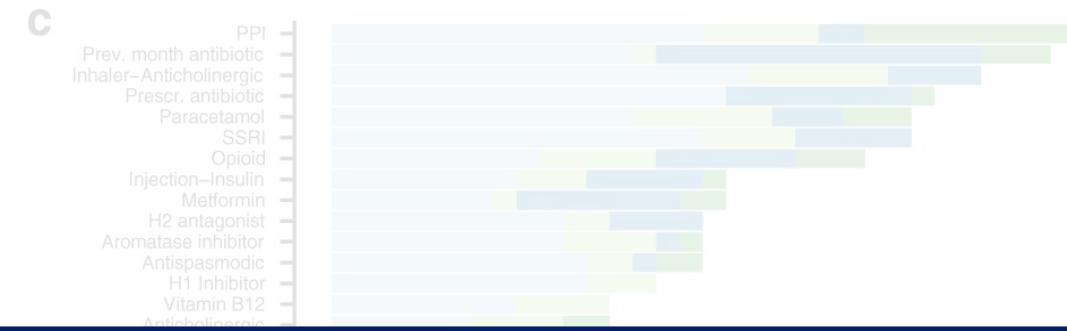
Zhernakova  
et al. 2016  
*Science*

# Microbiome-drug associations in population cohorts

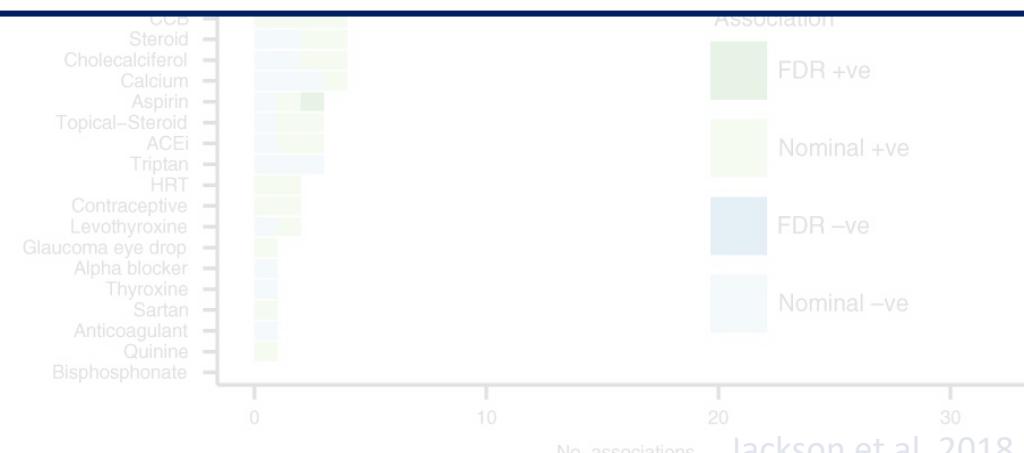
In TwinsUK biobank (n=1724, 16S sequencing)  
associations between **19 out 52 medications**  
and the gut microbiota were found



# Microbiome-drug associations in population cohorts



Population cohorts: Polypharmacy potential confounding effect ?



# Considering polypharmacy reduces the number of associations

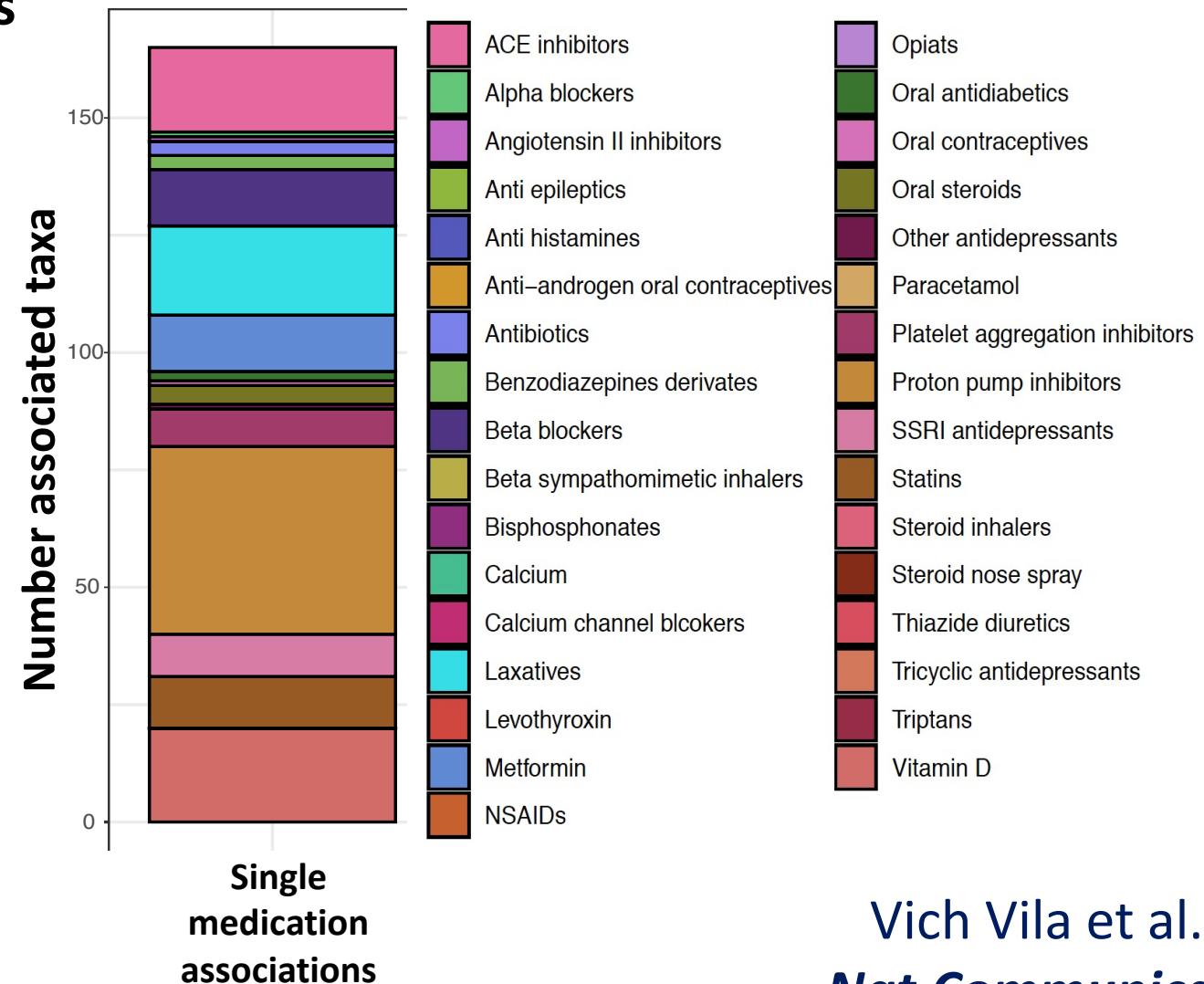
## Meta-analysis in 3 independent cohorts

Population cohort  
n=1140

IBS cohort  
n=289

IBD cohort  
n=454

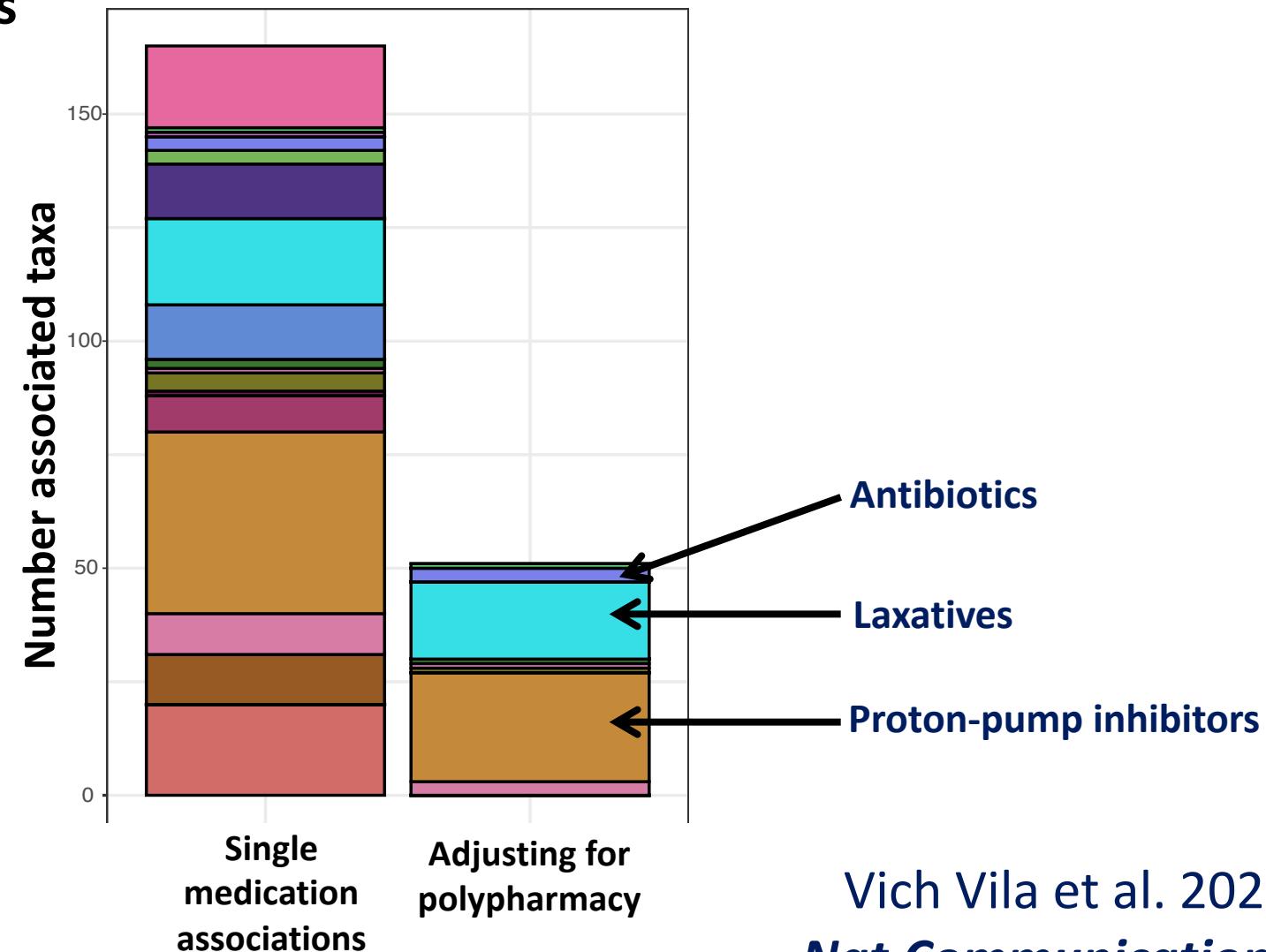
**154 associations  
between bacterial  
taxa and 17 different  
types of medications**



# Considering polypharmacy reduces the number of associations

Meta-analysis in 3 independent cohorts

After correcting for co-medication use  
51 association to 8 medications  
remained significant



# Microbiome-drug associations in population cohorts



## Dutch Microbiome Project

8,208 individuals (metagenomes)

