

# Thorne HealthTech<sup>1</sup>

**Defining a Healthy Microbiome: Insights from  
Deeply Phenotyped Human Cohorts**

**Tomasz Wilmanski**

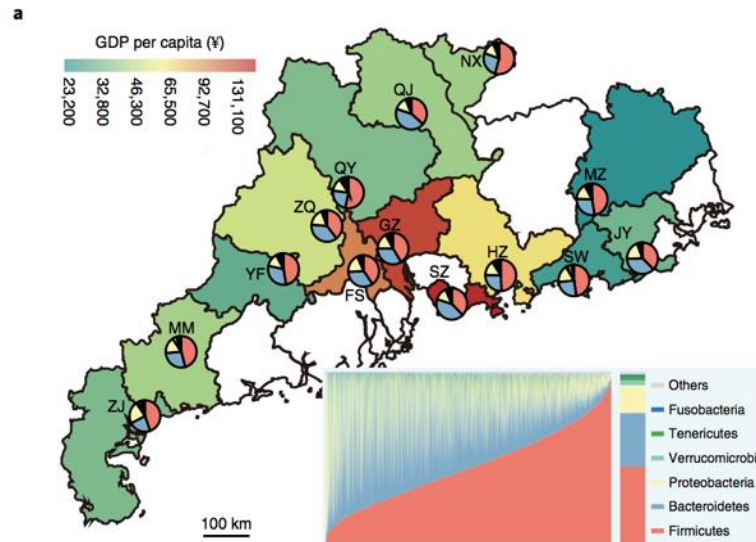
**VP Health Algorithms**

# Microbiome Stories

- 1) Blood based biomarkers for gut microbiome monitoring
- 2) Gut microbiome changes across lifespan and longevity
- 3) Gut Microbiome in statin therapy personalization

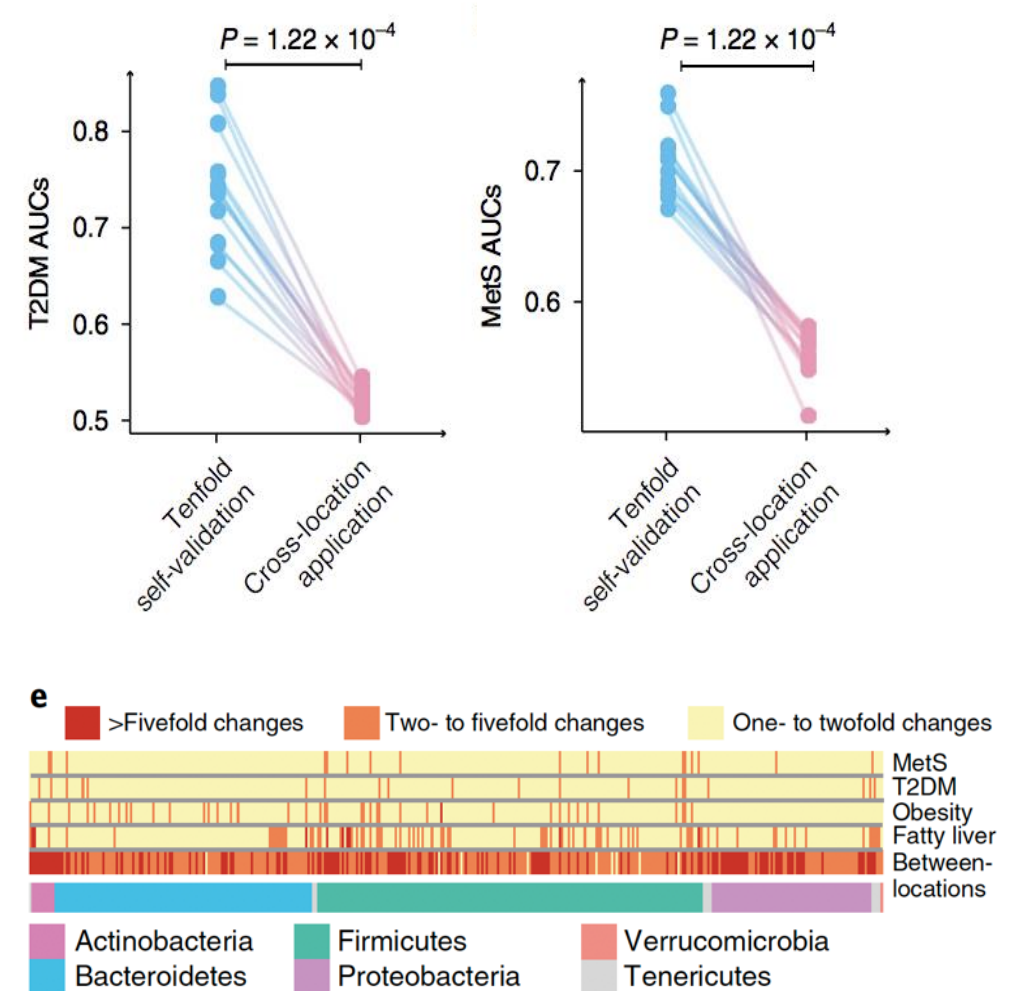


# Defining a Reference 'healthy' Microbiome Has Proven Challenging



## Conclusions

*“Localized baseline and disease models need to be built in order to predict metabolic risks”*



He et al., Nat. Medicine (2018); 24:1532–1535

# Alternative to Defining a Healthy Gut Microbiome: Focus on Host Physiology

16S rRNA Sequencing

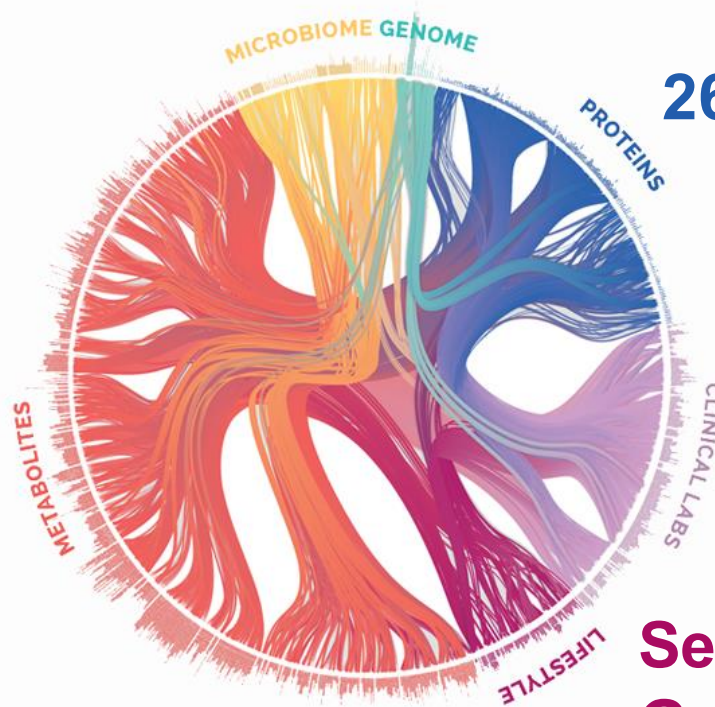
whole genome sequencing

263 plasma proteins

77 clinical labs

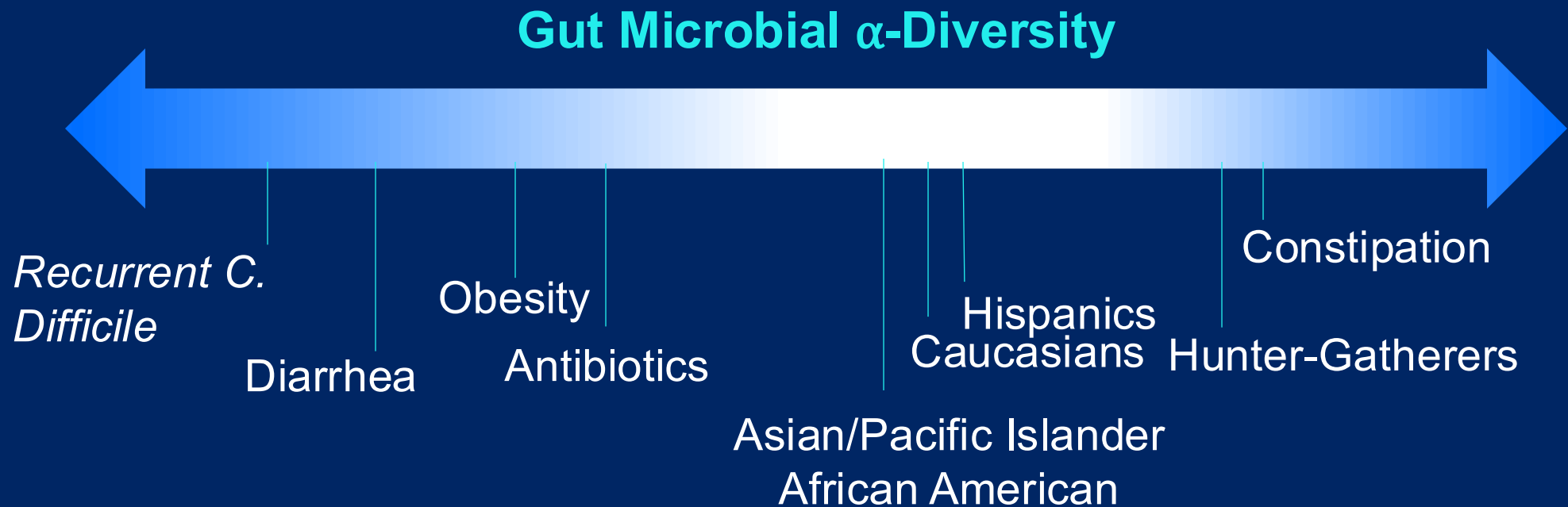
650+ plasma  
metabolites

Self-reported  
Gastrointestinal health/  
disease diagnosis  
Dietary Questionnaires