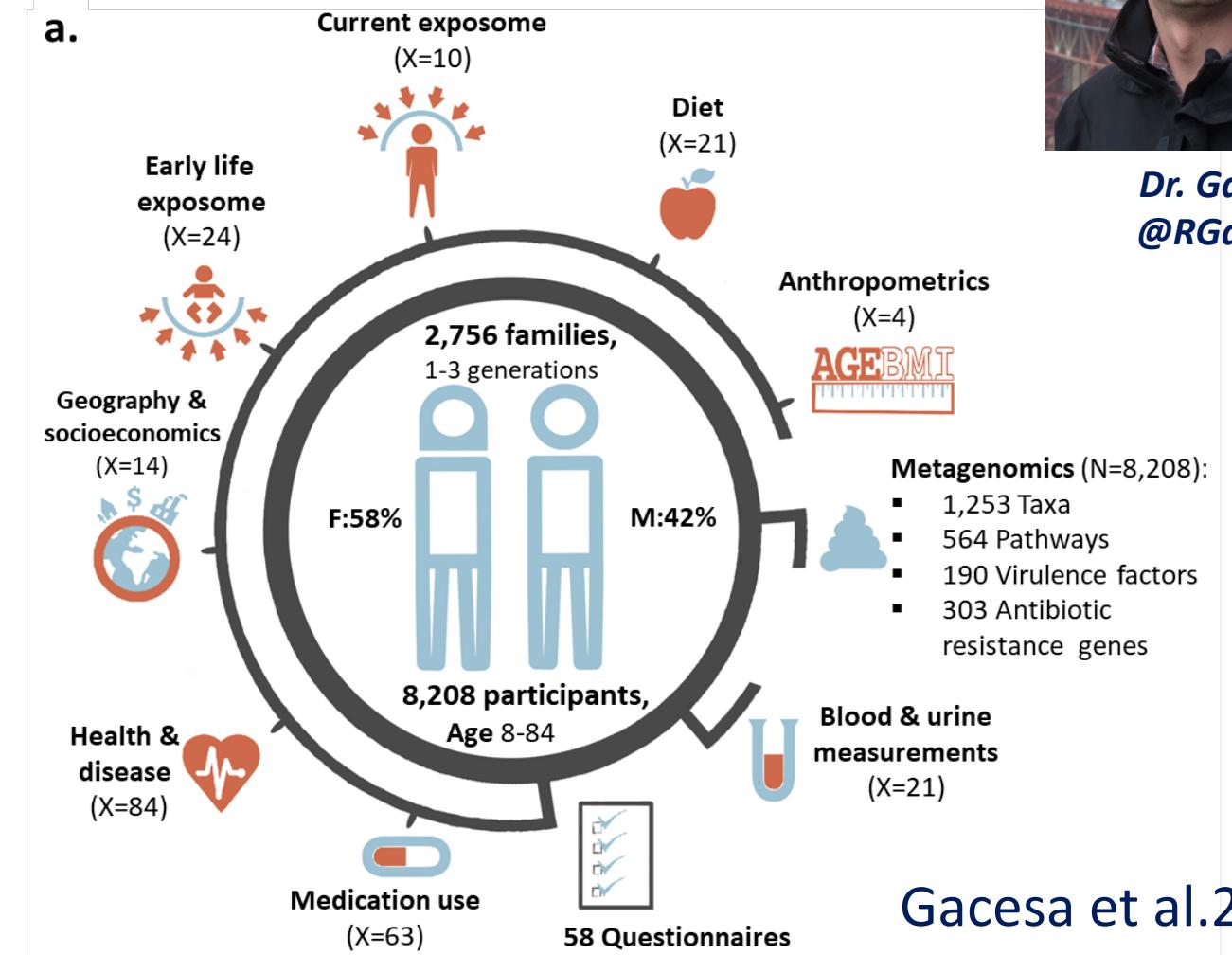
1253 taxa

564 pathways

241 meta-data entries

241 factors can explain  
only ~13% of microbiome  
inter-individual variation

Do you want to know more?  
Check session A6  
*Gut Microbiota Variation associated with Lifestyle*