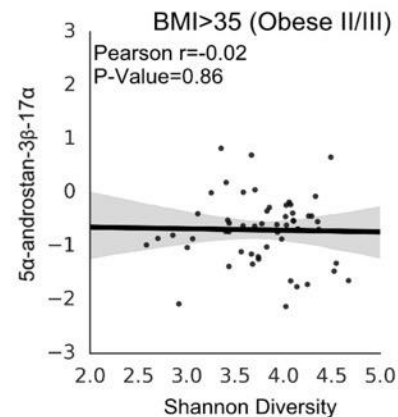
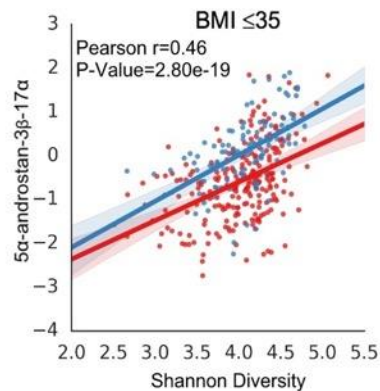
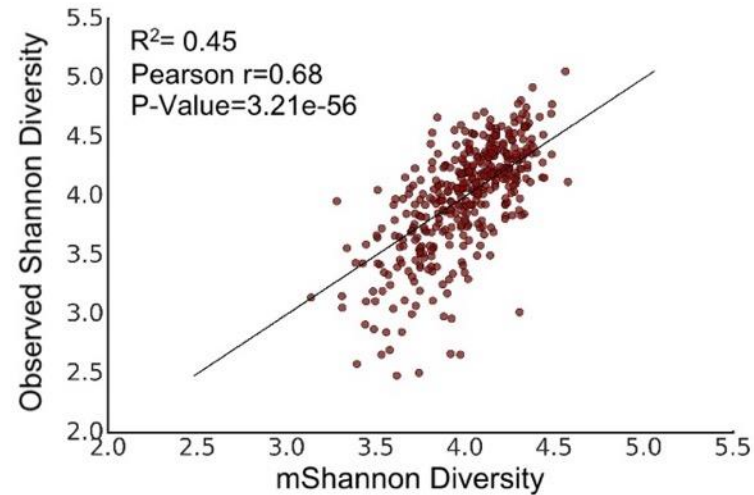
# Gut Microbial Diversity as marker of Microbiome Health

- Tends to be more consistently associated with disease conditions than specific microbes
- Is there an **optimal range** for gut microbial diversity?

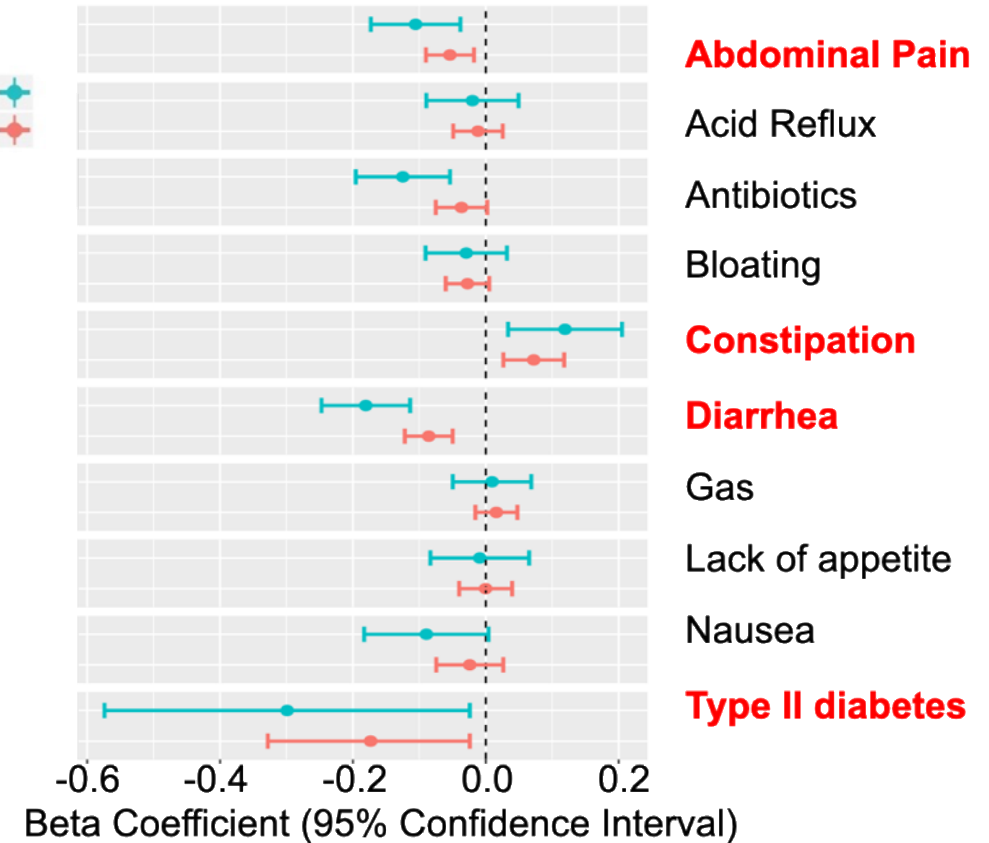


Brooks et al., PLOS Biology (2018); 16(12): e2006842  
Schnoor et al., Nature Communications (2014); 5:3654

# Blood Metabolome Predicts Microbiome Diversity in the Gut



Shannon  
mShannon



# Identified Metabolites Exert Biological Effects in the Host



Indole propionate



TMAO



Imidazole propionate  
Hippurate



Secondary Bile acids

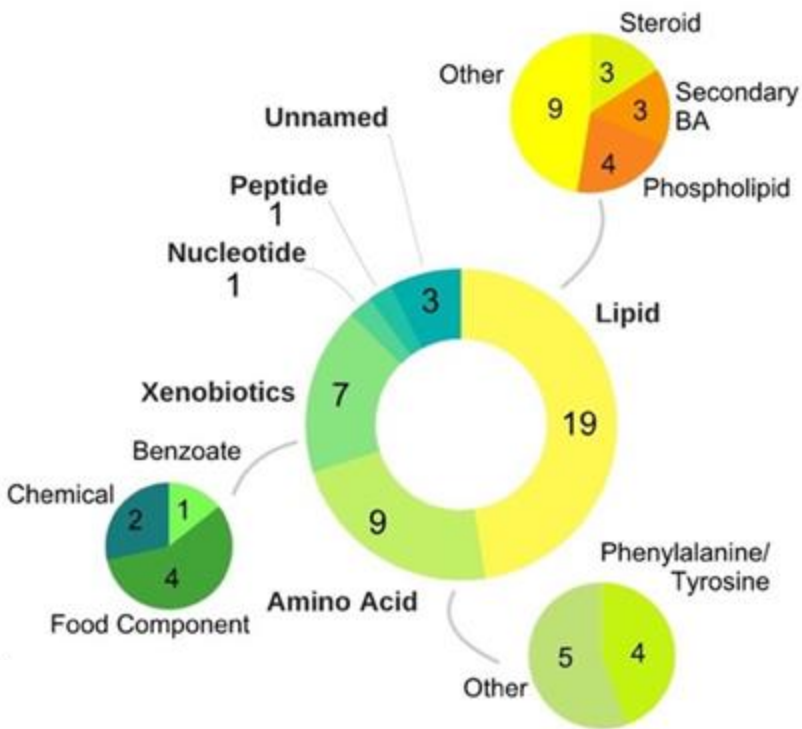


P-cresol  
sulfate

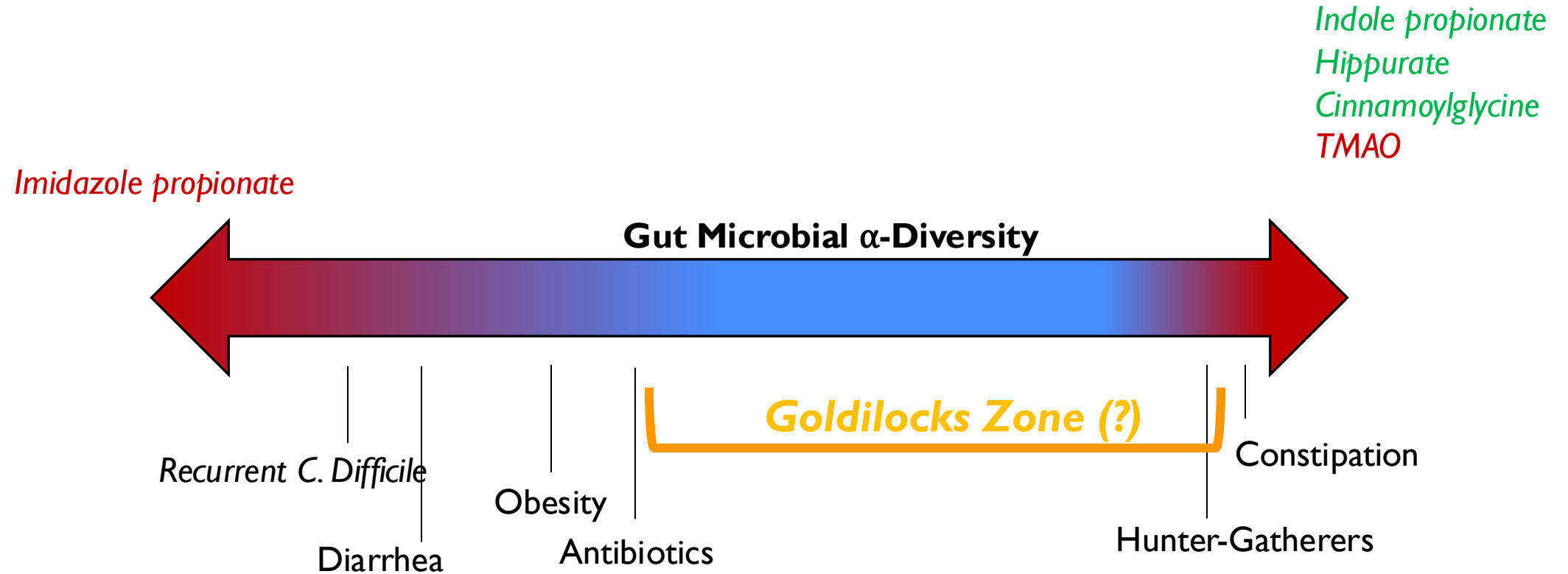


Imidazole propionate

 Negative predictor  
 Positive predictor



# An Optimal Gut $\alpha$ -Diversity?



*Beneficial metabolites*

*Detrimental metabolites*

# Exploring Gut Microbiome Patterns Across Healthy Aging and Longevity

The New York Times

## A Changing Gut Microbiome May Predict How Well You Age

People whose gut bacteria transformed over the decades tended to be healthier and live longer.



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# Healthy Gut Microbiome across Lifespan: Insights From Older Populations and Centenarians



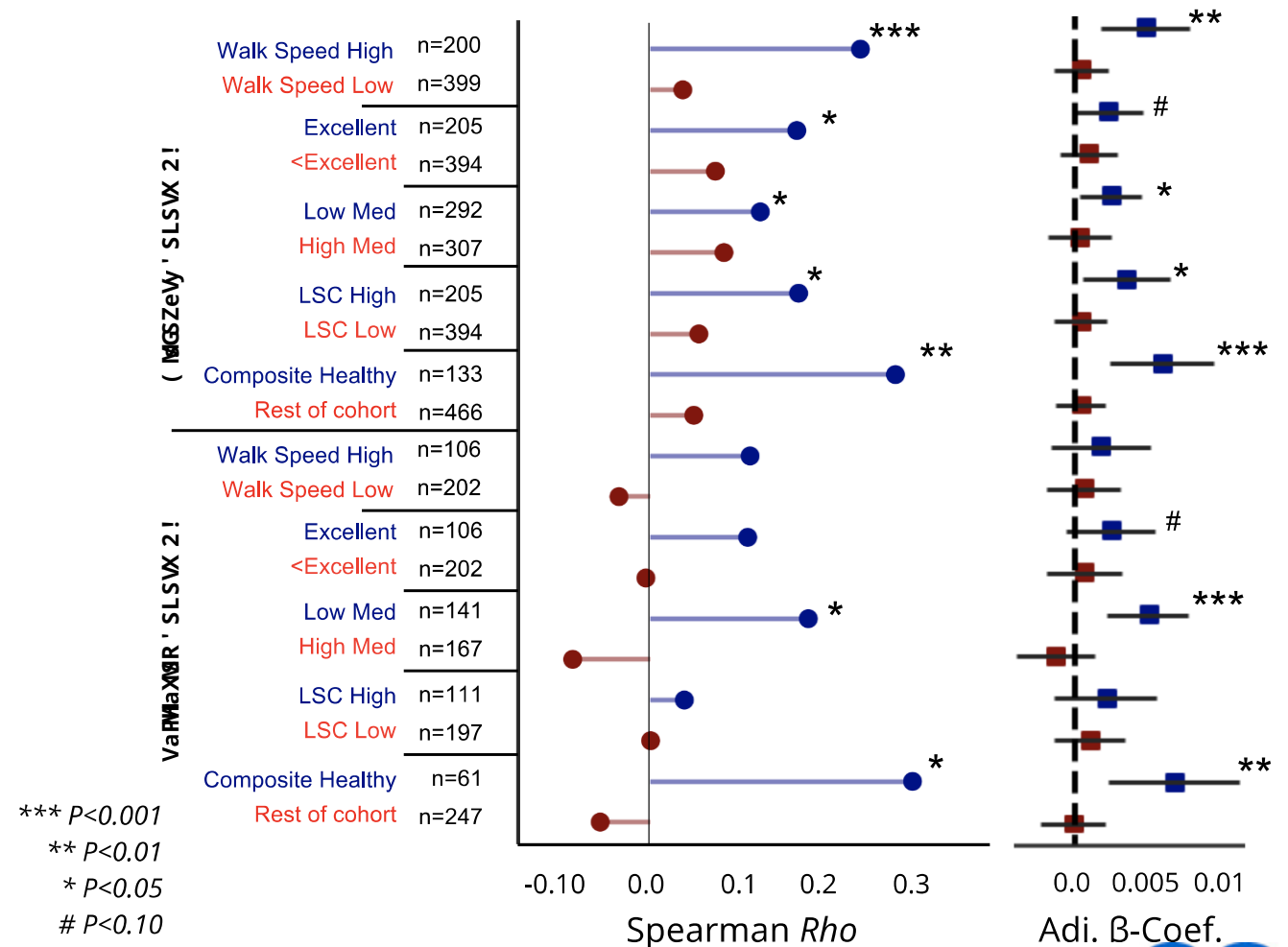
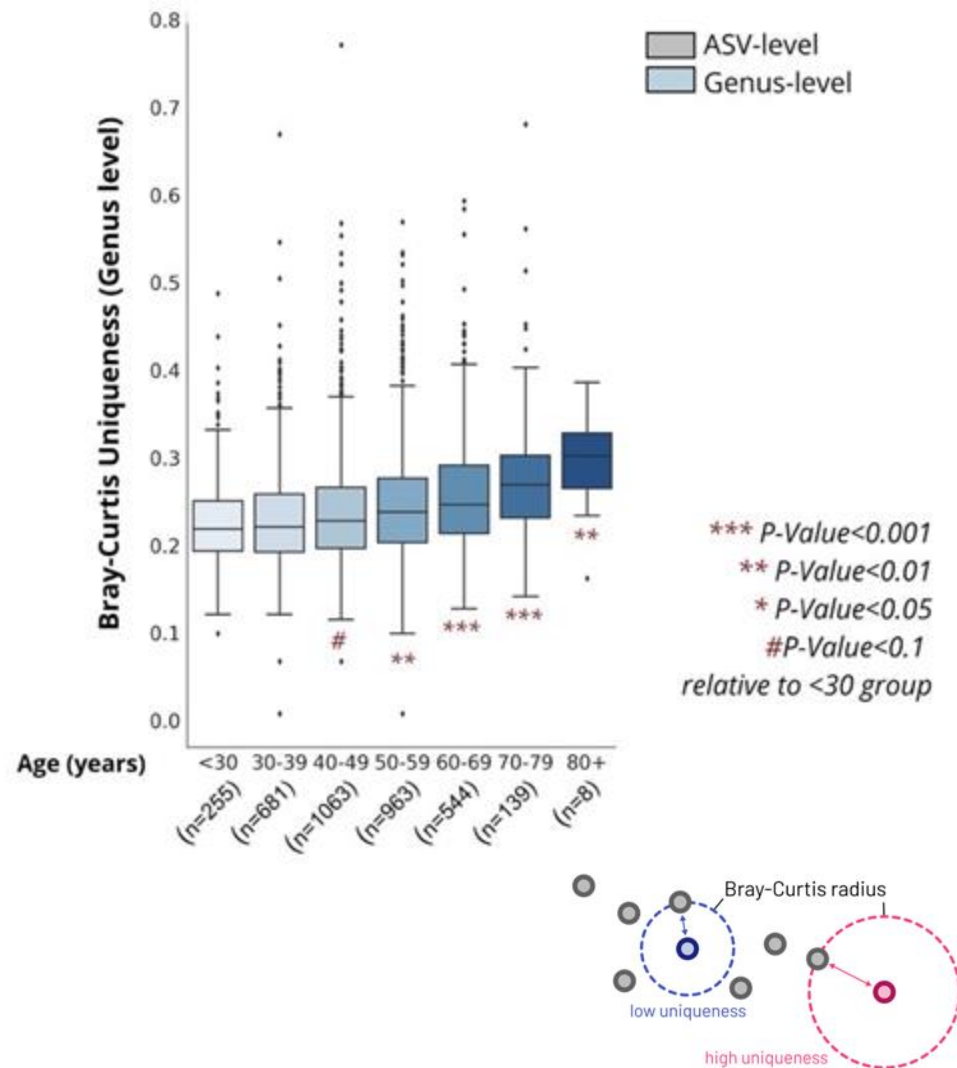
Colonization  
High Instability