Gacesa et al. 2021  
*BioRxiv*

Dr. Gacesa  
@RGacesa

# Microbiome-drug associations in population cohorts



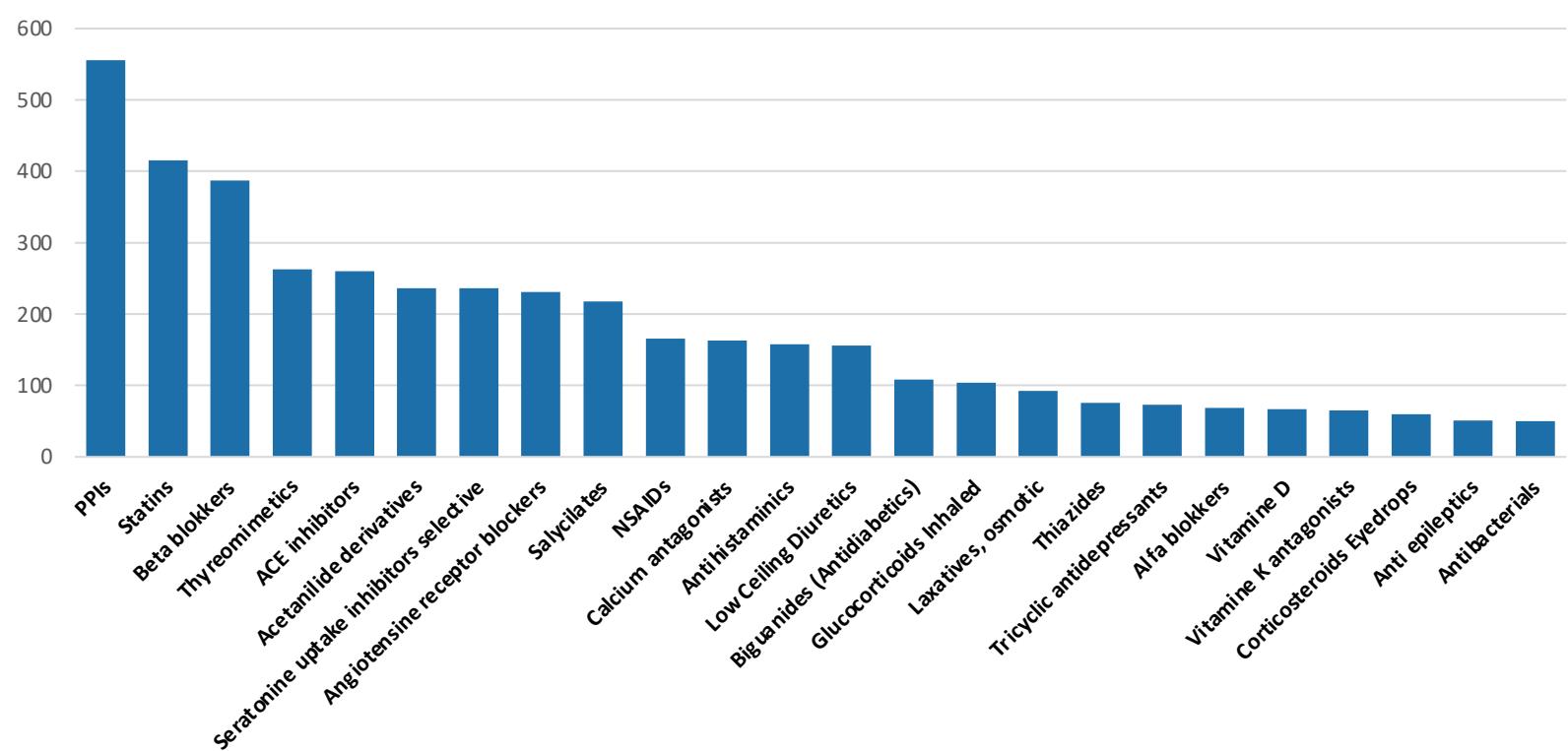
## Dutch Microbiome Project

**63 different medications categories (Anatomical Therapeutic Chemical)**

**Proton pump inhibitors (7%), statins (5%), and beta-blockers (4%)**

**Low antibiotic prescription in the NL (0.61%)**

*Dr. Gacesa  
@RGacesa*

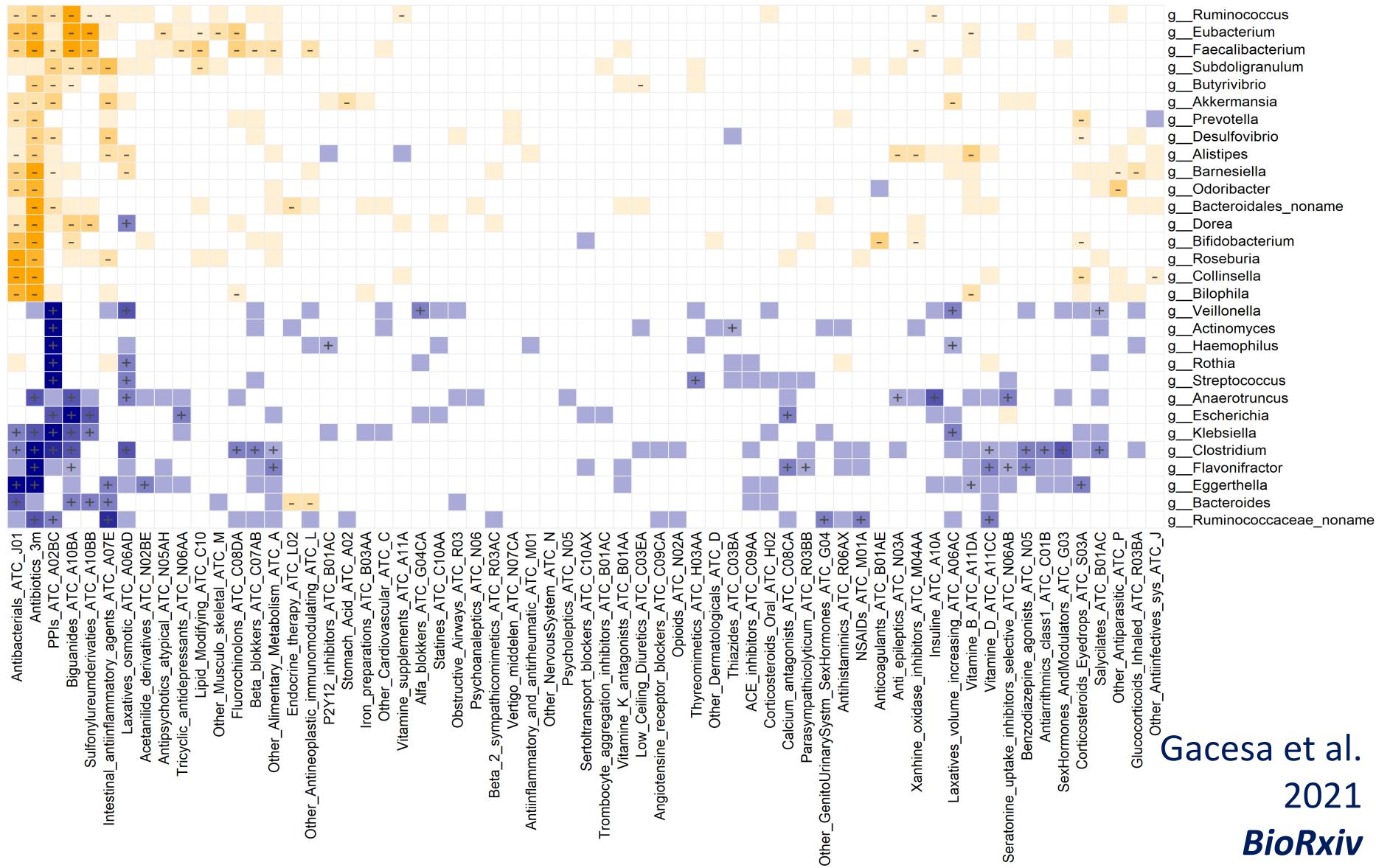


Gacesa et al.2021  
*BioRxiv*

# Microbiome-drug associations in population cohorts

31/59 bacterial genera  
were associated to >1  
type of drug

59 bacterial species  
90 bacterial pathways



Gacesa et al.  
2021  
*BioRxiv*

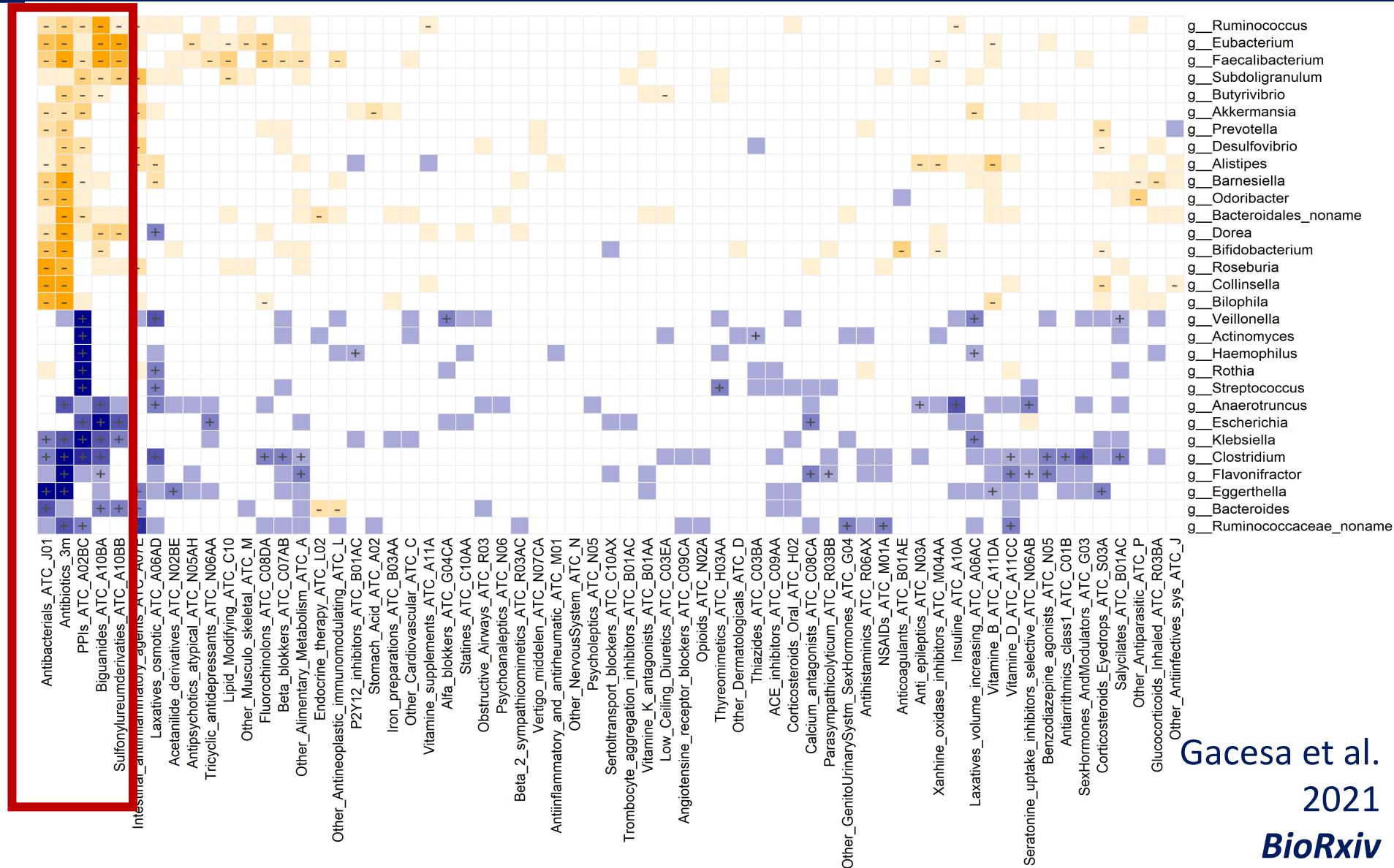
# Microbiome-drug associations in population cohorts

Largest effects:

PPI 84 taxa

Antibiotics 56 taxa

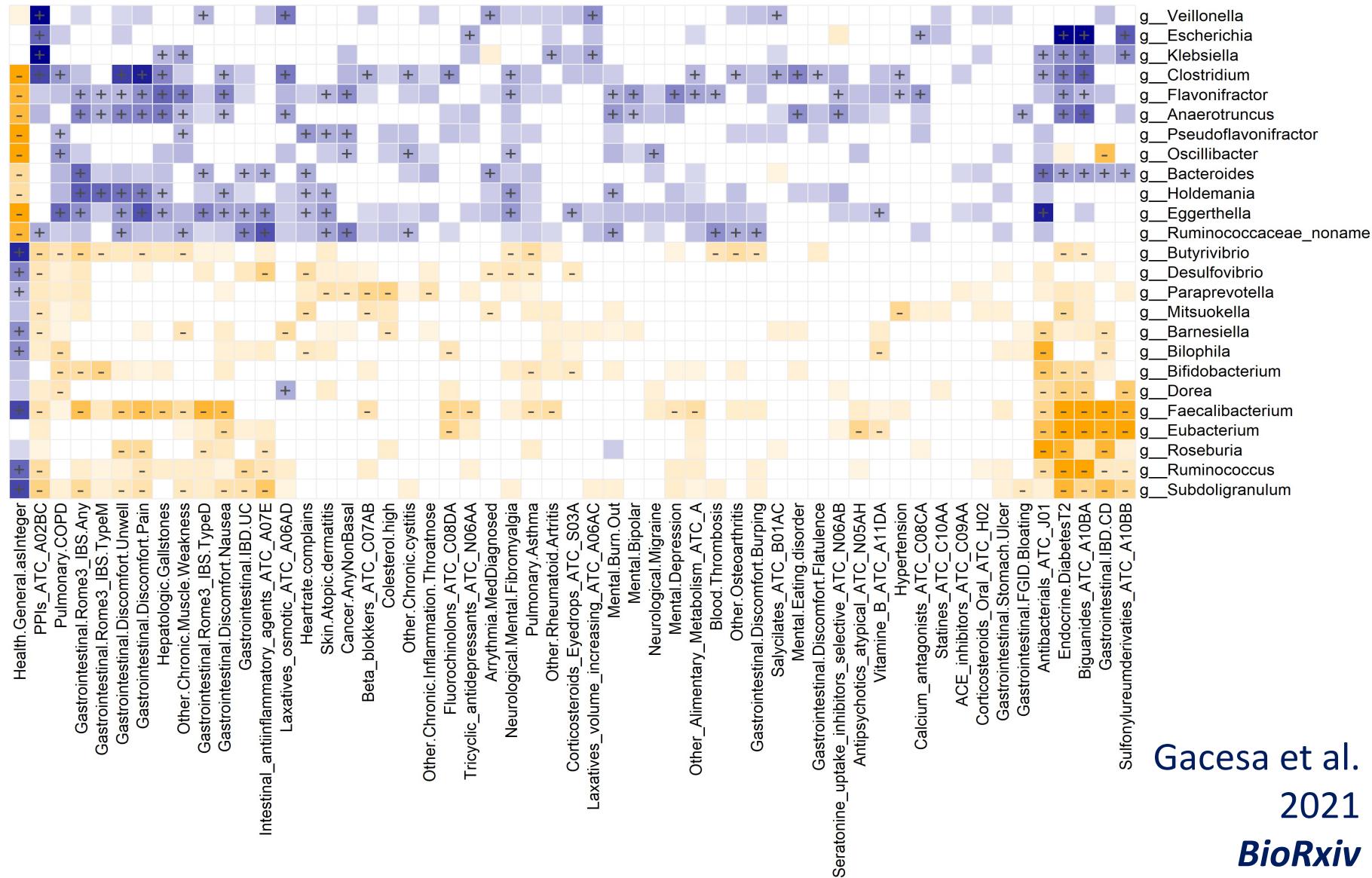
Antidiabetics 47 taxa



# Microbiome-drug associations in population cohorts

Drug-disease analysis:

Multi-variate models  
Including drugs and  
disease, suggest that  
most signals are  
independent



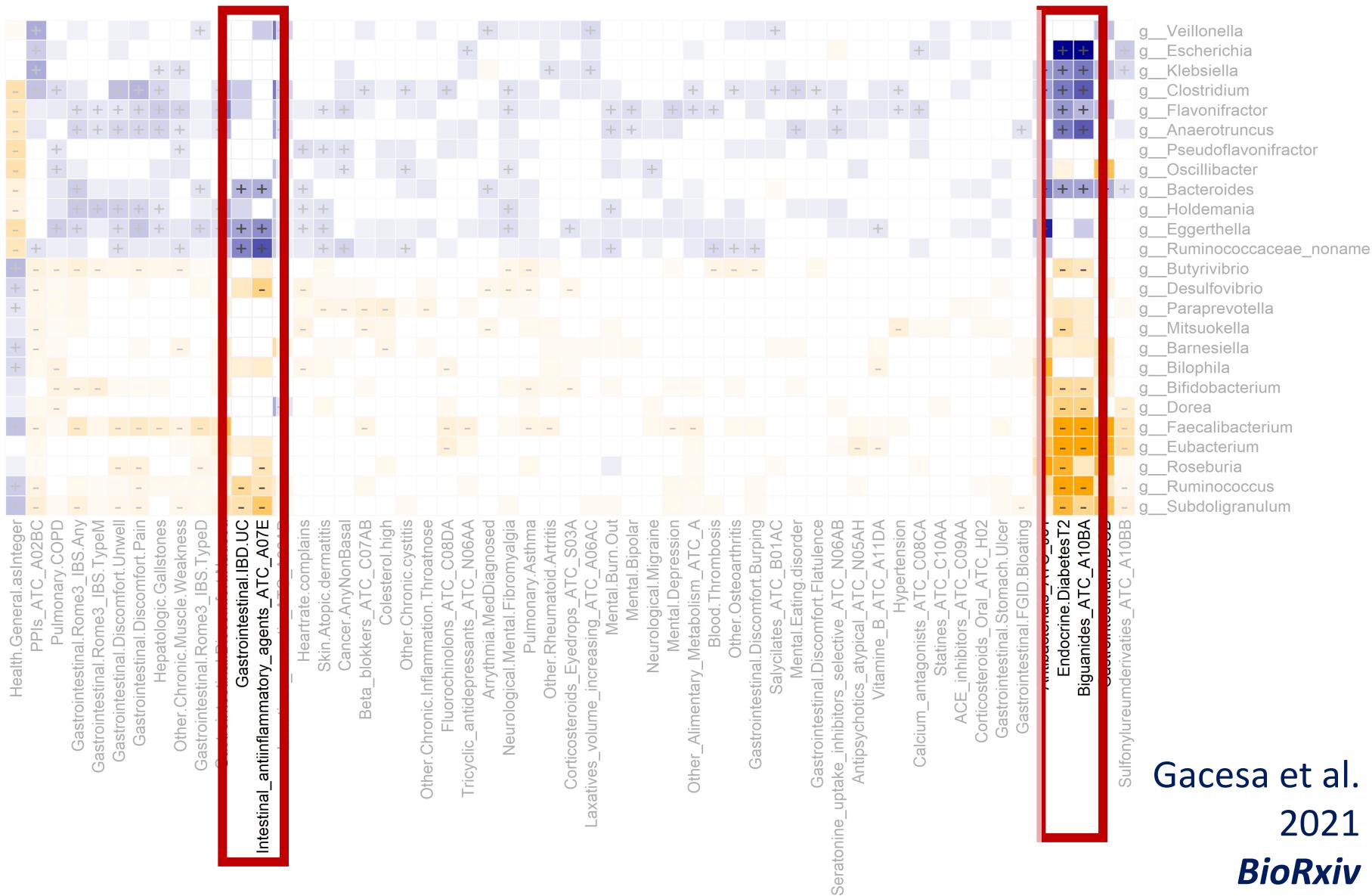
Gacesa et al.  
2021  
*BioRxiv*

# Microbiome-drug associations in population cohorts

Drug-disease analysis:

Overlapping signal  
T2D and anti-diabetics

Strongest signal  
increase abundance  
of *E.coli*



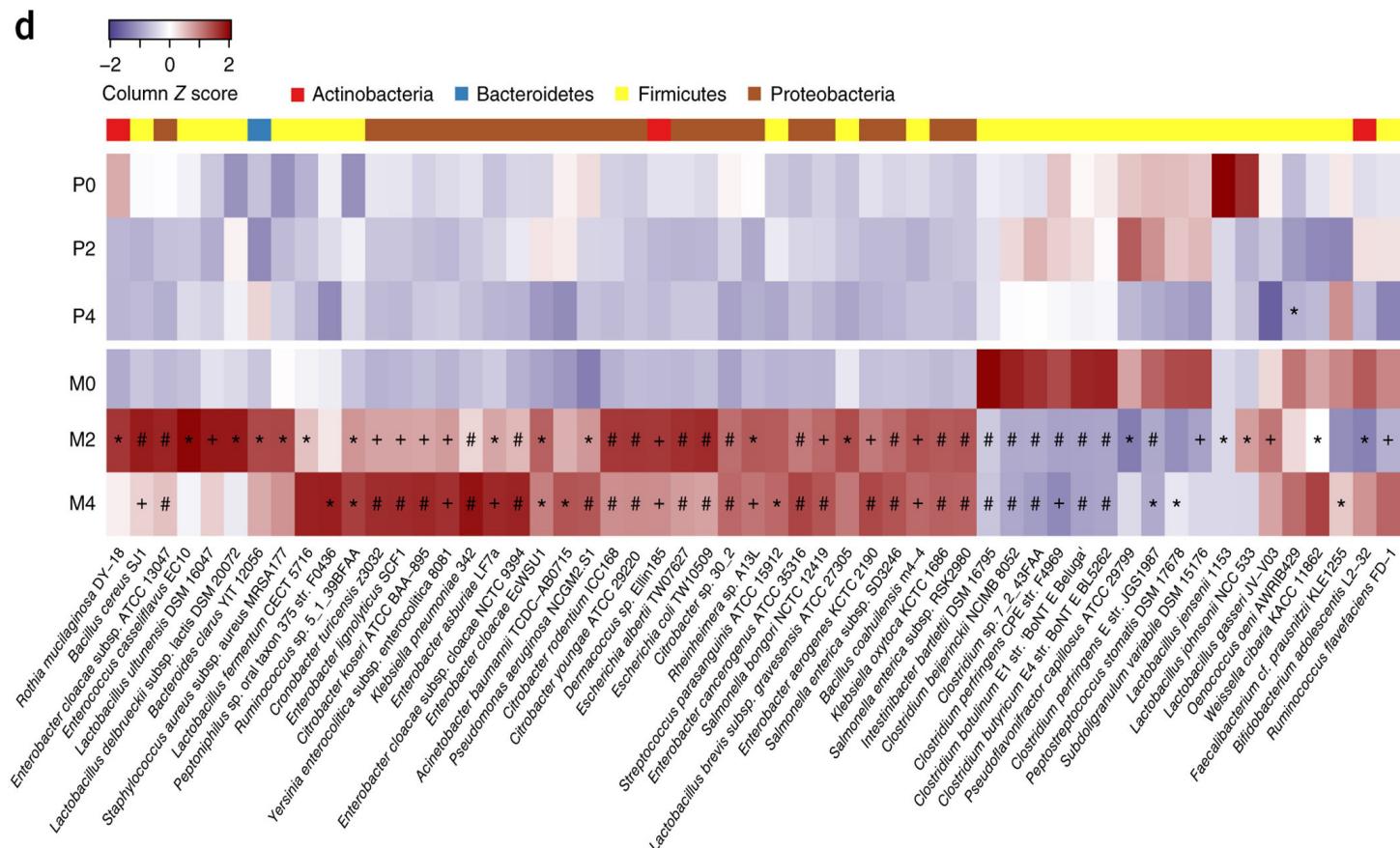
# Metformin induces changes in the microbiome

## Treatment-naïve T2D individuals

## **Placebo (n=18) & Metformin (n=22)**

## **After 4 months: 81 species altered**

*in-vitro* analysis suggested that these effects are indirect



Wu et al. 2017  
*Nat. Medicine*

# Proton Pump inhibitors (PPIs)

Top 10 commonly used drugs world wide

12% of the population in NL used omeprazole in 2018 (on prescription)

Very effective for acid related disorders: peptic ulcers, reflux and dyspepsia

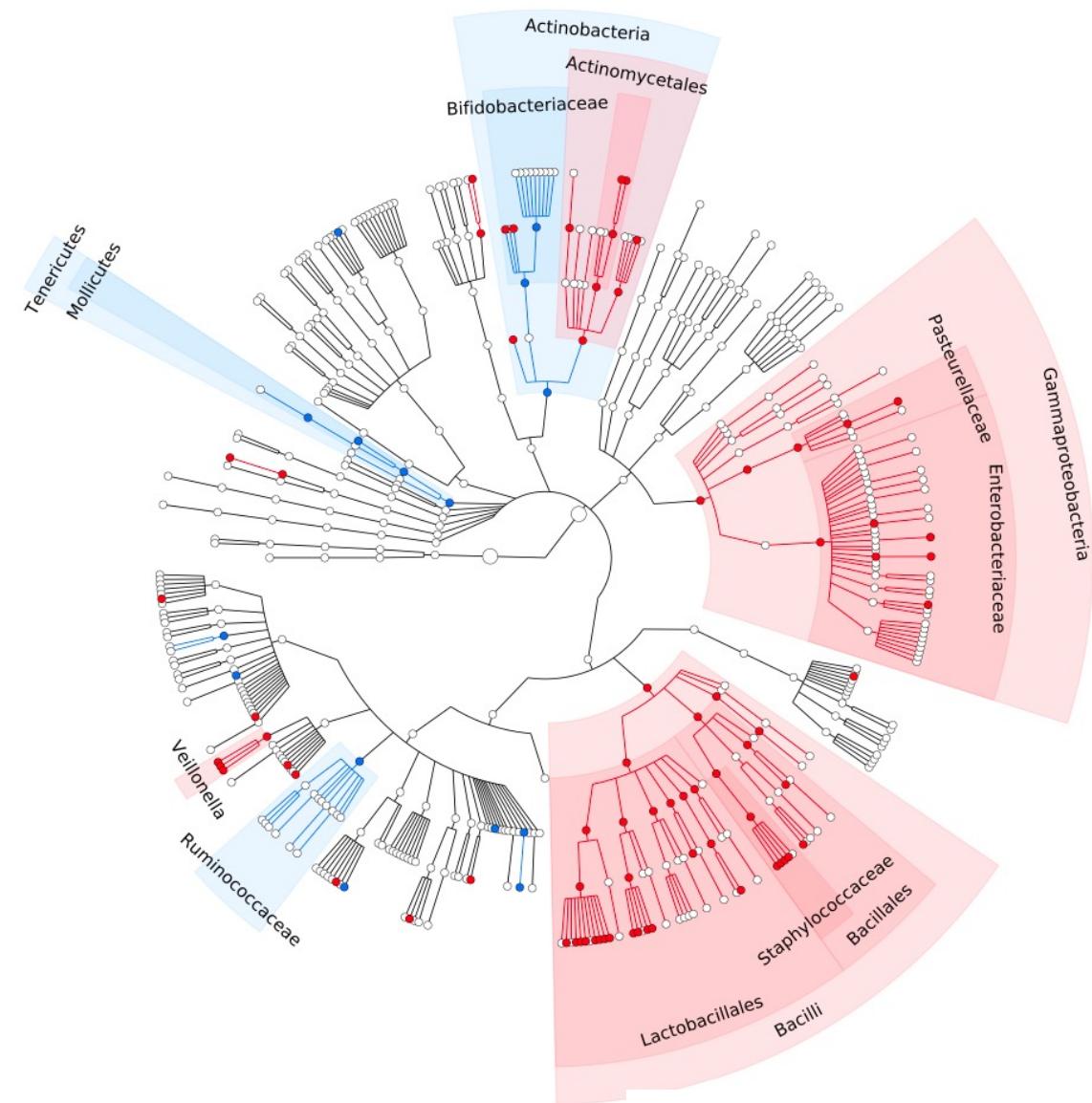


# PPI affects the gut microbiota

Cross-sectional meta-analysis  
in 3 cohorts (n=1815)

Decreased abundance Ruminococcaceae  
and Bifidobacteriaceae

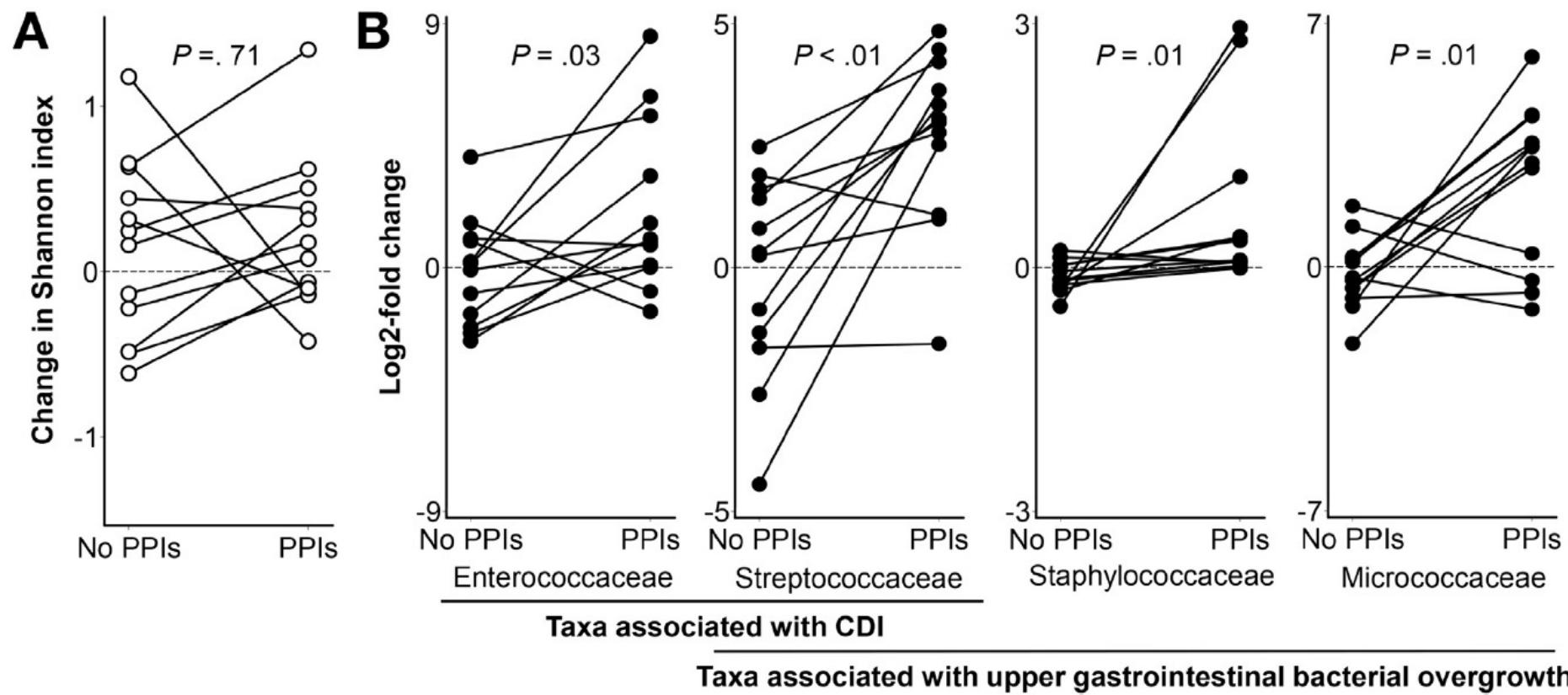
Increased abundance of *Streptococcus*,  
*Rothia* and Enterobacteria