Stability

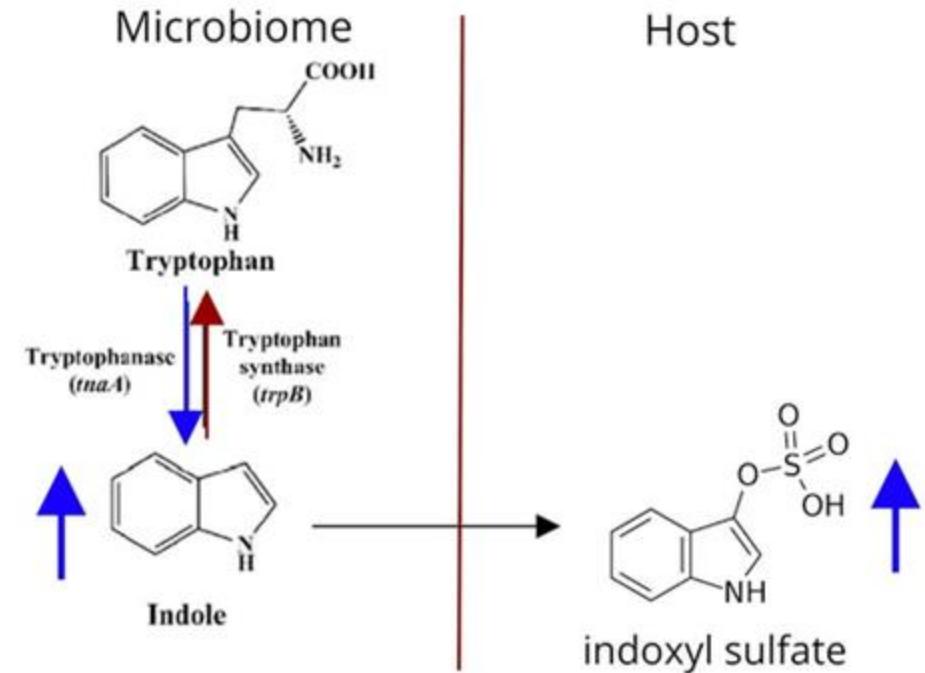
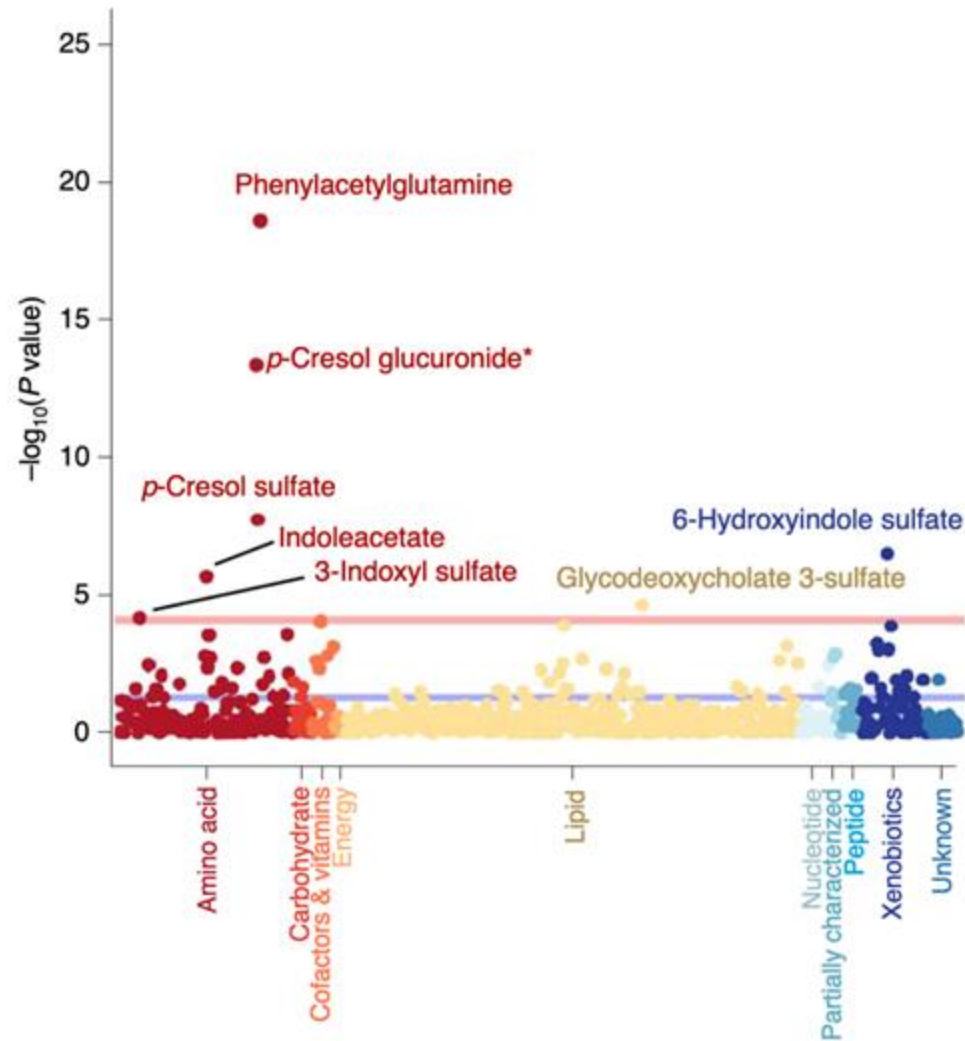
Gradual compositional  
changes, accelerated  
by comorbidities and  
life events (frailty,  
entering long-term care  
facilities, nursing  
homes, etc.)  
Alpha diversity ↓

Severe changes:  
Depletion of core  
microbes, increase  
in rare taxa  
Alpha diversity ↑

# Gut Microbiome Becomes Increasingly Unique with Age and Reflects Healthy Aging in Older Adults (78-98 years old)



While species become increasingly personalized in healthy aging, the resulting metabolic features are consistent

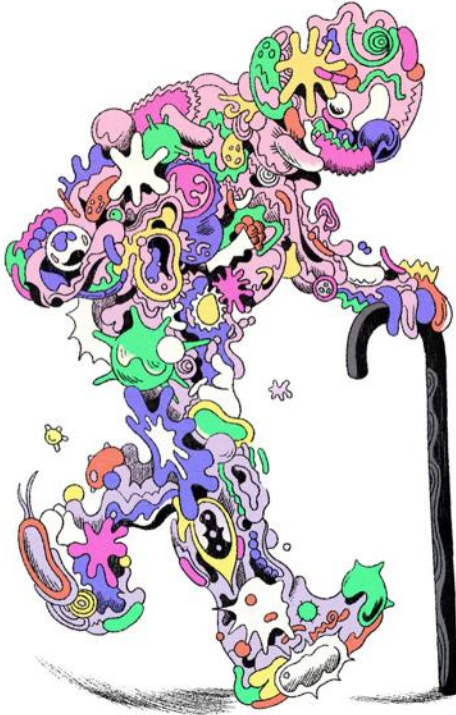


# Gut microbiome is important for healthy aging and is highly personalized

The New York Times

## A Changing Gut Microbiome May Predict How Well You Age

People whose gut bacteria transformed over the decades tended to be healthier and live longer.