# PPI influences microbiome on the long term

12 Healthy volunteers taking PPIs for 4 weeks

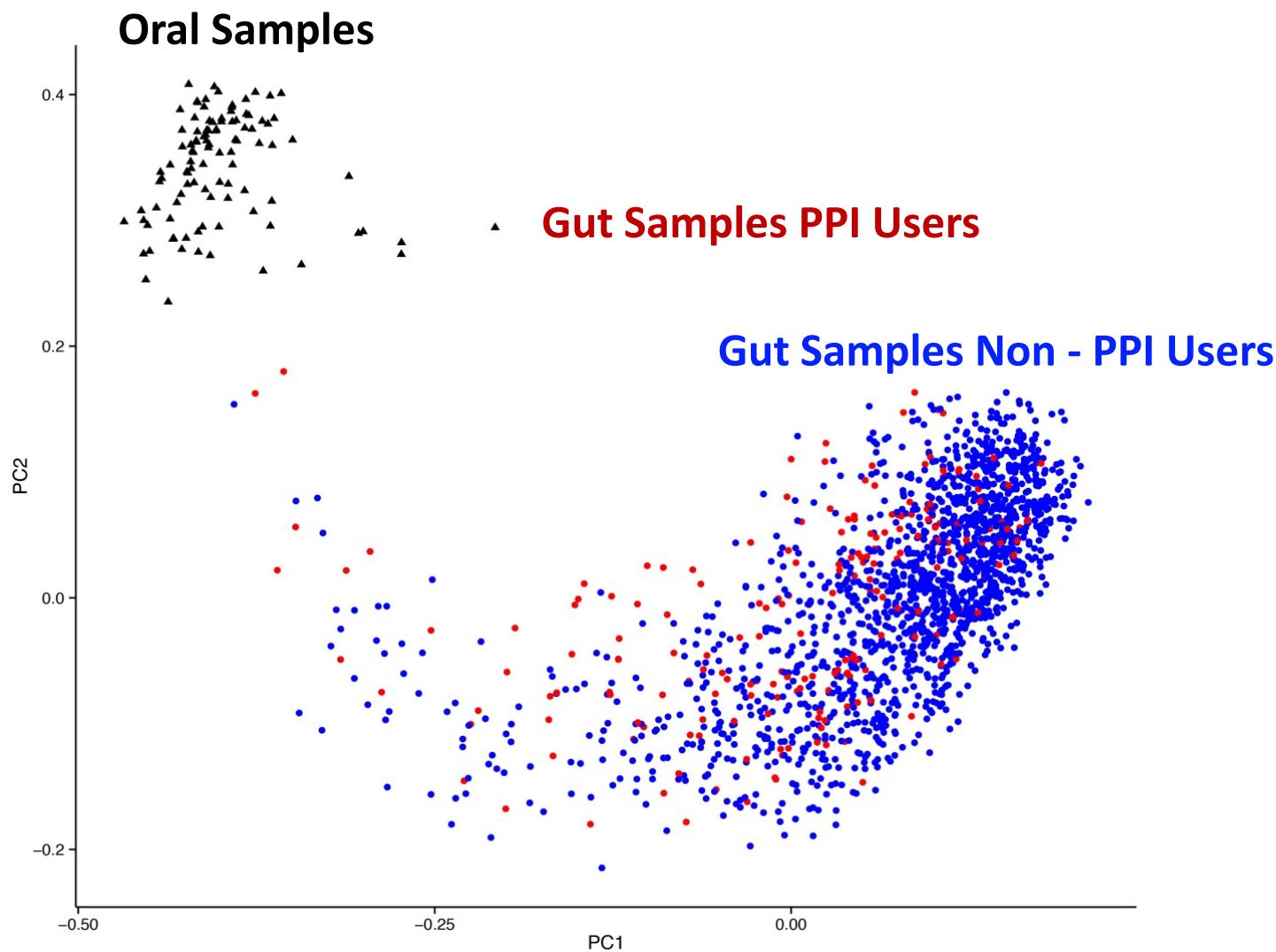
No changes in microbial diversity, but increase in *Streptococcus* and *Enterococcaceae*



# PPI: oralization of the gut microbiota?

Samples from PPI users tend to cluster closer to oral samples

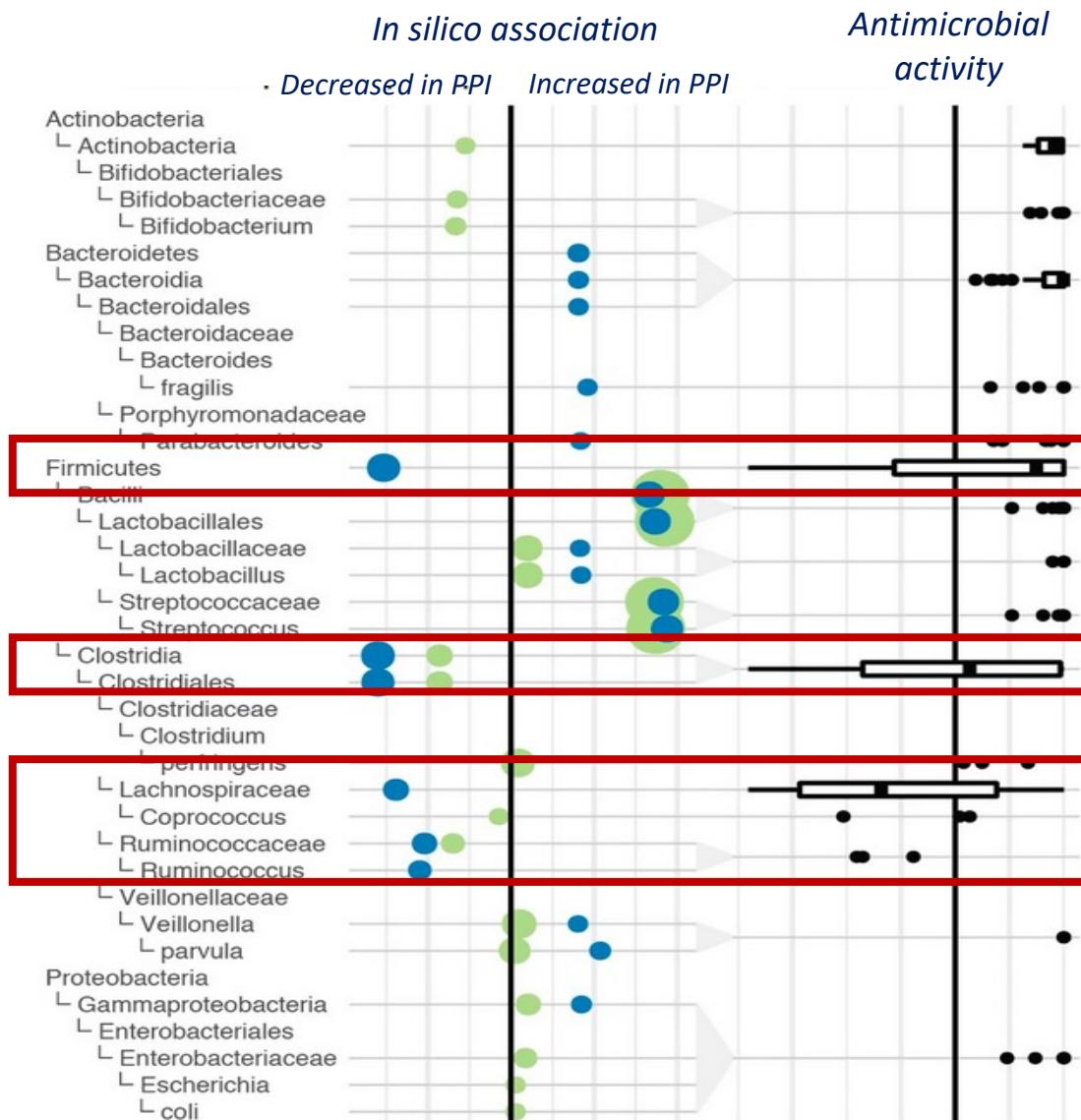
> Reduction of gastric acidity allows the translocation from the upper to the lower part of the gastrointestinal tract?



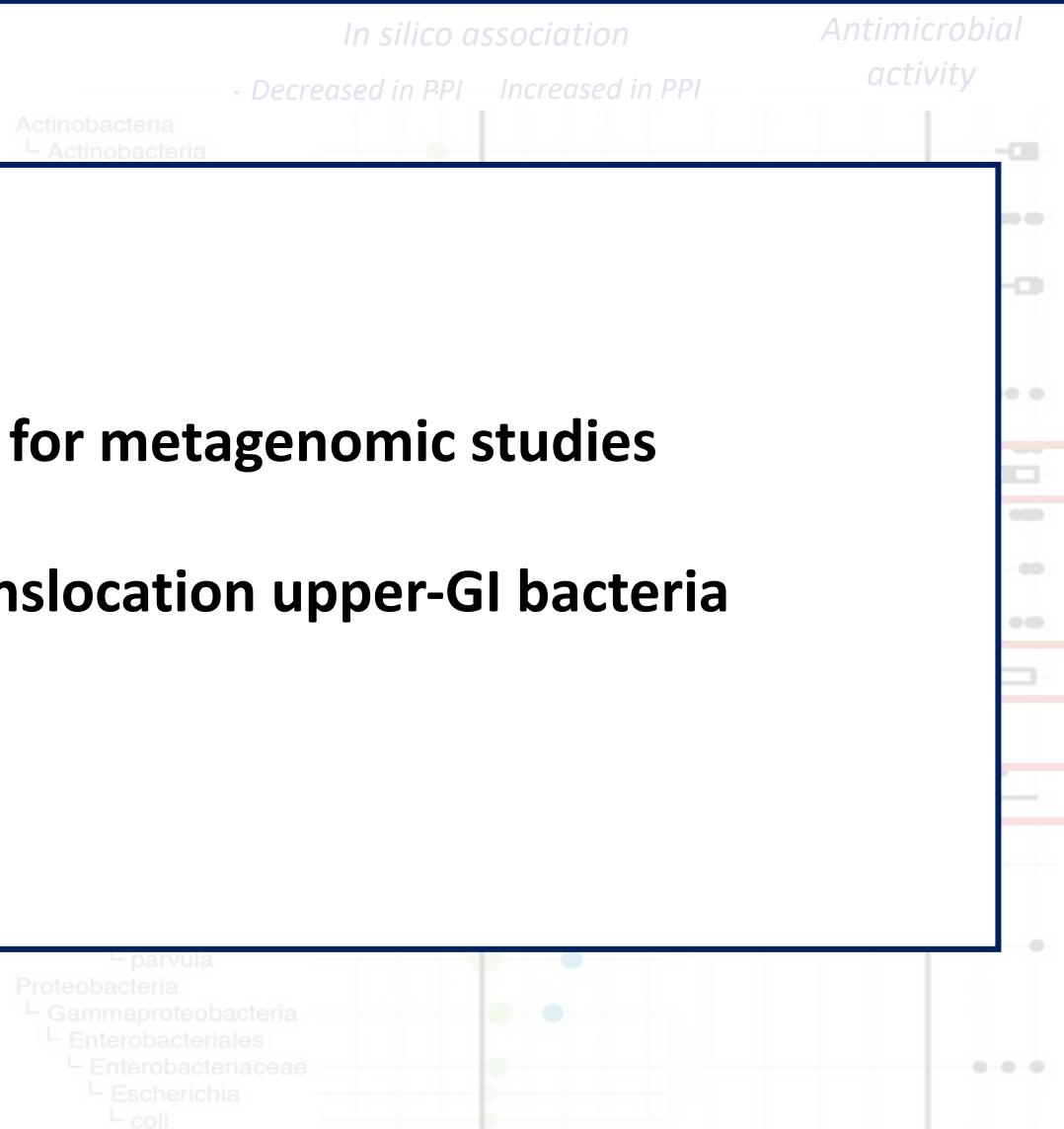
# PPI inhibits bacterial growth

PPI showed to inhibit the growth of several bacteria.

*In-vitro* observation were consistent with associations in *in-silico* analyses



# PPI inhibits bacterial growth



## Proton-pump inhibitors:

- 1) Large impact on the gut microbiota -> cofounder for metagenomic studies
- 2) Alteration of the gut environment may allow translocation upper-GI bacteria
- 3) Affecting bacterial growth
- 4) Increased risk for enteric infections?

# Pharmacomicobiomics: a bi-directional relation

The relation between the drug-microbiota is complex and bidirectional

Scenario 3: Microbiota modulate response to treatment

Can we improve efficacy ? Can we design personalized treatments?