Wilmanski...Price (*Nature Metabolism*, 2021)

### **Microbiome Uniqueness Increases with Age:**

*From around age 50, each person's microbiome becomes more distinct, influencing personalized health approaches.*

### **Stable Metabolic Processes in Healthy Aging:**

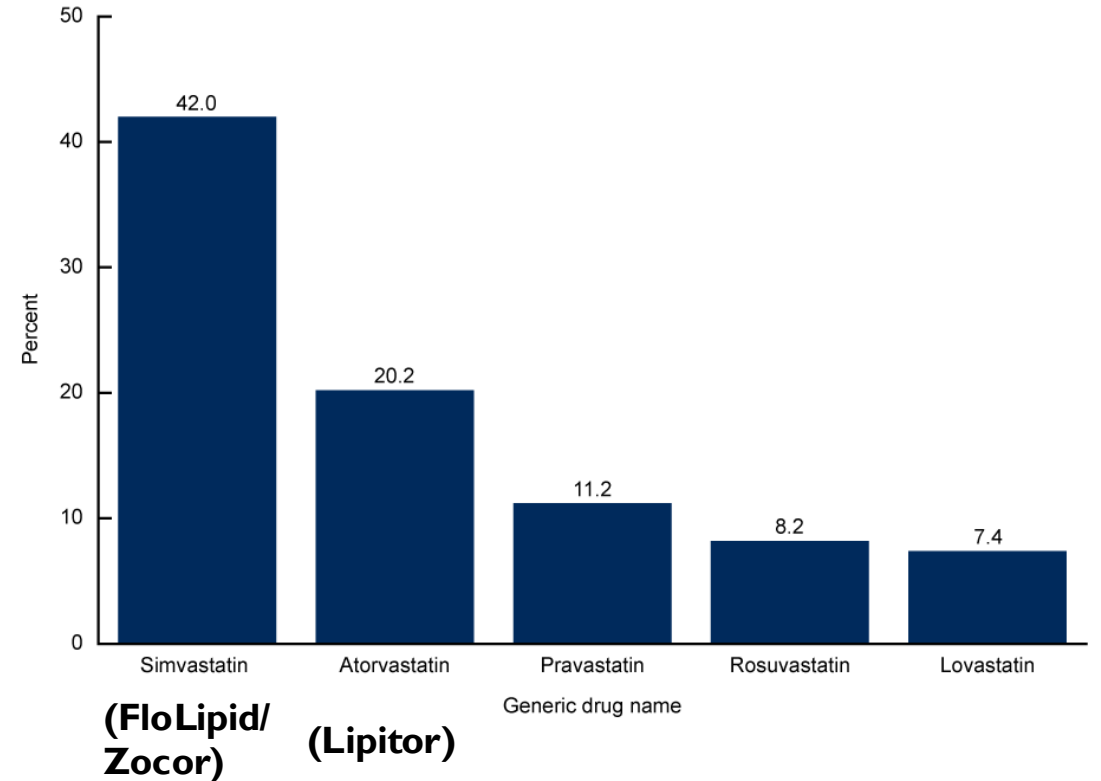
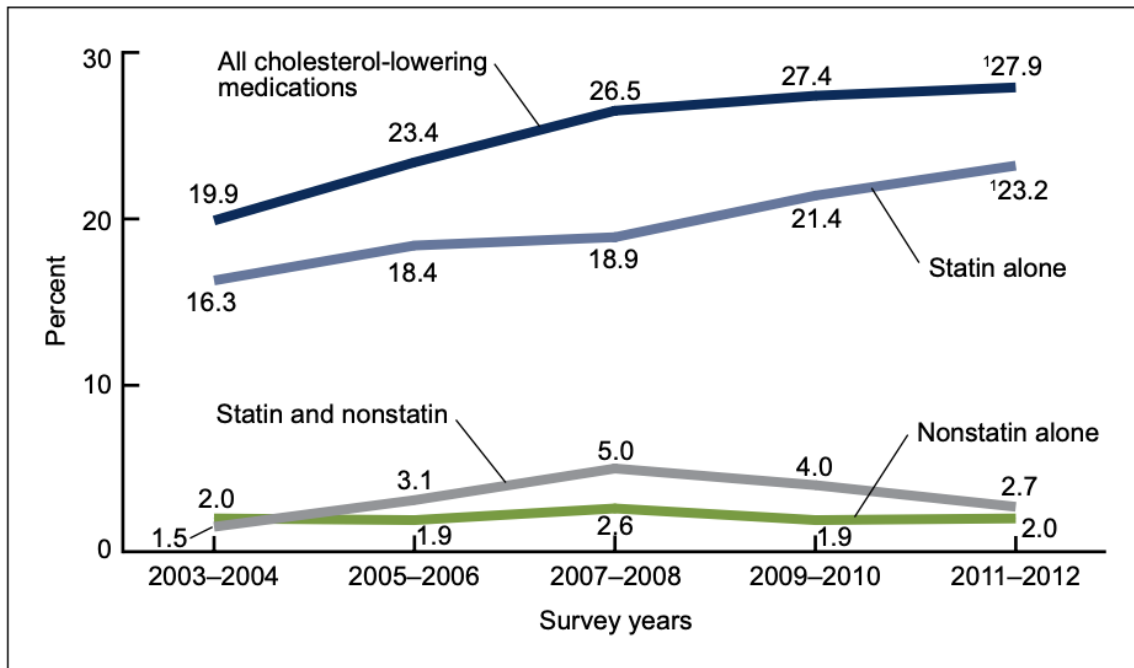
*Despite increased uniqueness, key metabolic functions are conserved in those who age healthily.*

**Microbiome Predicts Mortality Risk:** *The unique characteristics of an individual's microbiome can predict overall mortality risk in the elderly.*



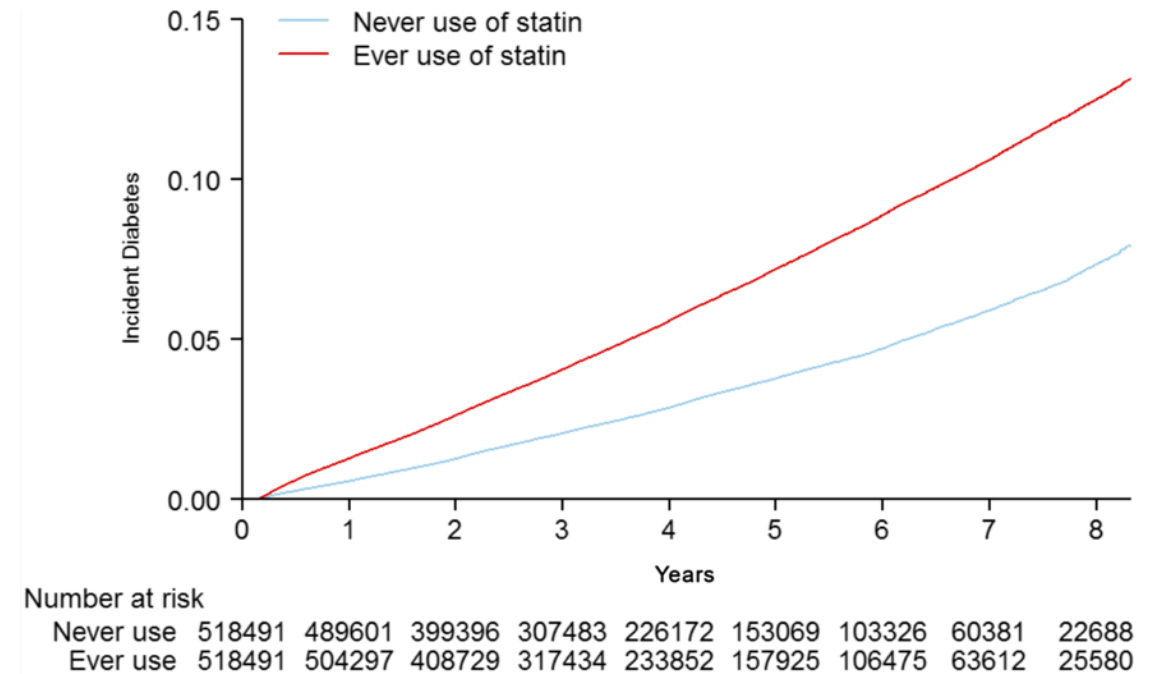
# Drug Interactions and the Gut Microbiome

Figure 1. Percentage of adults aged 40 and over who reported using a prescription cholesterol-lowering medication: United States, 2003–2012



# Statin Use and Known Side Effects

- Headaches
- Nausea
- **Myopathy**
- Liver damage
- **Disrupted glucose control**  
(increased risk of type II diabetes)
  - increased risk with duration of use
  - dose-dependent increased risk

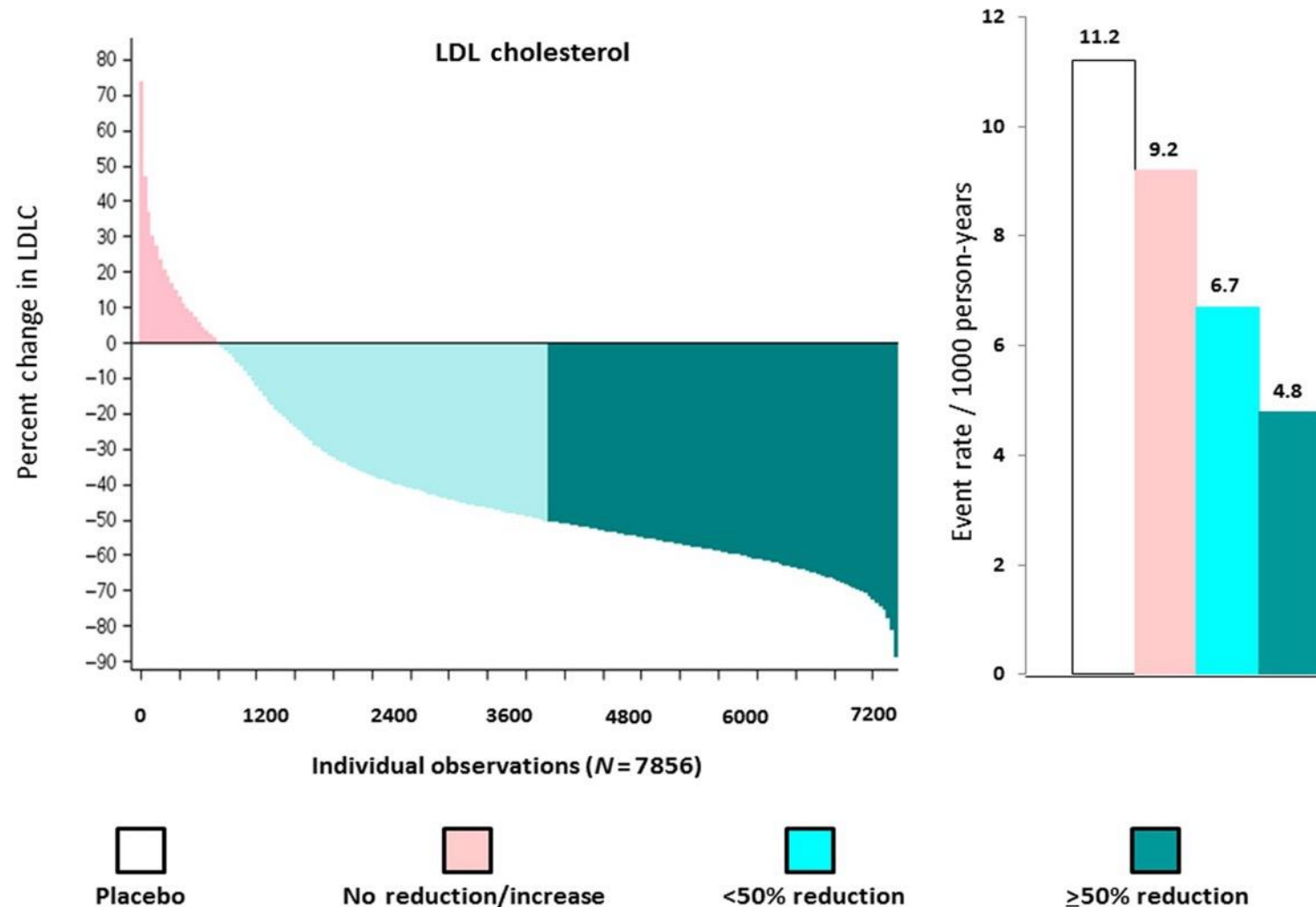


## Time- and Dose-Dependent Association of Statin Use With Risk of Clinically Relevant New-Onset Diabetes Mellitus in Primary Prevention: A Nationwide Observational Cohort Study

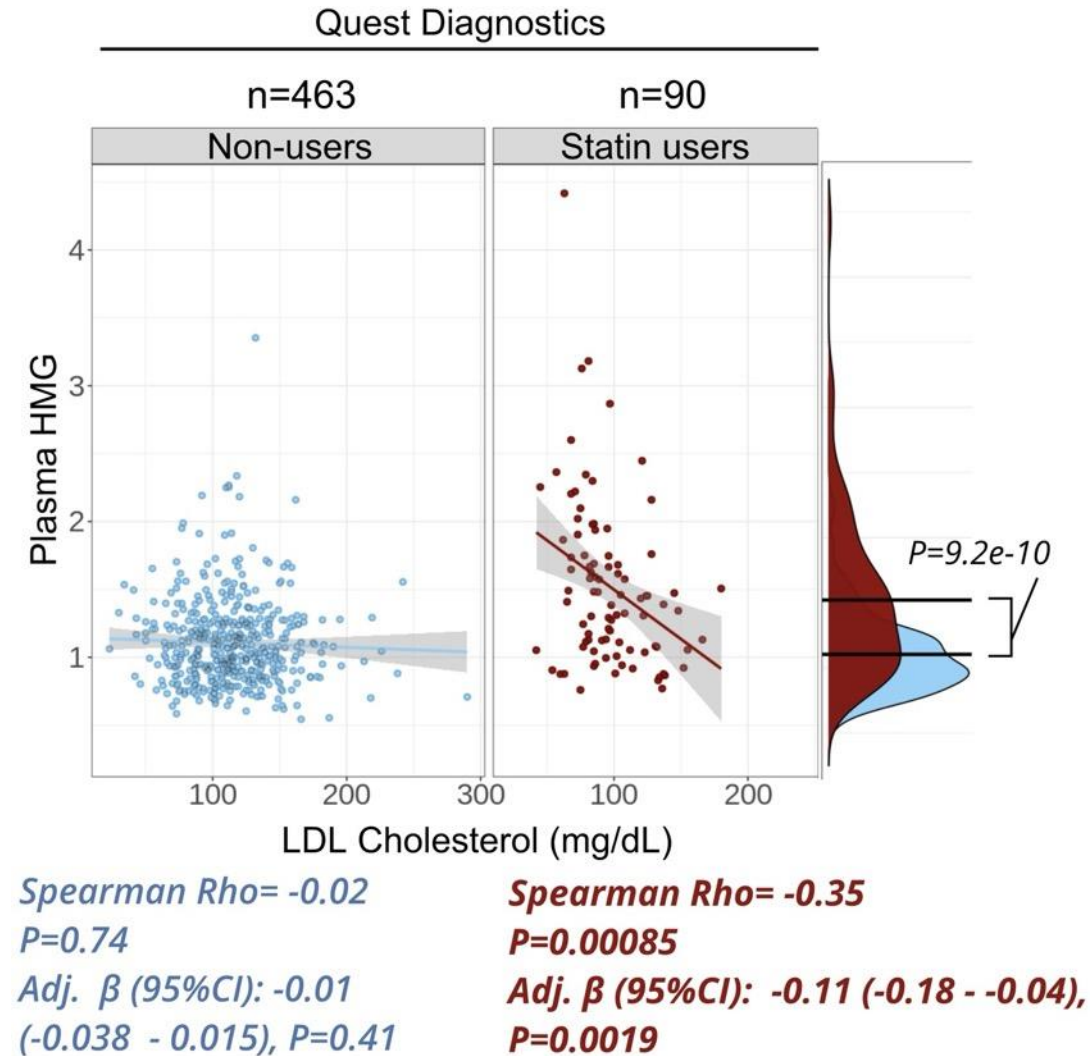
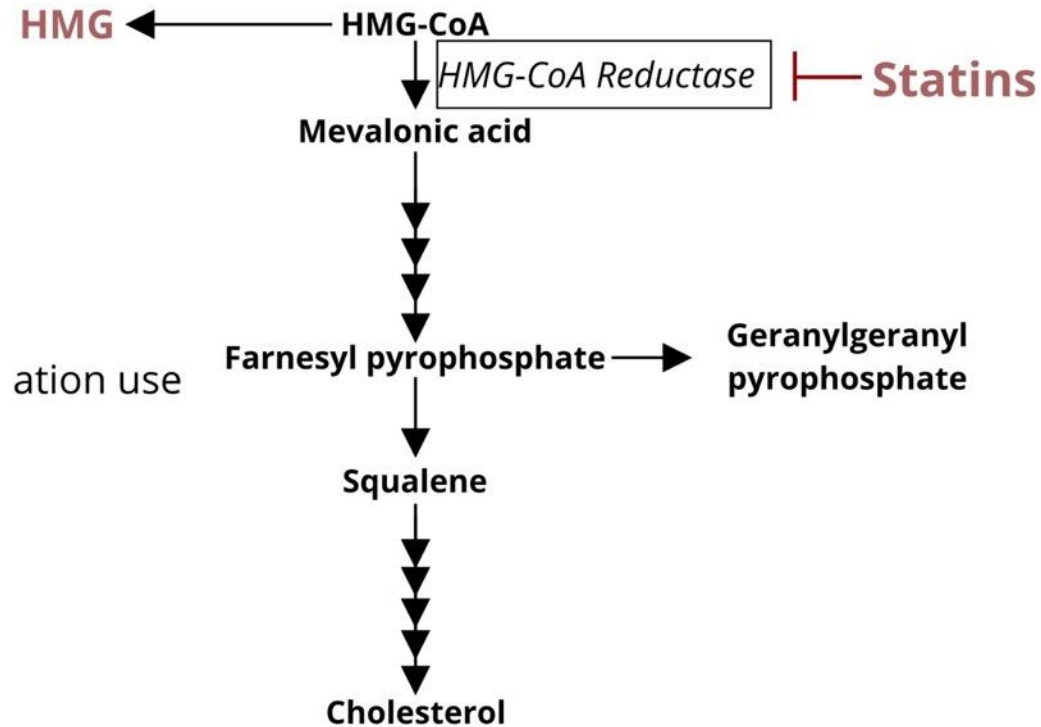
Min Jung Ko, Ae Jeong Jo, Yun Jung Kim, Shin Hee Kang, Songhee Cho, Sang-Ho Jo, Cheol-Young Park, Sung-Cheol Yun, Woo Je Lee , and Duk-Woo Park 