Doestzada et  
al. 2018  
*Protein cell*

# Can microbiome predict vedolizumab response?



The biological drug Vedolizumab is used to treat IBD (Blocking the  $\alpha_4\beta_7$  integrin)

Response rate: ~50%, no response prediction available

Growing evidence that microbiome can predict response

*Dr. Collij  
@CollijValerie*

# Can microbiome predict vedolizumab response?

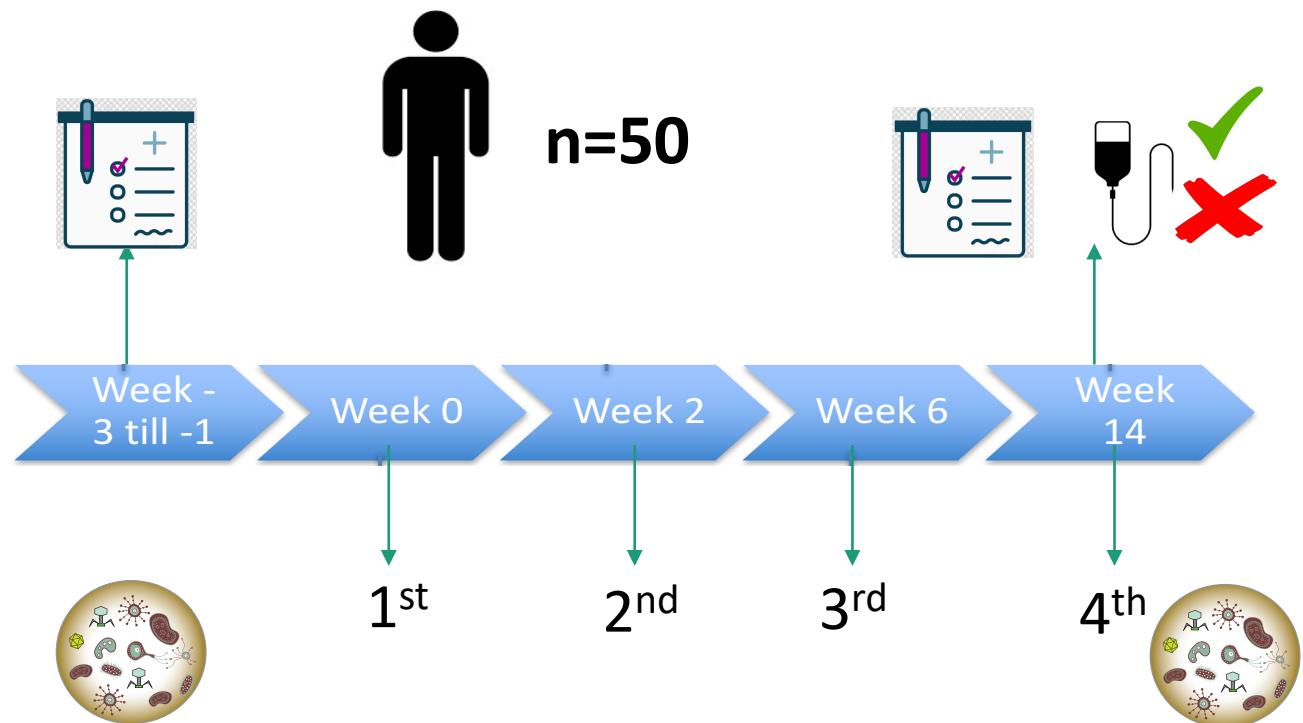


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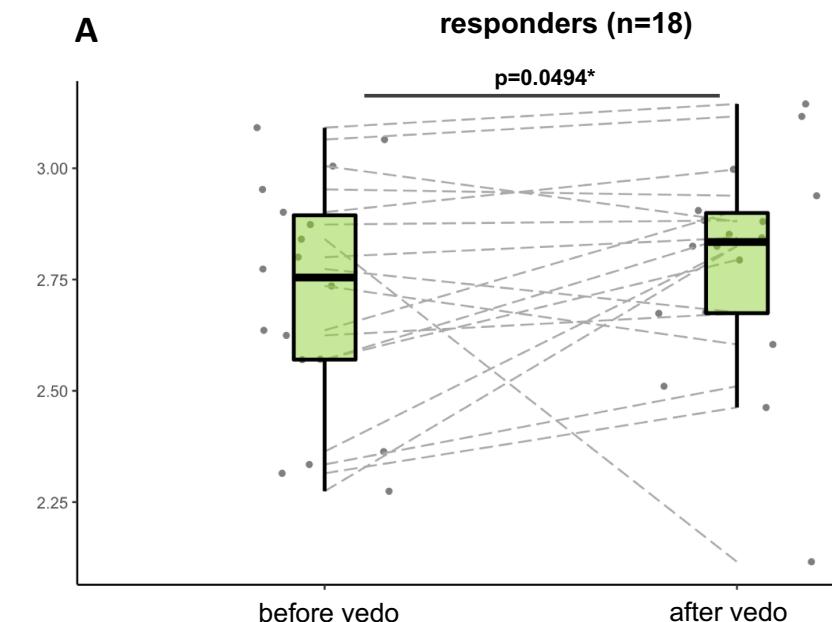
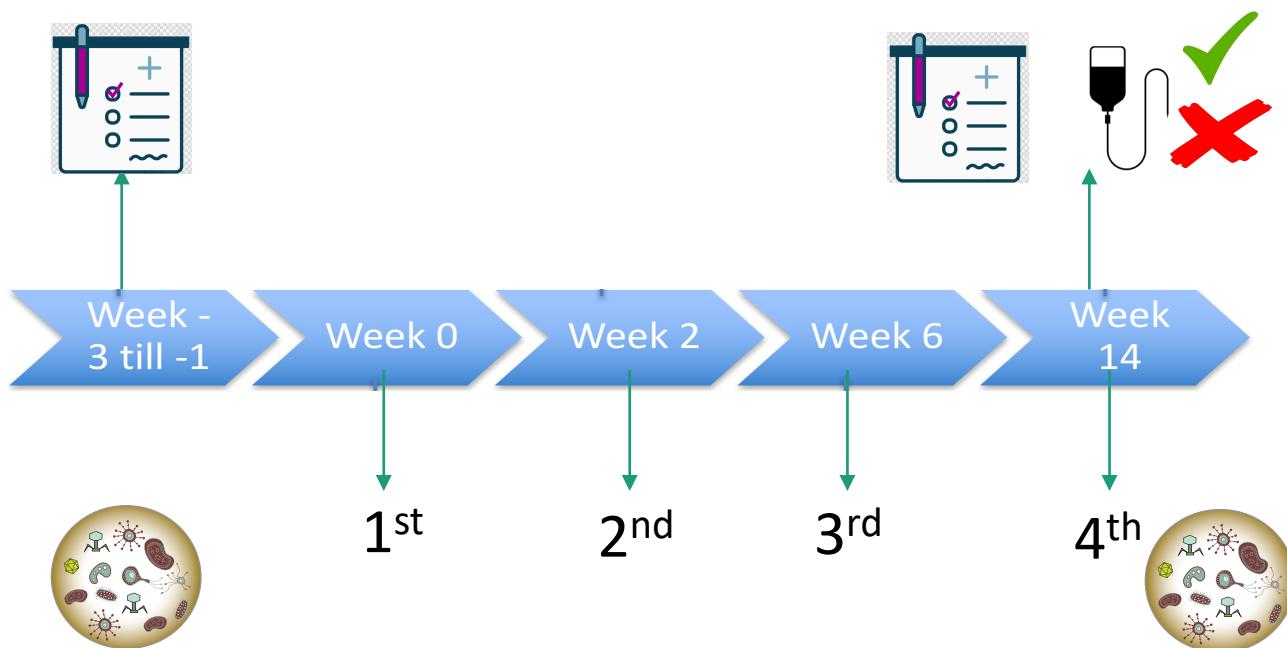
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@CollijValerie

Responders show (slightly) improvement in bacterial richness



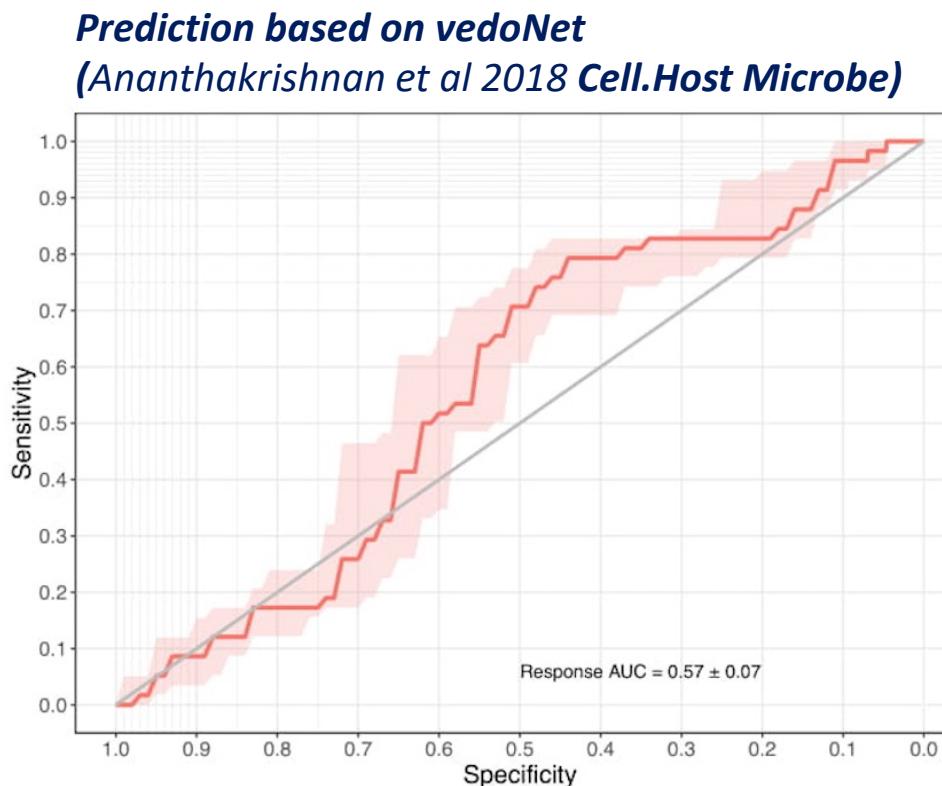
# Can microbiome predict vedolizumab response?



Can baseline microbial composition predict response to vedolizumab?

No replication using a model from an IBD study group in the U.S.A

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@CollijValerie



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# Can microbiome predict vedolizumab response?