Originally published 15 Apr 2019 | <https://doi.org/10.1161/JAHA.118.011320> | Journal of the American Heart Association. 2019;8:e011320

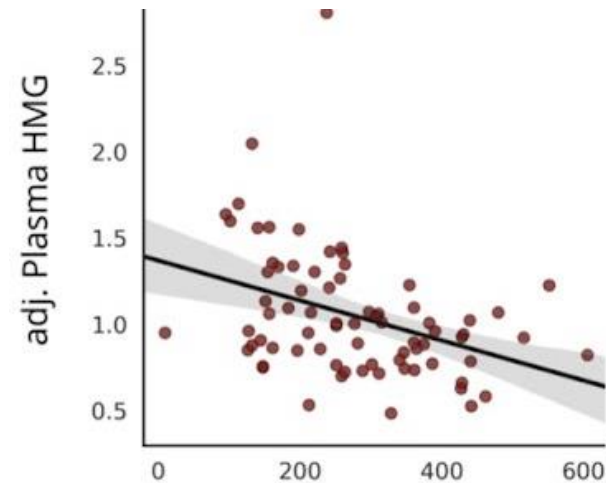
# High Level of Heterogeneity in Statin On-Target Response



# Does Gut Microbiome Composition Predict Response to Statins?



# Gut Microbiome Diversity Correlates with Markers of Statin On-Target Effects

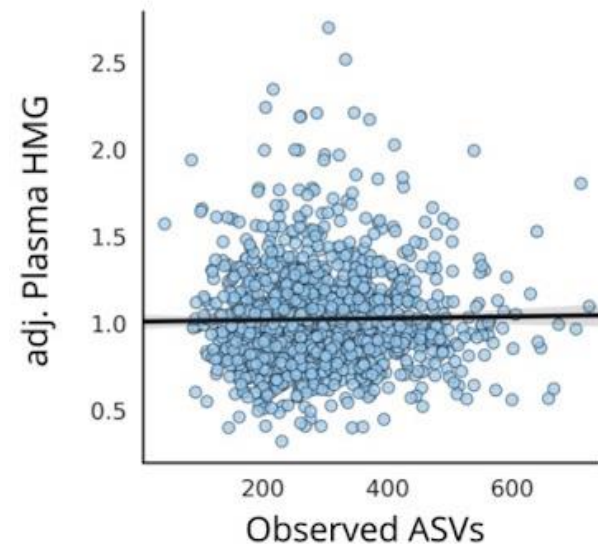


Statin Users with therapy intensity data (n=75)

*Spearman Rho*= -0.41  
*P*=0.00026

*Adj.  $\beta$  (95%CI)*: -0.00096  
(-0.0017 - -0.00023) *P*=0.0096

Models adjusted for sex, age, BMI, omics vendor and **dosage intensity**



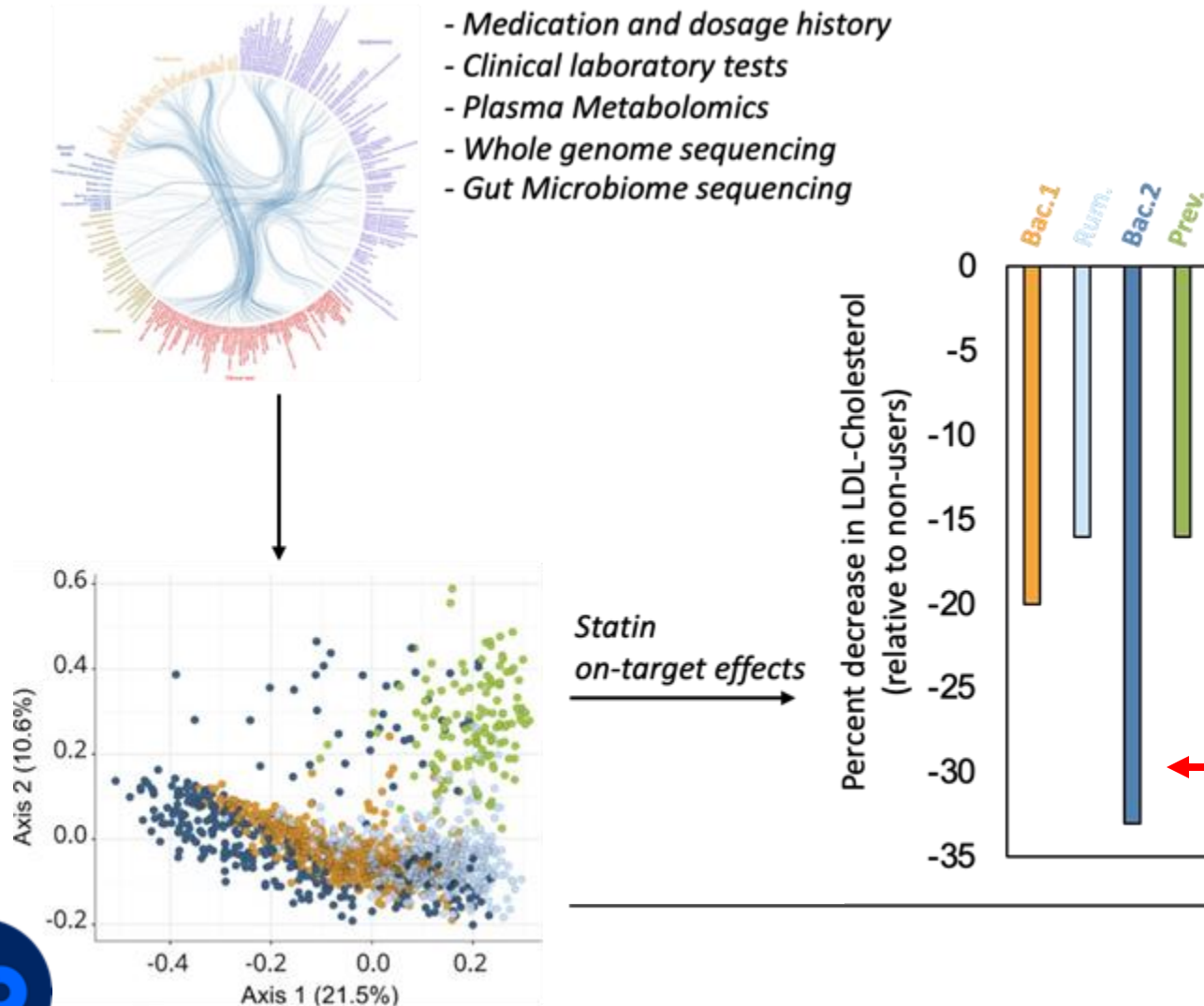
Non-Users (n=1315)

*Spearman Rho*= 0.02  
*P*=0.41

*Adj.  $\beta$  (95%CI)*: 9.2e-06  
(-0.00016 - 0.00017)  
*P*=0.91

# Gut microbiome influences statin efficacy

Statins have a *very weak* (but detectable) effect on microbiome composition, while microbiome composition has a strong effect on host *responses* to statins



**Doubled** lowering of LDL cholesterol observed with this type of microbiome

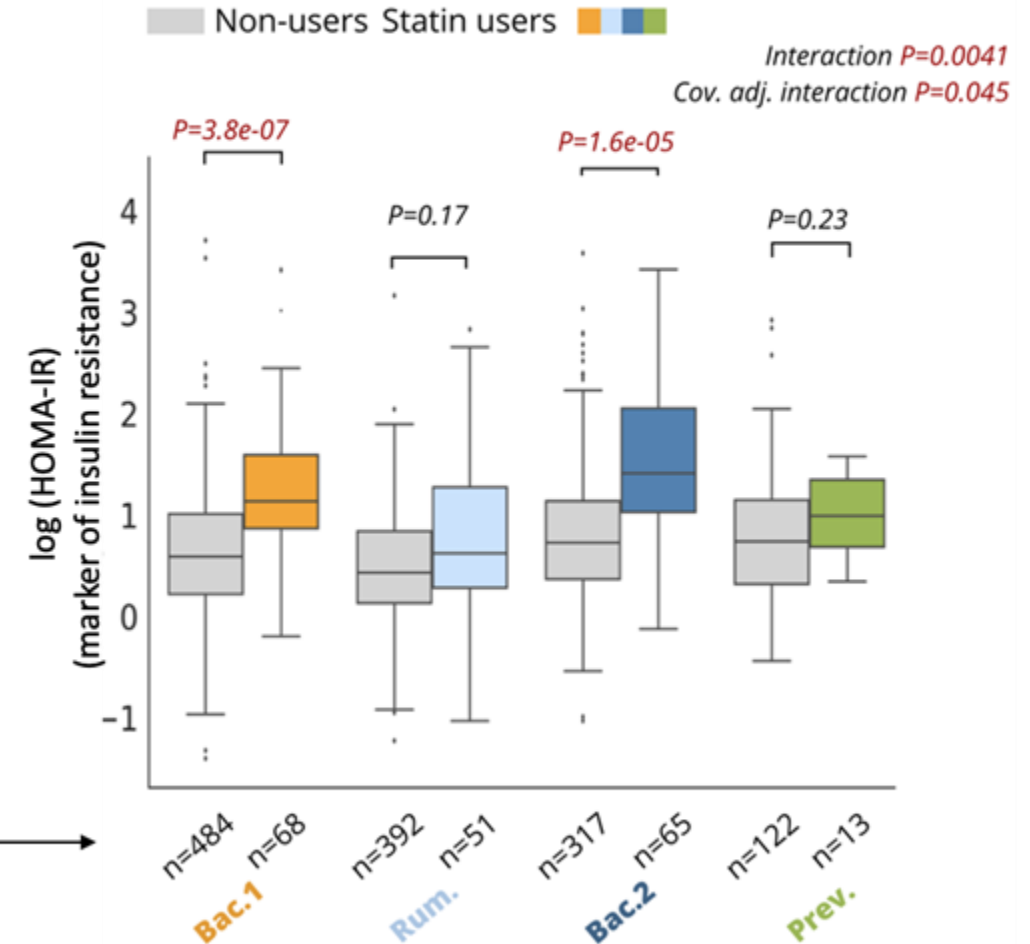


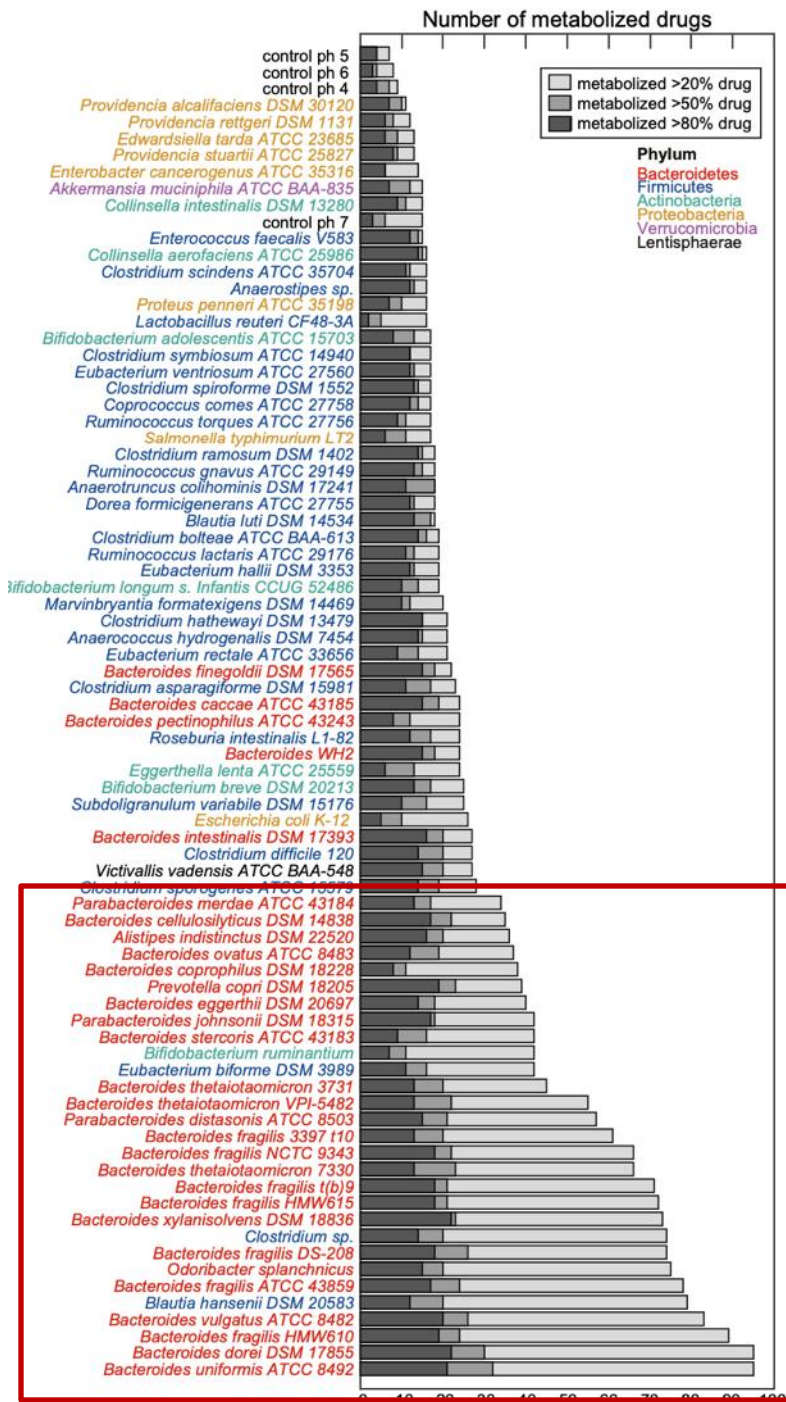
# Gut microbiome is also Associated with Metabolic Side Effects of Statins

Two types of microbiome showed signs of diabetes increase, while two did not

Statins have a *very weak* (but detectable) effect on microbiome composition, while microbiome composition has a strong effect on host *responses* to statins

Statin  
off-target effects





# Why are *Bacteroides* dominant microbiomes at higher risk of metabolic complications?

***Bacteroides* species are major drug metabolizers *in-vitro***

- Microbiome activation of the pro-drug?
- Microbiome modified statin metabolites have off-target effects?

# Thank You!

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**Thorne HealthTech**

If interested, feel free to reach  
out:

[twilmanski@thorne.com](mailto:twilmanski@thorne.com)

[www.thorne.com](http://www.thorne.com)