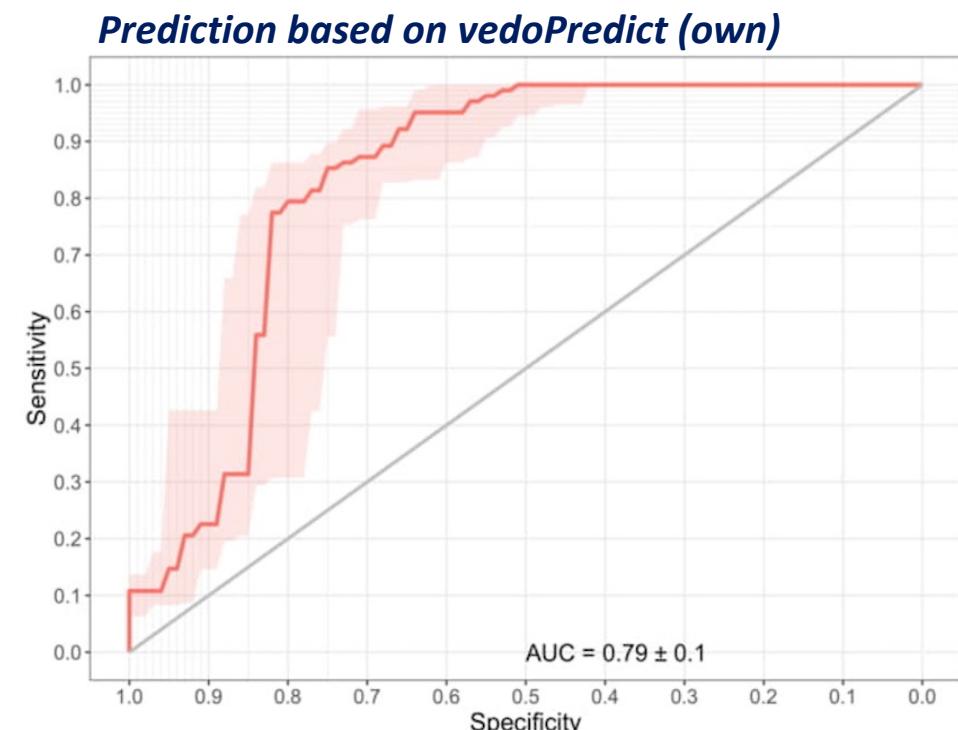
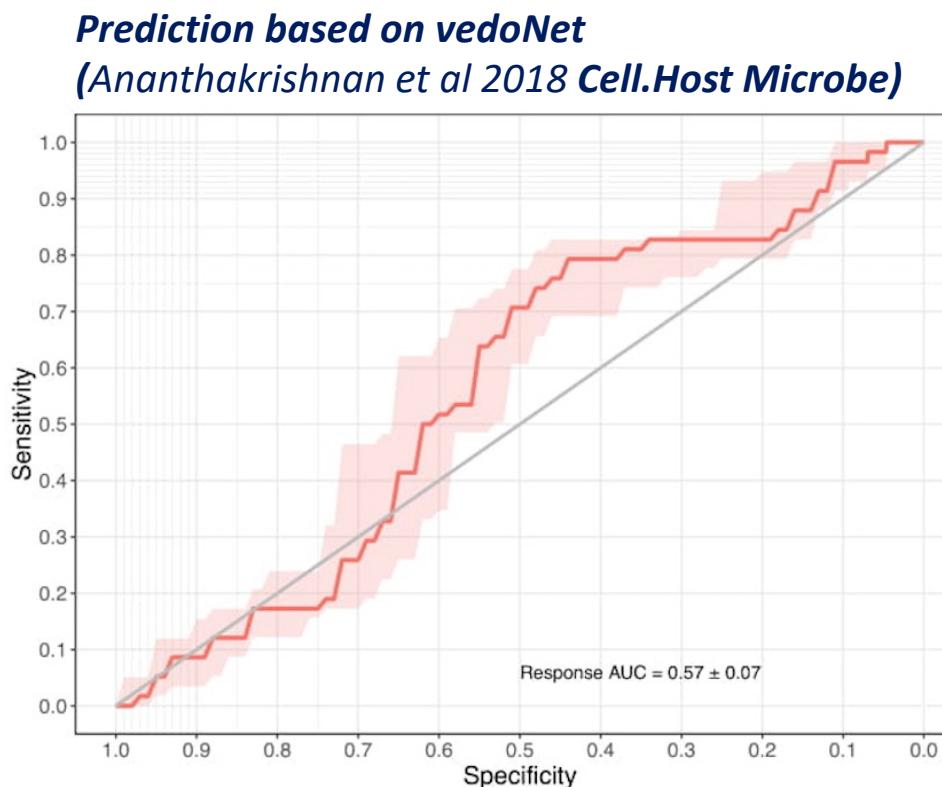


Training a prediction model in our cohort reached a good classification

Results are promising but seem to be cohort specific

Geographical and technical differences?

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@CollijValerie



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# Microbiome-immune interactions modulate cancer therapy

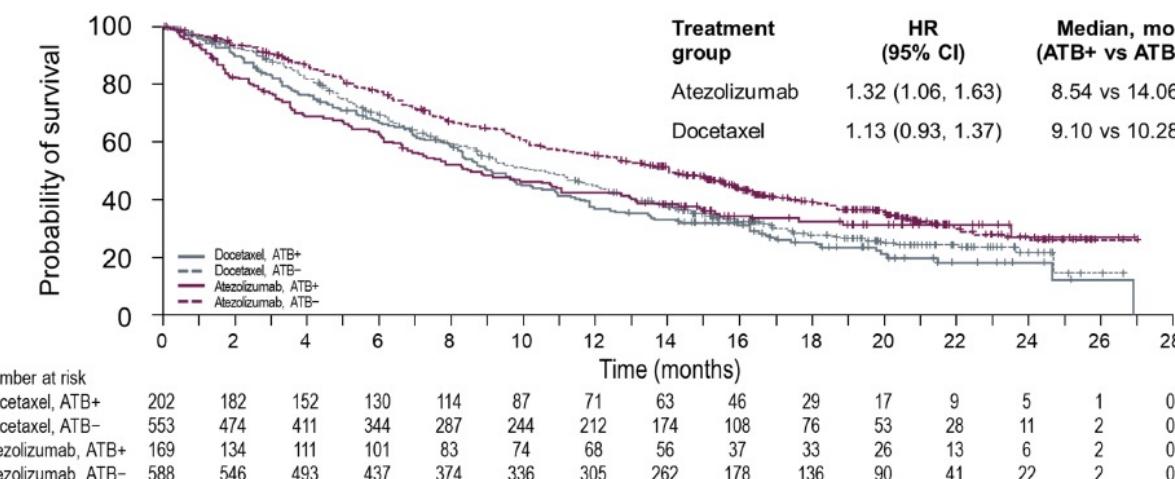


Evidence suggests that microbiome composition defines the response to immune checkpoint inhibitors therapy

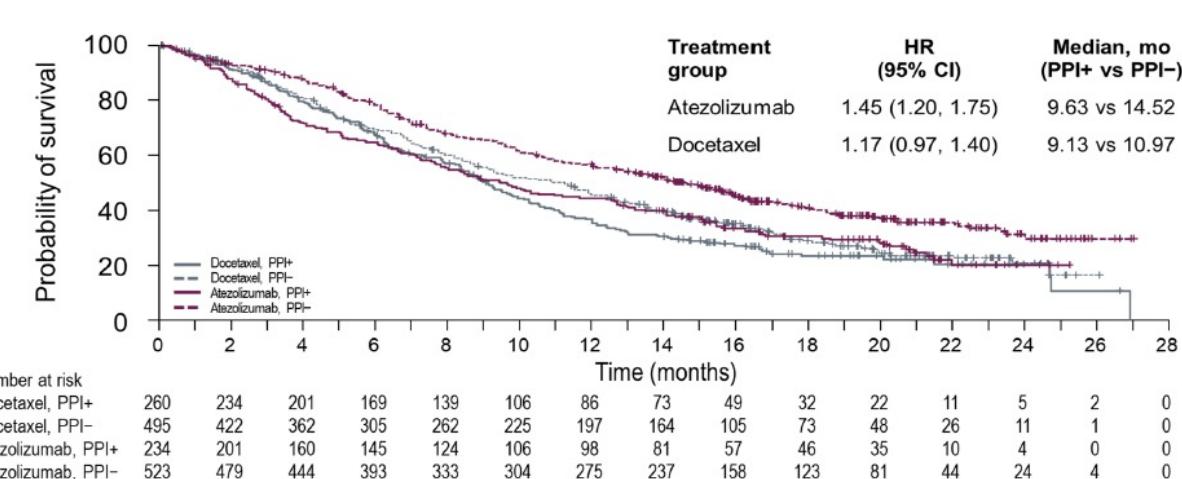
Dr. Björk  
@AwfulDodger

Germ free mice, PPI and Antibiotic users have lower progression-free survival

A AB



B PPI



# Microbiome-immune interactions modulate cancer therapy

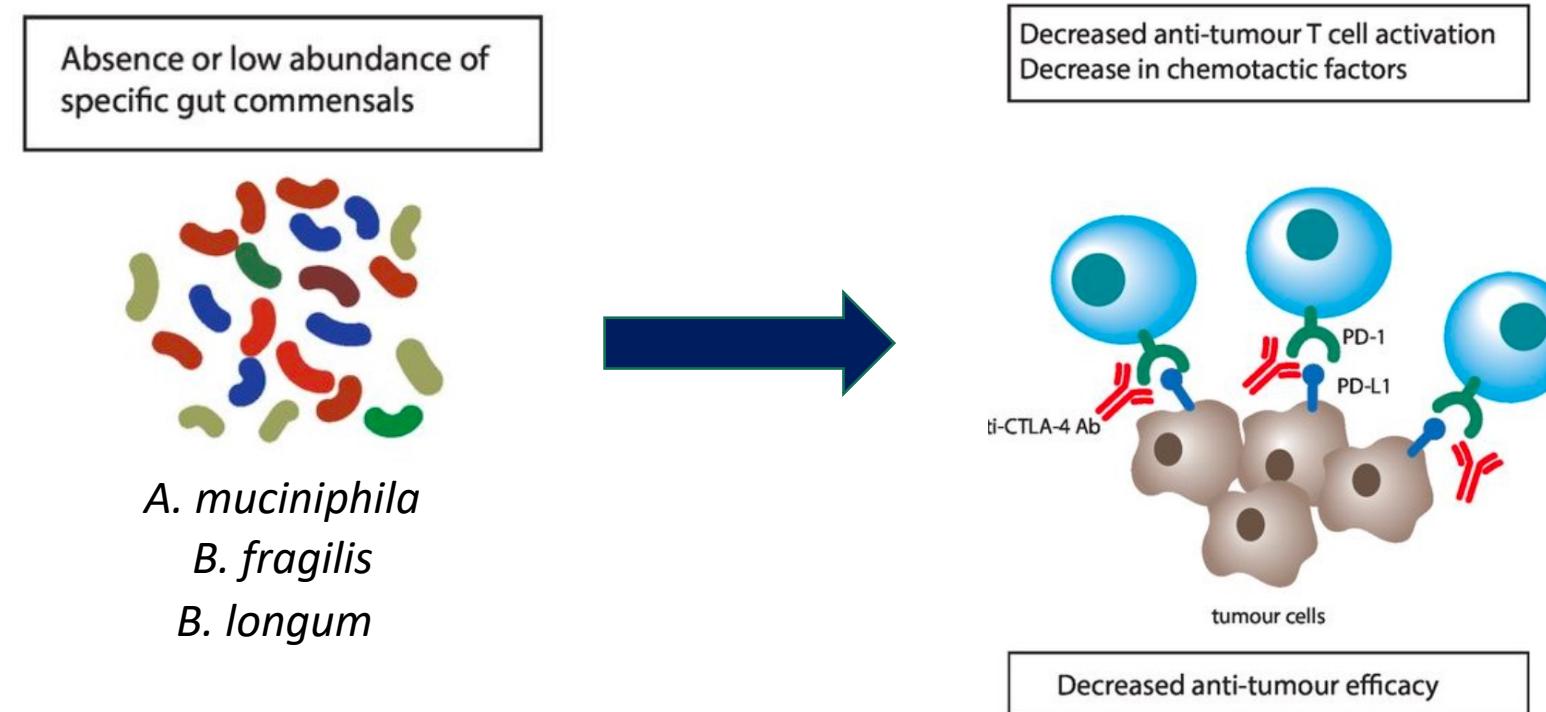


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Dr. Björk  
[@AwfulDodger](#)

Discrepancy between studies: No universal microbiome biomarker has been found



# Microbiome-immune interactions modulate cancer therapy

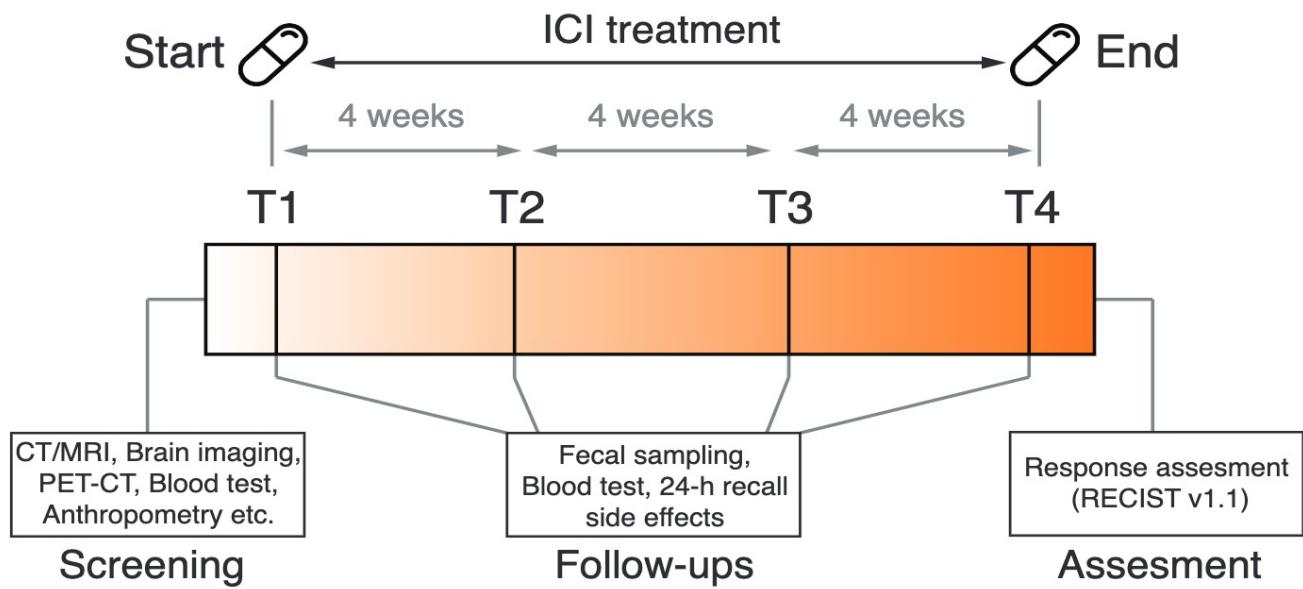
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Discrepancy between studies: No universal microbiome biomarker has been found



**PRIMM UK (n=55)**

**PRIMM NL (n=55)**

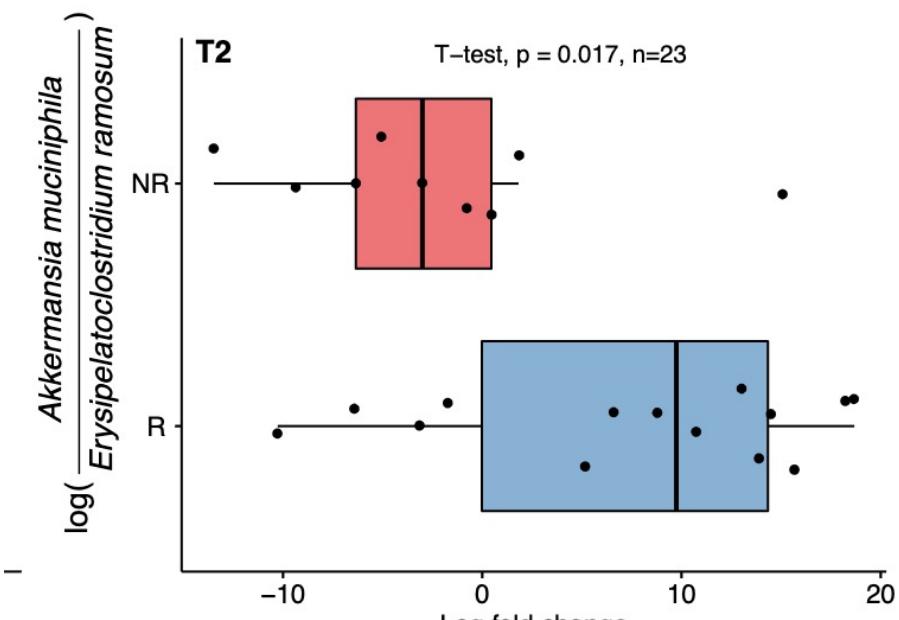
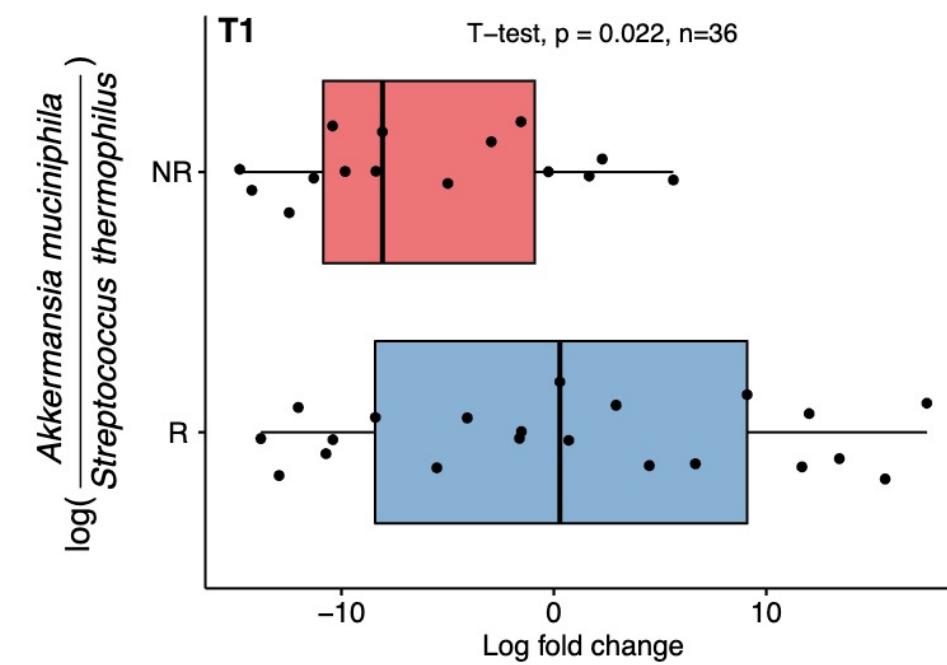
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# Microbiome-immune interactions modulate cancer therapy



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At baseline responders have higher abundance of *Akkermansia muciniphila*



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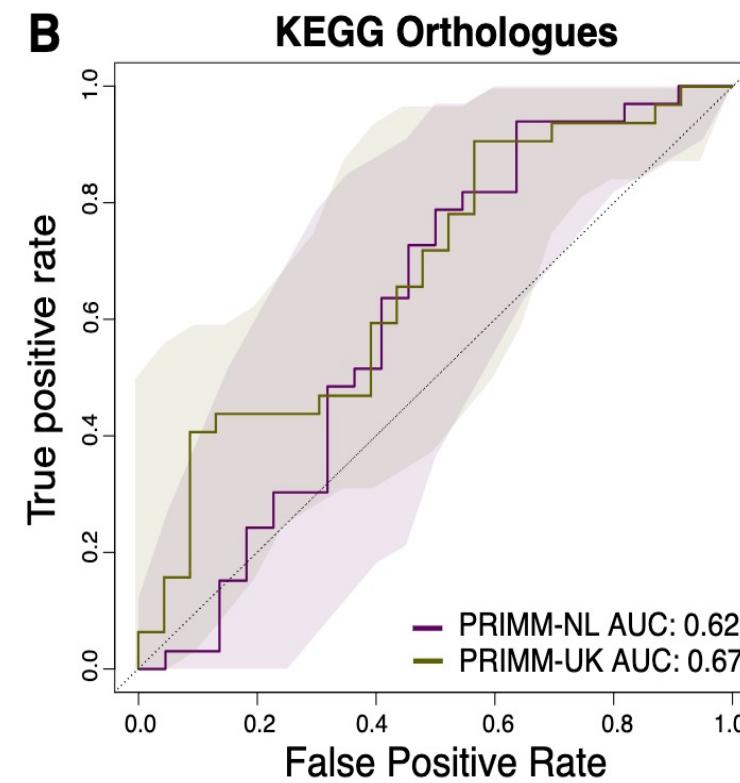
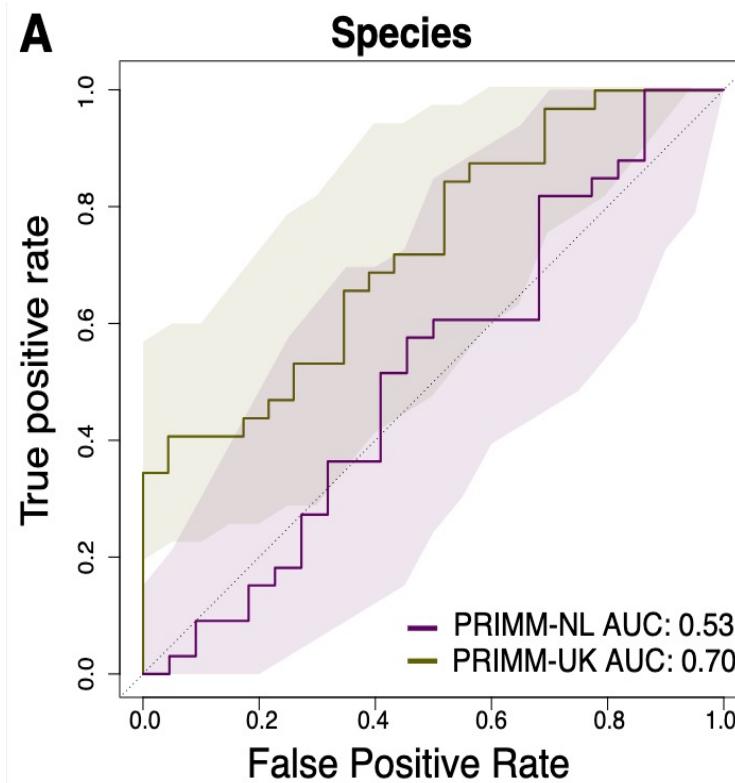
# Microbiome-immune interactions modulate cancer therapy



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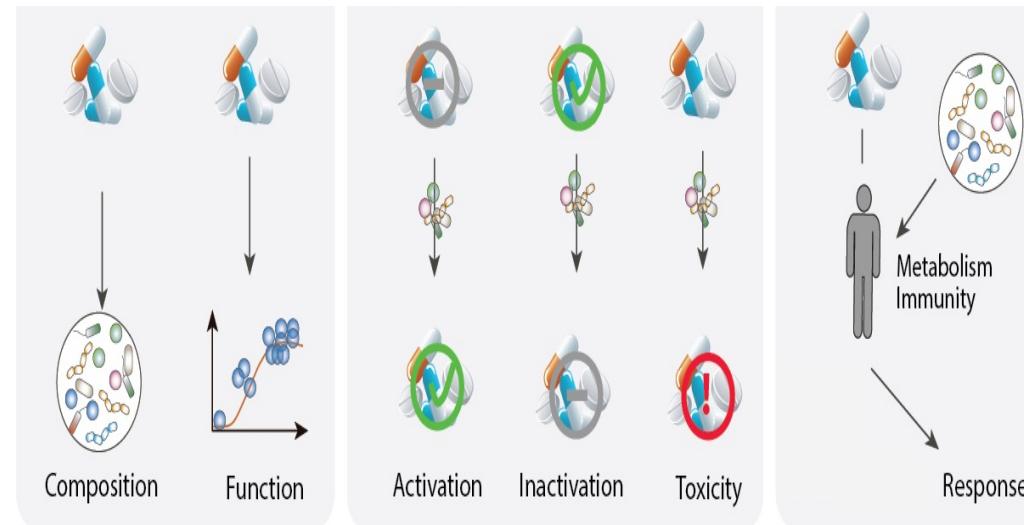
Baseline predictive power is cohort dependent: bacterial genes perform better

Next steps: metabolomics analysis



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# Take home messages



**Drug-microbiome relations are complex and bi-directional**

**Population-based studies can help to reveal interactions but not directionality**

**Medication use should be recorded and considered in any human microbiome study**

**Large variation between studies/methods/cohorts: replication before implementation**

# Future perspectives

- 1) More efforts should be put in the functional characterization of the gut microbiota  
(e.g. metabolomics / culturomics)**
  
- 2) Fill the gap between 1 bug – 1 drug associations and ecosystem perspective  
(e.g. organ-on-a-chip)**
  
- 3) Small intestine microbiota is understudied: relevant for oral administrated drugs  
(e.g. levodopa)**

# Groningen Microbiome Center



university of  
groningen

**lifelines**

 1000IBD

MAAG  
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STICHTING

 **IB** Genetics

  
Netherlands Organisation for Scientific Research

 SEERAVE  
FOUNDATION

 Novogene

 Takeda

 Johnson & Johnson

## Dept. Gastroenterology UMCG



# Thank you for your attention

## Moltes gràcies

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Dept. Genetics

University Medical Center Groningen



@arnauvich



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